Business/Science/Technology

"The screening of these TCM (Traditional Chinese Medicine) products...could lead to a new generation of TCM-derived drugs and would help capture a share of the profitable pharmaceutical industry." *Modernization of Traditional Chinese Medicine in Hong Kong* (Chapter 2, Page 44)

Nancy Y. Ip, Ph.D.
Director, Biotechnology Research Institute & Associate Dean of Science
The Hong Kong University of Science and Technology

"Given sufficient funding, Hong Kong's sound infrastructure and research talent position the SAR to make a significant impact in the application of transgenics in the area of gene and drug target discovery." *Transgenic Animal and Gene Targeting Technology in Hong Kong: Current Status and Future Prospects* (Chapter 5, Page 102)

Kathryn S.E. Cheah, Ph.D.
Chair of Biochemistry and Head of Department
The University of Hong Kong

"The steady increase in research funding for academic research (to a total of HK$423.3 million for 1997-98) probably reflects the Government's conscious decision to upgrade and enhance higher education in Hong Kong. It is estimated that between 1991 and 1996, Hong Kong recruited some 3,500 new academic staff from the international community." *Role of Research Grants Council in Developing Biotechnology in Hong Kong* (Chapter 12, Page 203)

Lap-Chee Tsui, Ph.D.
Geneticist-in-Chief, The Hospital for Sick Children, Ontario, Canada
Professor, The University of Toronto, Ontario, Canada
Chairman, Biology & Medicine Panel, Hong Kong Research Grants Council

Marcus Tsui
Deputy Secretary, Hong Kong Research Grants Council
Assistant Secretary-General for Research, University Grants Committee of Hong Kong

"One good thing that the recent financial crisis precipitated is the realization by government as well as investors that Hong Kong's economy is too dependent on paper investments, such as stocks and real estate. I hope this change in attitude will drive Hong Kong to pay more attention to investing in technology-based industry, including biotechnology." *Biotechnology in Hong Kong: Investors' Sentiments* (Chapter 15, Page 265)

Walter K.K. Ho, Ph.D.
Chairman, Department of Biochemistry
The Chinese University of Hong Kong

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Edited by Albert Wai-Kit Chan, Ph.D., J.D.

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Email: kitchanlaw@aol.com

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Dedicated to Alexandra Yeung-Wah Chan,
my wonderful baby daughter
who makes my life more meaningful.

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Editor's Note

The idea for this book was conceived in the summer of 1997, when I traveled to Hong Kong to witness its handover to China. I spent much of my trip reminiscing with old friends, many of whom are scientists. I found myself curious about not only the social, political and economic future of the new Special Administrative Region but about the future of science in Hong Kong. Nowadays, you cannot talk about science without referring to biotechnology, so you can say that I was interested in the future of biotechnology in Hong Kong. Does biotechnology have a place in Hong Kong? Can it compete with other businesses for funding and survive?

I came to the conclusion that publishing a book about biotechnology would be the best way to explore these questions. Biotechnology touches almost every aspect of science, so it was necessary to include the viewpoints of more than 30 writers. Their opinions are laid out here, and I hope their words shed light on the subject of biotechnology in this region.

This book would not have come about without the help of various people. First, I would like to thank Mr. Yuk Lam Lo for all his help. Yuk Lam was instrumental in inviting many of the contributors and lending structure to the book. I must also thank Mr. Michael Tam, general manager of United States-China Intellectual Property Institute, for his generous assistance in putting this book together. My gratitude further extends to Mr. Sam Lai, who designed the cover for the book and the flyer announcing its arrival. Dr. King-Lau Chow was also involved in the design process. Of course, this book would not have happened without the efforts of all our dedicated writers. Finally, I would like to thank my lovely wife, Sharon King Lee, the real "editor" of this book. Without her help, the publication of this book would not have been possible.

Albert Wai-Kit Chan, Ph.D., J.D.
December 15, 1998
New York

Preface

We are living in the Golden Age of Biotechnology. Over the last 30 years, a number of basic tools have been developed, thus enabling a more clear and advanced understanding of molecular and cellular biological fundamentals. The complete genomes of a wide range of microorganisms and plant organelles have now been fully determined. The completion of the optimal task of sequencing the Human Genome is in sight. In addition, a program is under way to determine the protein complement of cells. This effort, termed "Proteomics," promises to fuse the genomic information content with the function of proteins. Finally, advances in gene delivery technology make the promise of gene therapy a realistic one. When all of these technological advances are combined with the almost-daily discovery of disease-causing genes and their underlying mutations, the challenge to produce commercial products that will have a major impact on health care, agriculture and other industrial processes is imminent.

In this book, a wide ranging survey of the current status of biotechnology in Hong Kong is presented. It is the goal of this volume to present the context for the emergence of commercial biotechnology in Hong Kong. The first and second sections describe the status of the industry in Hong Kong and offer contrasts to similar developments around the world. There is no doubt that, in the United States, enormous efforts in the area of genomics and its application to drug discovery are under way. Companies like Human Genome Sciences, Inc., Rockville, MD; Incyte Pharmaceuticals, Palo Alto, CA; Sequena Therapeutics, La Jolla, CA; and Millennium Pharmaceuticals, Inc., Cambridge, MA, are forming strategic alliances with pharmaceutical companies to develop the next generation of gene-based drugs. Where does Hong Kong stand in this emerging market? The first two sections describe, through a series of articles, a variety of research efforts in Hong Kong which range from Traditional Chinese Medicine to agriculture to gene therapy. These chapters review programs and initiatives currently underway in Hong Kong, thus providing a preliminary view of the opportunities that lie ahead.

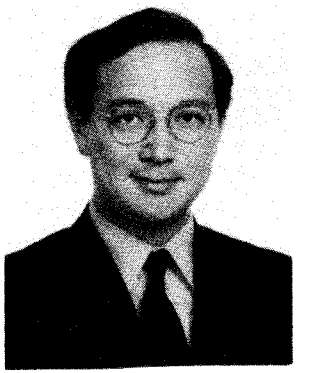
There is no question that the explosion of technology in basic biological research has created significant opportunities for the commercial development of DNA diagnostics, agricultural products and gene therapies. A main point that must be considered in this new age of commercial molecular biology is that these efforts create new demands on government, educational, financial, and regulatory

systems. In the specific case of biotechnology in Hong Kong, the mechanisms for funding these efforts must be put in place, and a work force sophisticated enough to compete on a worldwide basis must be nurtured. In addition, the role that China will play in this emerging biotechnology industry must be determined. The next five sections of the book cover these issues in detail. Finally, some current observations and reflections on Hong Kong biotechnology from leaders in and outside of Hong Kong have been assembled to further help put the status of the industry in context.

It is our hope in this book to explore the status and potential for biotechnology in Hong Kong and to discuss the strengths and weaknesses of the effort. Biotechnology is clearly the industry for the next millennium, and its development is essential for economic growth in any industrialized region of the world. We establish here the potential for the development of the biotechnology industry in Hong Kong. We thank all the authors who have contributed insightful articles to this book and trust that their efforts will continue to have a strong impact on the future of biotechnology in Hong Kong. Hopefully, we raise important questions that will elicit discussion and point the way forward in this most important endeavor.

The Honorable Raymond Ch'ien
Executive Council Member
The Government of The Hong Kong Special Administrative Region

Yuk Lam Lo
Chairman, Biotechnology Committee
Industry Department
The Government of The Hong Kong Special Administrative Region



***Raymond K.F. Ch'ien, C.B.E., J.P.**, is chairman of Inchcape Pacific Limited and director of Inchcape plc. Inchcape Pacific Limited, a subsidiary of Inchcape plc, is a diversified distribution company active in the automotive, industrial products, branded consumer products, office equipment and logistics services sectors of the Greater China market. Ch'ien is a member of the first Executive Council of the Hong Kong Special Administrative Region of The People's Republic of China. He also serves as chairman of the Industry & Technology Development Council, the region's highest consultative body on industrial development policy. Ch'ien holds a Doctorate in Economics from the University of Pennsylvania.*



***Yuk Lam Lo** is chairman of The Biotechnology Committee of the Hong Kong Government Industry Department and president of Bio-Rad Pacific Ltd. Lo received his B.S. degree from the University of Waterloo, Ontario, Canada. He is an honorary consultant at Beijing Medical University and a visiting professor at Xiamen University and Chinese Academy of Preventative Medicine in China. Lo is a special advisor to The Hong Kong University of Science and Technology and is on the advisory committee at City University of Hong Kong and The Hong Kong Polytechnic University. He is also chairman of Phoenix (BIOTECH), Ventures Capital International Ltd. and a director at Gland Pharma Ltd. in India.*

Current Biotechnology Activity in Hong Kong

Chapter 1

The Hong Kong Institute of Biotechnology, Ltd.: Its Role in Downstream Development in Hong Kong

By

~ Albert Y. Chang, Ph.D. ~
Director
The Hong Kong Institute of Biotechnology, Ltd.



***Albert Y. Chang, Ph.D.**, is director of the Hong Kong Institute of Biotechnology. Chang received his B.S. in chemistry from National Taiwan University in Taipei; his M.S. in biochemistry from the University of California, Berkeley; and his Ph.D. in biochemistry from the University of Illinois in Champaign-Urbana, where he also was a postdoctoral fellow in the Virus Laboratory. Chang was formerly the managing director for pharmaceutical R&D laboratories at the Development Centre for Biotechnology in Taipei. Prior to that, he worked at The Upjohn Co. in Kalamazoo, Michigan. Chang has published a total of 104 papers, book chapters and meeting abstracts.*

The economic success of the Hong Kong Special Administrative Region (HKSAR) of the People's Republic of China (PRC) has been phenomenal in the past 20 years. Its per capita expenditure-based Gross Domestic Product (GDP) at constant (1990) market prices rose steadily from HK$40,746 in 1975 to HK$1,289,352 in 1995, reaching a level comparable to that of developed countries.[1] In this period there were substantial redistribution of the contribution to production-based GDP by various economic sectors. In 1980, the manufacturing sector contributed the most at 23.7% of the total, which was followed closely by the financing, insurance, real estate and business services (FIRB) sector and the wholesale, retail import/export trades, restaurants, hotels (WRRH) sector, each at 23.0% and 21.4%, respectively.[1] In 1996, contribution of the manufacturing sector dropped to the lowest spot at only 7.2% of the total, while those of the FIRB and WRRH sectors remained at the top, each at 24.9% and 25.4%, respectively.[1] In absolute terms, the manufacturing sector also showed a decrease in productivity from HK$99.8 billion in 1992 to HK$80.1 billion in 1996.[1]

The decline in its manufacturing sector was attributed to the steep increase of the land and manpower costs in Hong Kong that prompted its businesses to move their manufacturing plants across the border to South China. In order to revert this trend, both the public and private sectors in Hong Kong have made concerted efforts to upgrade Hong Kong's manufacturing sector from labor- and land-intensive industries to research & development (R&D)-based high-tech industries. In the early '90s, the Hong Kong Government Industry Department set up two funding schemes, the Applied R&D Co. and the Industrial Support Fund (ISF), to support R&D projects which are beneficial to the industrial and technological development of the Region. In recent years, funding awards have focused on high-technology industries, such as those based on biotechnology and information technology.

To provide the basic infrastructural support to promote the biotechnology industry in Hong Kong, the Hong Kong Jockey Club Charities Trust (HKJCCT) which is a philanthropic organization in Hong Kong's private sector donated a total of HK$300 million to establish two research institutes devoted to biotechnology R&D. The Biotechnology Research Institute (BRI) at The Hong Kong University of Science & Technology was given the task to carry out the upstream discovery research while The Hong Kong Institute of Biotechnology Ltd. (HKIB) at The Chinese University of Hong Kong (CUHK) was assigned as the downstream development

laboratory to support Hong Kong's biotechnology industry. This Chapter is devoted specifically to HKIB and its role in the downstream development of biotechnology products in Hong Kong.

Sources of Funding

In 1989, with a one-time donation of HK$170 million from the HKJCCT, HKIB was established as a nonprofit private company by the Council of CUHK with a mandate to achieve financial self-sufficiency in due course. Its mission is to provide the catalyst and essential infrastructure for the emergence of a successful biotechnology industry in Hong Kong. Aside from donations by the Vitasoy International Ltd. and the Wei Lun Foundation Endowment Fund in the private sector, HKIB has relied on ISF grants to support its industrial development activities in human therapeutics, plant micropropagation, incubation program, and consultation services. The Hong Kong Government Industry Department has given HKIB strong support as reflected by the success rate of its ISF proposals. Four applications out of six were funded in 1994, five out of eight in 1995, three out of four in 1996 and three out of three in 1997. These ISF grants enabled HKIB to gradually build the facilities and programs necessary for the attainment of its objectives.

The facilities include the GMP Manufacturing Technology Centre, the Incubation Programme, the Plant Micropropagation Laboratory, etc. The programs include the Hong Kong Pharmaceutical Technology Centre, which provides consultation on GMP manufacturing to the local pharmaceutical industry; the Biotechnology Information Office, which supplies information on technology, intellectual property rights and the competition; and, most important, the center provides a qualified and highly motivated work force. The process of putting these facilities and programs in place is discussed in the following sections.

Human Therapeutics

At the present, human therapeutics remain the most profitable products in the global biotechnology industry. With an ISF grant in 1994, HKIB established a multipurpose Bioprocessing Unit (BPU) to develop manufacturing processes for fermentation-based products on a pilot-plant scale. In 1996, with another ISF grant, the BPU was upgraded to a GMP Manufacturing Technology Centre (GMP-MTC). GMP-MTC is fully equipped

to develop and produce clinical-grade biomaterials under Good Manufacturing Practice (GMP) guidelines for Phase I and II clinical trials of innovative products in human subjects.

HKIB's GMP-MTC has a molecular biology laboratory to carry out its own bioengineering projects as well as to provide contract gene cloning services to global clients. The molecular biology laboratory was established by an ISF grant in 1995. The center's process development laboratory has the capability to develop manufacturing processes using microbial, plant, insect and mammalian cell cultures. Its pilot plant has a fermentation and bioprocessing capacity of 100 to 350 liters. The center's Class 10,000 clean room accommodates its purification suite to process clinical grade protein or DNA products under GMP conditions. Its Quality Control (QC) Laboratories and Quality Assurance (QA) Office ensure that its own manufacturing operations meet the World Health Organization's (WHO) and Food and Drug Administration's (FDA) GMP guidelines.

Since the establishment of its BPU in 1994, HKIB has actively searched for worthwhile projects to utilize its pilot plant. Malaria remains one of the world's major health problems and up to 500 million people may be infected with the parasite, resulting in approximately two million deaths annually. There is an urgent need to develop an effective vaccine to prevent the spread of malaria. Therefore, in 1996, HKIB applied for and was subsequently awarded, via a competitive process, an R&D Partnership Grant in malaria vaccine development by the UNDP/World Bank/WHO Special Programme for Research Training in Tropical Diseases. The R&D Partnership Grant was used to train research personnel in HKIB's GMP-MTC to scale up production of a transmission-blocking malaria vaccine candidate developed by Dr. David Kaslow, head of the Malaria Vaccine Section of the National Institutes of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health (NIH) in the U.S. The vaccine candidate is based on Pfs25, the predominant surface protein of Plasmodium falciparum zygotes. The antigen TBV25H (Transmission-Blocking Vaccine based on Pfs25 with a Histidine tag) is expressed in yeast and its purification process uses a nickel-NTA agarose column.[2] HKIB signed a Cooperative Research and Development Agreement (CRADA) with NIAID, NIH in January 1998.

HKIB filed a Drug Master File (Type I) on its Phase I microbial fermentation facility with the FDA in May 1998. The

facility was also inspected by the Therapeutic Goods Administration (TGA) of the Australian Government, and a GMP Certification on the facility has been issued by the TGA. NIAID and HKIB will jointly file Investigational New Drug (IND) applications with the FDA and HKSAR's Department of Health to carry out Phase I clinical trials of the TBV25H vaccine in Hong Kong and the U.S. simultaneously. HKIB will manufacture the bulk clinical trial materials for the Phase I human studies.

HKIB also plans to use its GMP facility to develop vaccines and biopharmaceuticals for other life-threatening diseases such as AIDS. A collaboration between HKIB and the Institute for International Vaccine Development in the U.S. to develop HIV vaccines is currently under discussion. HKIB is also actively seeking opportunities to offer its facilities and services in the development of human therapeutics to global pharmaceutical companies in the expansion of their businesses in China and Southeast Asia.

Plant Micropropagation Programme

As agriculture remains one of the top-priority industries in China, it is imperative for the HKSAR to develop and maintain a judicious amount of agriculture R&D, although the HKSAR per se lacks sufficient arable land to sustain an agriculture industry. Therefore, HKIB established a plant micropropagation programme with the following objectives:

- To develop mass propagation protocols of high-value ornamental and medicinal plants.
- To develop plant cell culture technologies in a bioreactor culture system on a two-to-20-liter scale.
- To investigate morphogenesis events involved in the development of propagation protocols in order to better understand micropropagation processes and to optimize conditions.

With ISF grants obtained in 1994 and 1997, HKIB has successfully produced cell culture-based micropropagation protocols for the following ornamental herbaceous plants: Ananas, Anoectochilus formosanus, Cordyline terminalis,

Drosera burmanii, Gladiolus spp., Jovibarba, Kalanchoe blossfeldiana, Lilium spp., Oxalis triangularis, Platycerium bifurcatum, Saintpaulia ionantha, Scindapsus aureus and Spathoglottis plicata. In collaboration with a group of local businessmen, desktop ornaments containing these live herbaceous plants are being produced for the mass consumer market. Under the persuasion of its business partners, HKIB has also embarked on the development of the micropropagation processes of the following woody plants: Bauhinia purpurea, Armeniaca, Cerasus spp., Camellia and Coffea arabica for the same purpose. In addition, HKIB will transfer the developed protocols and processes to companies that are interested in large-scale production of these plants in the open field.

HKIB is also developing manufacturing processes for ginseng cells in liquid cultures. A fast-growing strain has been isolated and successfully cultured in two-liter bioreactors. Its ginsenosides content has also been verified. The process will be transferred to food-and-beverage companies to provide the active ingredients in ginseng-based drinks and foods.

The Incubation Programme

The development of biotechnology products is time consuming and capital intensive. For HKSAR to develop a biotechnology industry, the region must provide low-cost laboratory facilities for entrepreneurs to develop their technologies into products. It is for this purpose that HKIB fashioned a 16,000-square-foot, second-floor space in its five-story R&D building into an incubator facility. The facility provides furnished laboratories, offices, shared common-use equipment, technical and management services, for companies to start their R&D activities in Hong Kong. Such facilities and services enable companies to minimize up-front investment during the initial product- or service-development stages. Companies can rent space at a flat monthly charge or sign up for a back-loading scheme that allows HKIB to share profits with the entrepreneurs. There are eight labs, each of which can accommodate four to six persons. Presently, the facility has the following client companies:

HKIB/Techpool Research Laboratory Ltd.
This is a joint venture company between HKIB and Hong Kong Techpool Ltd. with the business

goal of adding value to human urine-derived biopharmaceuticals manufactured by Techpool in Guangdong Province.

Leadergene Ltd. The Company was founded to utilize a unique expression vector in bacteria that facilitates the secretion of cloned gene products. Its initial products include porcine growth hormone-releasing factor and human growth factors.

Cell Therapy Technologies Centre Ltd. The Company focuses on utilizing cell therapy technologies such as autologous cord blood banking, etc., in medical applications.

BF Goodrich Laboratory (Hong Kong) This is a research laboratory set up by BF Goodrich of the U.S. to develop formulation technologies for drugs, cosmetics, consumer products, etc., in Hong Kong for the regional markets.

SGS Hong Kong Ltd. This is a testing laboratory set up by SGS Societe Generale de Surveillance Holding SA of Switzerland to provide to the regional biotechnology industry testing services which comply with Good Laboratory Practice (GLP) guidelines.

Consultation Services

On August 30, 1995, the Pharmacy and Poisons Board of the Hong Kong Government Department of Health issued a schedule for implementing GMP guidelines in Hong Kong's pharmaceutical industry. The implementation schedule was divided into three phases. The target completion dates for Phase 1, 2 and 3 were December 31, 1996, 1998 and 2000, respectively.

In 1995, HKIB obtained an ISF grant to set up a GMP Support Services Unit to provide consultation on GMP implementation to the local pharmaceutical industry. The Unit assisted two local companies in implementing Phase 1 GMP guidelines for its manufacturing operation in 1996. Another local company which had been selling its products in Australia sought help from the

Unit in responding to deficiencies cited by the Australian Government's regulatory agency, TGA, after an inspection in 1996. The Unit successfully provided consultation services for the Company to upgrade its manufacturing operation to meet the requirements. Furthermore, the Unit has supplied a wide range of consultation services to a number of local companies in their attempts to meet Phase 1 GMP requirements.

With the success of the GMP Support Services Unit, HKIB was awarded another ISF grant in 1997 to expand the Unit into the Hong Kong Pharmaceutical Technology Centre (HKPTC). A Governing Committee consisting of representatives from the HKSAR Government, the Hong Kong Pharmaceutical Manufacturers Association Ltd. and HKIB was formed to oversee the center. Its immediate objective is to assist the local pharmaceutical industry in meeting existing GMP requirements in manufacturing according to the guidelines and schedule established by the HKSAR Government. Its long-term goal is to continue serving the local industry as it develops and upgrades pharmaceutical technologies in Hong Kong.

The HKPTC has developed a database on the Internet to provide information on Hong Kong pharmaceutical companies and published a Hong Kong Pharmaceutical Industry Directory (HKIB's homepage features a list of Hong Kong pharmaceutical companies: http://www.hkib.org.hk). It prepared a "General Plant Operation Manual" with more than 100 commonly used Standard Operating Procedures (SOP) to be distributed to local pharmaceutical companies. The center also prepared a series of GMP training videos and slides for local companies. It organizes a series of GMP training courses for local pharmaceutical industry staff. The HKPTC also publishes a quarterly newsletter on the global development of issues related to GMP and pharmaceutical technologies. Finally, the center offers GMP consultation services to the local industry. Initial services include: GMP compliance and quality management, GMP documentation, GMP audits, plant site selection and feasibility study, conceptual plant facility design and layout, and testing and validation.

In 1997, HKIB received an ISF grant to establish the Biotechnology Information Office to provide services to local biotechnology companies who want up-to-date information on technology, intellectual property rights, and markets, and a way

to monitor new product development by global competitors. In addition, the Office helps these companies promote themselves as well as their products in the global marketplace via the Internet and other communications channels.

The Future

Presently, with the Incubation Programme and its consultation services, HKIB is helping Hong Kong upgrade its existing biotechnology-based industry to meet global standards. This will enable the local companies to add value to their existing products and to expand their businesses in the regional and overseas markets. With increased profit margins from their existing products, these companies may be able to venture into new value-added product lines that require more research and development. In such a scenario, a R&D-intensive biotechnology industry will gradually emerge in Hong Kong.

HKIB's more ambitious goal is to help HKSAR further solidify its industrial technology base by attracting multinational pharmaceutical companies to use the region to develop and manufacture new products. Currently, there is a worldwide shortage of GMP facilities to produce Phase I and II clinical grade materials of innovative vaccines and biopharmaceuticals, particularly those indicated for diseases prevalent in densely populated Third World countries. Since these products present relatively little profit incentive, global pharmaceutical companies are reluctant to invest and engage in the development of such products. It is HKIB's wish to fill this void and to play a significant role in the global initiative to develop vaccines and biotherapeutics to treat or eradicate life-threatening diseases such as malaria, virulent variants of hepatitis, etc. In order to achieve this goal, HKIB hopes to expand its capabilities in GMP manufacturing to include a mammalian cell culture pilot plant and a formulation and packaging facility. With its TBV25H malaria vaccine project close to the clinical development stage, HKIB will soon be able to establish capabilities to carry out clinical trials under GCP guidelines. HKIB will thus build up a vertically integrated strategy to attract multinational companies to use HKIB's services to develop their innovative products in HKSAR. HKIB is located on the campus of CUHK and the HKSAR Government is building a Science Park on reclaimed land adjacent to CUHK. The Science Park will be available for the global companies to use in setting up manufacturing facilities

for products which are successfully developed using HKIB as the contract manufacturer of their Phase I and II clinical materials. It is HKIB's plan to use this strategy to attain the objective of attracting multinational pharmaceutical companies to use HKSAR as a center for developing, manufacturing and marketing their innovative products.

Finally, HKIB hopes to continue the Plant Micropropagation Programme to generate technologies that can be used to mass produce agriculture products cost effectively on arable land by Mainland Chinese farmers. Such a scenario is in line with the recommendation that Hong Kong serve as the nerve center for businesses by retaining control of off-site manufacturing on the Mainland, a suggestion made by a group of Massachusetts Institute of Technology researchers in the recently published book, **Made By Hong Kong**.[3]

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Chapter 2

Modernization of Traditional Chinese Medicine in Hong Kong

By

~ Nancy Y. Ip, Ph.D. ~
Director, Biotechnology Research Institute
&
Associate Dean of Science
The Hong Kong University of Science and Technology



***Nancy Y. Ip, Ph.D.**, is director of the Biotechnology Research Institute at Hong Kong University of Science and Technology, where she is also a professor in the Department of Biology and associate dean of Science. Ip received her Ph.D. in pharmacology from Harvard Medical School, Massachusetts. She has been awarded 15 patents and has published more than 90 scientific papers on neuroscience in reputable journals and 100 abstracts at international meetings. She is a recipient of the prestigious Croucher Foundation Senior Research Fellowship Award and is a member of the Biological Science and Medicine Panel of Research Grants Council of Hong Kong. Ip was a postdoctoral fellow at Harvard Medical School and Sloan-Kettering Institute. She has worked as the head of the medical genetics group at Lifecodes Corp., Valhalla, New York, and senior staff scientist at Regeneron Pharmaceuticals, Inc., Tarrytown, New York. Ip is currently a project director at Shanghai Research Center of Life Sciences of the Chinese Academy of Sciences and a member of the editorial board for Acta Pharmacologica Sinica. She is also a founding member of the Life Science and Biotechnology Joint Laboratory of the Chinese Academy of Science and HKUST and a Council member of the recently established International Molecular Biology Network for the Asia-Pacific Rim.*

Traditional medicine refers to the ways of protecting and restoring health that existed before modern medicine. They have been passed down from generation to generation in both written and unwritten form, and have met the needs of local communities for many centuries.[1] These systems may embrace several areas of health care, including prevention, diagnostics, medicinal treatment and non-medicinal treatment of disease. For the purpose of this chapter, the definition of traditional medicine will be confined to consumable medicinal products.

In China, traditional medicine has evolved since the beginning of civilization. The use of medicinal drugs can be traced to 1000 B.C. Around the second century B.C., the Classic of Materia Medica already listed 365 healing remedies. At the end of the 16th Century, Li Shi Zhen wrote the Ben Cao Gang Mu, or Great Herbal, where the list of remedies reached about 11,000; the medicinal materials, mainly plant extracts, numbered 1,892. The pharmacological value of the voluminous empirical data accumulated over three millenniums have been affirmed gradually with advanced research techniques.

This chapter will focus on the development of Traditional Chinese Medicine (TCM) in Hong Kong. TCM market trends and regulatory issues concerning TCM will be outlined first as background. Opportunities and challenges facing Hong Kong's TCM industry will be highlighted in the course of the discussion. The sketch serves as an account of the multiple factors and synergistic efforts needed to advance the local TCM industry into the global market.

Trends in TCM Interest

Global - Markets

Most populations in developing countries still rely predominantly on indigenous traditional medicine for meeting their primary health care needs. During the last decade, however, there appears to be a back-to-nature trend of avoiding synthetic medications and a favoring of herbal products by the young and affluent in developed nations.[2] The annual growth rate of herbal products, from 1985 to 1992, was 10-15% in most regions around the world. The combined sales in major markets worldwide were reported at greater than US$12 billion in 1994.[3] While the sales of herbal products appear impressive, they are still small in comparison to global sales of conventional pharmaceuticals (US$195-$225 billion).[4]

The United States herbal products industry was at US$1.27 billion in 1995, with the top 10 herbs accounting for 55% of herb sales (**Table 1**).

Herb	Percent of Total Sales
Echinacea	9.9%
Garlic	9.8%
Goldenseal	7.0%
Ginseng	5.9%
Gingko biloba	4.5%
Saw palmetto	4.4%
Aloe	4.3%
Ma huang and other ephedra products	3.5%
Siberian ginseng	3.1%
Cranberry	3.0%

Table 1: The top 10 bestselling herbs in the U.S.[5]

A U.S. survey released in 1997 showed that the herbal industry has grown significantly and that the market is now estimated to be $3.24 billion, with approximately one-third of the nation's adults using herbal remedies.[5] St. John's Wort is a herb that has recently attracted considerable attention as a treatment for depression.[6] The leading uses of herbal remedies in the U.S. are for colds, burns, headaches, allergies, rashes, insomnia, PMS, depression, diarrhea, and menopause.[5]

The acceptance of alternative medicines in Europe has been more rapid than in the U.S. market.[7] A survey among Member States of the European Union in 1991 identified about 1,400 herbal drugs used in the European Economic Community. In 1993, herbal product sales in Europe (US$6 billion) far exceeded sales in Asia, from which many of the original materials were obtained.[7] In Germany alone, the largest herbal product market in the European Union, herbal product sales reached US$3 billion during the same period.

Global - Regulatory

Because of the regulatory policies or marketing strategies in both the American and European markets, herbal products are usually sold as health supplements at considerably lower prices than conventional pharmaceuticals. The stance of the U.S. Food and Drug Administration (FDA) has been that all drugs, whether they are synthetic chemicals, herbal preparations, or drugs of an herbal origin, must meet the same set of strict FDA criteria in

order to be marketed. These regulatory hurdles have made the development of herb-derived drugs rather unattractive. Most TCM preparations are made up of a complex mixture of herbs and ingredients, and the possible large number of active components within the mixture poses a major challenge in drug development. This challenge combined with the difficulty of securing patent protection for natural products has also discouraged the development of these products as drugs. Since a patent is a condition for profitability, drug companies would not take the risk of investing in herbal medicines without one. As a consequence, these herbal medicines are sold as dietary supplements, which are subject to less vigorous regulation.

FDA regulations for these supplements are relatively stringent compared to those of regulatory bodies in other countries. However, as the positive effects of herbal medicines become more recognized, a more relaxed regulation of herbal products in the West appears to be evolving. The U.S. Congress passed the Dietary Supplement Health and Education Act (DSHEA) in 1994, making it necessary for the FDA to reevaluate registration guidelines for herbal medicines.[8] With the DSHEA, the burden of challenging a supplement's safety rests with the FDA. The DSHEA defines dietary supplements and dietary ingredients; outlines guidelines for literature displayed where supplements are sold; provides for the use of claims and nutritional support statements; and requires ingredient and nutrition labeling. The act also establishes a new framework for assuring safety and grants the FDA the authority to establish Good Manufacturing Practice (GMP) regulations. The DSHEA acknowledges that millions of consumers believe dietary supplements may help augment daily diets and provide health benefits.[8] The DSHEA was enacted to meet the rising concerns about safety and proper labeling that come with an increased acceptance and use of herbal products. The market for products falling under DSHEA guidelines is now estimated to be $3 billion in the U.S.

The success of the herbal product market in the European Union in the last several years can be partly attributed to the fact that Germany and France reimbursed consumers for 40% of all herbal products consumed. Prior to 1994, the regulation of herbal products in these two countries had been relatively relaxed. Recently, there have been evolving attitudes and impending changes in laws related to herbal products, which are encouraging for herb-derived drug development. The European Union laws

will soon regulate herbal medicines as drugs, basing product registration on quality, safety and efficacy.[4] In order to capture a piece of the profitable pharmaceutical market and to fully exploit the benefits of herbal medicines, the development of herb-derived drugs should be promoted.[7]

In the U.S., the FDA is exhibiting changing attitudes toward the development of herbal products as drugs.[9] Workshops such as Botanicals and the Regulatory Process (by the Drug Information Association for FDA, Nov. 1997), the fourth in an ongoing series, signify evolving attitudes toward herbal products. There is some disagreement on the degree of scientific testing that should be required to support safety and effectiveness of botanical products. The workshop focused on these issues, from both clinical and regulatory perspectives.[10] The changing attitudes are encouraging the development of herb-derived drugs as indicated by the dozens of Investigational New Drug (IND) applications that have been filed with the FDA recently. Last year's approval of the first U.S. patent on an herbal composite formula could help pave the way for its approval by regulatory bodies. Since the FDA and U.S. companies are dominant forces in the global pharmaceutical market, their shifting treatment of herbal medicine will help legitimize the market.[11]

Other organizations are being set up to respond to the needs of the fast-growing herbal products industry. The U.S. National Institutes of Health has opened the Office of Complementary and Alternative Medicine to evaluate herbal medicines. The World Health Organization (WHO), through the Traditional Medicine Programme, is also addressing the needs of the industry. WHO has stressed the need for governments to formulate national policies, study the potential usefulness of TCM, upgrade knowledge of practitioners, and educate the public about TCM products. Currently, WHO has 19 collaborating centers in 10 countries performing research on medicinal plants.[1]

Regional Trends

TCM has maintained its popularity in a number of Asian countries. In Japan, from 1974 to 1989, there was a 15-fold increase in the sale of *Kampos* (Chinese method) medicinal preparations in comparison to only a 2.6-fold increase in the sale of mainstream pharmaceutical products.[1] *Kampos* prescribed by doctors can be reimbursed by health insurance agencies. Since the establishment of the People's Republic of China in 1949, the

Chinese Government has promoted the complementary use of TCM and Western medicine. This policy has helped make affordable health care widely available and has reduced dependence on Western pharmaceuticals, which are imported or more expensive to manufacture.[7] TCM products account for 30-50% of the total medicinal consumption in China. In 1993, the total sales of herbal medicines in China amounted to more than US$1.6 billion.[12] Pharmaceutical sales, and TCM in particular, can be expected to increase with the growth of China's economy. As the countries in Asia become more affluent, demands for high-quality TCM products will also grow.

With the increasing worldwide interest in herbal medicines, there has been a simultaneous increase in the international trade of these medicines. TCM exports from China, however, currently account for only 5% of the total world TCM exports. Despite many years of research, a herbal drug that meets international regulatory standards has yet to come out of Mainland China or Taiwan.[11] As product quality improves and international regulatory standards change, TCM exports out of this region should increase.

With the global and regional market trends showing an increasing awareness of and interest in TCM products, Hong Kong must quickly secure itself in this specialized field of biotechnology. Hong Kong's TCM history, strategic location and ability to adopt innovative strategies in technical and business arrangements will provide it an added advantage as it pursues the many opportunities developing in the TCM industry.

Development of Hong Kong's TCM Industry

In Hong Kong, there are 224 establishments and 2,449 people engaged in the drugs and medicine sector, making it the largest in the local chemical industry. The sector accounted for 38.3% of the industry's total establishments and 35.9% of the industry's total employment in 1995.[13] The Hong Kong Department of Health is responsible for regulating the manufacturing and marketing of pharmaceuticals.[14]

About 350-500 local companies can be counted as TCM industrialists.[15] Most of them are members of the Hong Kong Chinese Patent Medicine Manufacturers' Association Ltd., Hong Kong & Kowloon Chinese Medicine Merchants Association Ltd. or Hong Kong Chinese Medicine Merchants Association Ltd. Because of the scarce natural resources, limited arable land and

climate, Hong Kong TCM industries emphasize processing and distribution, instead of herb cultivation and collection. They encompass mainly:

- Herb dealers who perform simple pretreatment of the herbal materials and then resell them;
- TCM manufacturers who produce formulated products using either powdered plant parts or semi-purified extracts;
- TCM producers who provide final processing and packaging of the imported semi-finished products; and
- TCM distributors.

Government involvement in the regulation of herbal medicines began only recently. A Working Party on TCM was established by the government in 1989 and, in 1994, the Executive Council approved the Working Party's recommendation for initiating regulatory measures for TCM practitioners and medicinal materials.[16]

While the major share of the global TCM market is currently dominated by Japan, Korea and Germany, the sale of Hong Kong TCM products is largely restricted to Chinese communities throughout the world. According to the Hong Kong Government Industry Department 1996 report on Hong Kong's Manufacturing Industries, Hong Kong exported HK$700 million worth of medicinal and pharmaceutical products (including non-TCM products) in 1995, which represented a minute portion of worldwide TCM sales of more than US$12 billion.[13] Scientific verification to define the quality, safety, and efficacy of these TCM products has not been available. However, substantial expansion into the global market is now becoming conceivable with the active participation of government and academia, as well as collaboration with China, which has the longest history and most active centers of TCM development.

Participation of Government and Academia

Government and academia support for TCM comes as part of an effort to redefine Hong Kong's role and position among the Asia-Pacific economies, which have all experienced great

economic changes throughout the '80s and '90s. Hong Kong has enjoyed immense success, along with Taiwan, South Korea and Singapore, as a low-cost producer in labor-intensive industries. However, with raising wages and land-rental rates, Hong Kong is losing its competitive advantage over other emerging economies in the Asia-Pacific region.[17] Over the last decade, contributions to Hong Kong's GDP from the manufacturing, financial and service sectors shifted from 23%, 17.7% and 20.5%, respectively, in 1983 to 11.1%, 25.8% and 27%, respectively, in 1993.[18] As a result, Hong Kong had to look toward building knowledge-oriented and technology-based industries.

This transition started with activities at tertiary educational institutions. Measures were taken to upgrade the technological content of industrial output by supporting university-based research and training. Examples include the establishment of the Research Grants Council (RGC) and a new research university, the Hong Kong University of Science and Technology (HKUST).[19] This alliance with industry could help academia further convince the government to promote biotechnology in Hong Kong.

Biotechnology, the technology for utilizing living organisms to make or modify products, has broad applications in industries such as medicine, agriculture and environmental protection.[20] This area has generated a great deal of attention because of the unprecedented promise and growth brought by rapid scientific advances, increased government support and strategic alliances.[21] The establishment of the Biotechnology Research Institute (BRI) at HKUST, as well as The Hong Kong Institute of Biotechnology (HKIB) at The Chinese University of Hong Kong (CUHK), with a donation totaling HK$300 million from the Hong Kong Jockey Club (HKJC), indicated the public sector's awareness of the potential of biotechnology.

Biotechnology Research Institute
The Hong Kong University of Science and Technology

The BRI was founded in 1990 with the mission of assisting Hong Kong's economic development through research, development and training of specialists in biotechnology. This would be accomplished by BRI's support of research projects; its encouragement of cooperation among government, academia, and industry; and its ability to attract world-class scientists. These efforts create the capital and human resources necessary to spawn progress in biotechnology.

Over the years, BRI has used its HK$130 million share of the donation from HKJC to build a solid foundation for a state-of-the-art research infrastructure which addresses carefully selected areas of biotechnology. This infrastructure includes facilities for animal care, plant growth, cell culture, fermentation, molecular structure, microscopy, and nuclear magnetic resonance. BRI also has cooperated with research and industrial organizations both regionally and abroad in its efforts to help Hong Kong become one of the important centers of biotechnology.

Some of BRI's projects have traversed all phases of the research and development spectrum, from basic research to commercial production. For example, BRI-supported research has led to the establishment of the Drug Delivery and Technology Center at HKUST, funded by Hong Kong's Industry Department, to introduce advanced drug-delivery technologies to pharmaceutical manufacturers. Other BRI-supported research resulted in the isolation of the active ingredient in a Chinese herb which is believed to provide protection against coronary heart disease and possibly retard the aging process. The research findings led to the development of health food products by the Hong Kong-based Lee Kum Kee Group.

One of BRI's major research focus areas is TCM. As suggested by the **Made By Hong Kong** study, which was conducted by the Massachusetts Institute of Technology (MIT) Industrial Performance Center, TCM is entitled to the highest priority in Hong Kong's future biotechnological development. The main reasons include:[7]

- The existence of a large library of compounds with well-known origin and proven efficacy. This would forego the problem of random screening and hence reduce the time and cost associated with product development.

- Hong Kong universities have had many years of research and development experience in TCM. Furthermore, the academic community in Hong Kong has already established networks and cooperative ventures with TCM institutions in China.

- Many people in the Hong Kong research and health care communities are familiar with the various types of TCM herbal compounds and indications. This indigenous TCM knowledge base coupled with: (1) the ability to communicate in both English and Chinese; (2) the advanced information technology available in Hong Kong; and (3) Hong Kong's proximity to and affinity with China, presents an edge not enjoyed by Western pharmaceutical companies considering joint development of herbal products in China.

BRI assessed the feasibility of an interdisciplinary research program focused on TCM, which was subsequently designated as a high-impact area of research at HKUST in 1997. The High Impact Area Research Project Support Programme at HKUST supports the research areas in which HKUST has strong reason to believe it can emerge as having a very high impact on the needs of Hong Kong and South China. Another milestone was the establishment of a BRI TCM Center for Drug Development, Safety, Standardization, and Reformulation at HKUST in 1997. The Center aims to provide much-needed high-technology services to the TCM industry and establish a solid basis for collaborative efforts between the TCM industries in Hong Kong and China. The infrastructure established will help to:

- Furnish supporting scientific documentation on TCM efficacy;

- Explore new therapeutic potentials of existing TCM;

- Provide leads for new drug development;

- Assist the local industry in refining and improving the quality and safety of TCM products;

- Establish standards and procedures for the standardization of TCM products; and

- Assist TCM manufacturers to develop new formulations.

Other Academic Institutions in Hong Kong

Other academic institutions have also taken active roles to enhance the applicability and marketability of TCM products. In 1979, the Chinese Medicinal Material Research Center (CMMRC) at The Chinese University of Hong Kong (CUHK) was established to facilitate and promote multi- and interdisciplinary research on TCM. Its aim is to document and evaluate true efficacy, to explore better applications and to upgrade the scientific contents of TCM.[22] Through the financial supports of outside donors, the Center now has its own labs and instruments. In addition to the individual RBC grants of the research fellows, the Center received funding from the Industry Department in 1995 to set up a "Laboratory for the Chemical Quality Control of Chinese Medicines and Health Foods." It also received an RGC Central Allocation grant to convert a database into an on-line service. The Center collaborates with the Institute of Chinese Medicine (Taiwan) and the Academy of TCM (Beijing) to develop Chinese databases for TCM. In 1997, CUHK received funding from the Industry Department for four TCM-related projects (**Appendix 1**). A B.S. degree program on TCM will start at CUHK in 1999.

At Hong Kong Baptist University (HKBU), a grant was received in 1997 from the Industry Department for TCM activities (**Appendix 1**). The "Institute for the Advancement of Chinese Medicine" was established in 1997. A degree program in TCM was launched in fall 1998 to provide students solid training in both modern biomedical sciences and practical TCM knowledge. The Hong Kong Jockey Club recently donated HK$105 million to HKBU for the construction of a building for Chinese Medicine.

The University of Hong Kong (HKU) was allocated a grant from the Industry Department in 1995 to set up a database on ethnobotanical drug discovery and quality assessment (**Appendix 1**). HKU has TCM programs in its School of Professional and Continuing Education. A degree program is expected to evolve from this in the near future.

Hong Kong Industry Department

The Hong Kong Government has put forth several important initiatives designed to build an industrial support infrastructure for biotechnology. These include the offer of industrial land, the establishment of incubator facilities, and the development of R&D funding schemes. Indeed, the groundwork for a solid biotechnology infrastructure foundation in Hong Kong was enhanced by support from the Hong Kong Government Industry Department. Several programs were implemented in the course of the last three years, including the Industrial Support Fund (ISF) Scheme, Applied Research & Development Scheme, and Cooperative Applied Research & Development Scheme.

The ISF was introduced in 1994 with the primary objective of developing new technologies as well as providing infrastructure support.[23] The Biotechnology Committee of the Industry and Technology Development Council (ITDC) was established to review and identify areas of opportunities for the biotechnology industry in Hong Kong. To date, 56 biotechnology projects have been approved for funding. The total funding of HK$133 million committed to these biotechnology projects since 1994 accounts for 17.3% of the total funding approved under the ISF.[24] ISF has tremendously increased the amount it allocated to TCM-related projects, from HK$2.452 million in 1996 to HK$38.905 million in 1997. A total of HK$49.452 million has been granted to 12 TCM-related projects since the onset of the scheme in 1994 (**Table 2**).[25]

Year	No. of TCM Projects Approved	Funding Approved (HK$m)
1994	0	0
1995	2	8.095
1996	2	2.452
1997	8	38.905
Total	12	49.452

Table 2: TCM-related projects funded by the Industry Department of Hong Kong (Refer to Appendix 1 for project details.)

Collaboration with China

The historical reunification of China and Hong Kong in 1997 has strengthened ties between two areas, and hence inspired numerous opportunities for collaboration. The Biotechnology Focus Study commissioned jointly by the Hong Kong Government Industry Department and the State Science & Technology Commission of the People's Republic of China in August 1996, identified TCM as one of the areas which presents the highest likelihood for Hong Kong and China to build synergism and attain success together.[2]

The assessment was based on the three factors essential to a world-class biomedical industry: capital, information and workforce. Hong Kong's sound financial sector and robust service sector have the potential to be key contributors in providing capital and information. Its bilingual and efficient workforce can add value to products entering the global market. China, on the other hand, can furnish technically capable product development staff through its vast network of academic and research institutions. There are currently 53 independent pharmaceutical research institutes and over 100 product development centers in China, employing over 5,500 researchers, most of whom have been trained overseas.[2]

Over the last few decades, China built a significant pool of TCM expertise and technology and gained substantial lead time in TCM research compared to other countries starting from scratch. Nonetheless, a globally competitive TCM industry in China is still restricted at the product development and commercial phase. Hong Kong, with its strong business infrastructure of communication, market information and international connections, can offer China the business know-how to refine and commercialize its TCM research results. These complementary roles provide a solid foundation for fruitful collaboration between China and Hong Kong.

The partnership is further strengthened through frequent interactions between institutions in China and Hong Kong. BRI, for example, in its efforts to expedite TCM development, has signed collaboration agreements with the National Research Center for the Technological Modernization of Chinese Medicine and the Chengdu Diao Pharmaceutical Company of Academia Sinica. It also sponsored a symposium at HKUST on "Advancing the TCM Industry into the Next Century: Current Challenges & Issues" to provide a forum for representatives from China, Hong Kong, Taiwan, the U.S., and Japan to review selected issues that are crucial to the development of the TCM industry.

Active academic involvement, a large governmental investment and political and geographical ties to China should provide the foundation for the emergence of a prosperous TCM industry in Hong Kong.

Challenges in TCM Development

To achieve broader applicability and customer acceptance of TCM products in the global market and to ensure future growth in

this industry, several areas of TCM development must be addressed. These areas include the scientific verification of the therapeutic actions of TCM products, the development of a new generation of herb-derived drugs and the improvement of existing TCM products by focusing on standardization, quality, safety, and reformulation. Hong Kong's research institutes, manufacturers, and government can all play a part in developing or improving TCM products.

Drug Development

The scientific merits behind TCM have been a subject of great controversy. Despite the extensive utilization of TCM products by a large population, the chemical basis of therapeutic actions remains relatively unexplored for most products. The therapeutic effect of a few TCM herbs has been scientifically proven, and they represent a promising source of new pharmaceuticals.

Scientific evidence shows TCM working effectively where conventional therapies have failed. For example, a randomized, controlled clinical trial conducted in Japan showed that *sho-saiko-to*, an extract of seven Chinese herbs, helps prevent liver cancer in patients with cirrhosis.[26] With runaway costs for drug development ($125-350 million over a five-to-10-year period), pharmaceutical firms are paying more attention to TCM as an alternative source of potential drugs.[7] During the 1980s, Merck and Co., Inc. and Upjohn Co. participated in collaborative efforts with Chinese institutions to evaluate Chinese herbs. As a result of these joint research efforts, a number of bioactive natural products were discovered. In 1995, New York-based Pfizer Inc. and the Academy of Traditional Chinese Medicine in Beijing entered a three-year agreement to study TCM. TCM, however, still remains relatively under-studied by U.S. pharmaceutical firms.[27] This may be attributed to a combination of cultural differences plus concerns over regulatory issues. Regulatory hurdles have thus far impeded the development of herb-derived drugs, but measures are now being taken to further scientific research on herbal remedies as an alternative approach to the discovery of new therapies.

A growing amount of research data has suggested that scientific basis underlies the actions of TCM. The potential rewards justify the challenge of sifting through this wealth of knowledge and integrating it with conventional medicine. The practice of combining several herbs comes from the belief that the multiple ingredients interact with each other to produce

synergistic therapeutic effects. This ancient concept is not readily compatible with modern medical theories. Thus, investigations into TCM conducted with theories and methods of modern science may also enrich Western medicine through the introduction of such new ideas and concepts.[27] The challenges that lie ahead:

- Determining the efficacy of known TCM products;
- Scientifically verifying the therapeutic action of known TCM products; and
- Screening for drug candidates.

On top of these challenges would be the need for expertise in the understanding of international regulatory standards. Determining the scientific merits of TCM products is a crucial step toward promoting their greater acceptance within the scientific community as well as by consumers and government regulatory bodies. The screening of these TCM products for potential drugs could lead to a new generation of TCM-derived drugs and would help capture a share of the profitable pharmaceutical industry.

Within the BRI TCM Center at HKUST lies the Bioassay and New Drug Facility. The major aim of the Facility is to document the efficacy of existing TCM products and to provide a scientific basis for their actions using a variety of modern research tools. Moreover, the bioassay approach may uncover new therapeutic sites of action for existing TCM products. Promising drug candidates will be evaluated in this Facility. Modern approaches to drug discovery rely, to a large extent, on the use of molecular and cellular models instead of animal disease models as screening targets. A number of investigators at BRI and HKUST are well established in specific areas of molecular and cell biology and are utilizing their discoveries as TCM drug screening targets for new drugs. Developing new drugs based on leads from Chinese herbs has an advantage over random screening (indiscriminate testing of synthetic or natural products for biological activity), since it is guided by experience from a long history of clinical practice. According to **A Pictorial Encyclopedia of Chinese Medicine**, almost 7,300 plants have been used in TCM, and about 60 new herb-derived drugs have been developed by Chinese scientists over the last 40 years.[28]

Several substances in TCM show pharmaceutical promise:

- A Chinese medical book written 2,000 years ago described the herb *Artemisia annua* as a remedy for malaria. Following this indication, Chinese researchers started to evaluate various extracts of the plant during the late 1960s. After initial failure, bioactivity-directed isolation finally yielded a new antimalarial drug, artemisinin (qinghaosu), in 1972.[29]
- Huperzine A, a novel *Lycopodium* alkaloid discovered from the Chinese medicinal herb, represents one highly promising compound for the treatment of Alzheimer's disease. Huperzine A has demonstrated potent memory-enhancing actions, long half-life, good blood-brain barrier penetration, and few side effects.[30] These findings have largely resulted from studies conducted at the Shanghai Institute of Materia Medica of the Chinese Academy of Sciences. In collaboration with these scientists, investigators at BRI are continuing studies on Huperzine A.
- The Institute of Zoology at Kumming (of the Chinese Academy of Sciences) has generated a large selection of lead compounds which have originated from animal and insect sources. For example, neurotoxin isolated from snake venom has been shown to exhibit potent analgesic effects and may hold the key to the treatment of narcotic drug addiction. BRI plans to elucidate the mechanisms of action of these potentially marketable products using a variety of biological assays.
- BRI is using high throughput screening assays that can identify novel lead compounds from TCM that can be tested for their therapeutic potential in the treatment of various neurodegenerative diseases. Research collaborations are underway with TCM research institutions in China to study potential drug candidates for memory enhancement, epilepsy and insomnia.

Through scientific verification of the therapeutic actions of TCM products and the development of TCM-derived drugs, the short-term solution of selling TCM products as health supplements can gradually be overcome.

Standardization and Quality Control

In order to harness the medical and commercial potential of TCM and promote its wider acceptance in countries outside Asia, not only does the effectiveness of TCM products have to be proven by established scientific criteria, TCM products must be formulated and prepared according to Western pharmaceutical quality control standards. The composition of Western pharmaceutical products is precisely defined, and both the nature and amount of each chemical substance contained in the preparation are exactly known. In fact, the effectiveness of individual ingredients must be proven scientifically in order to obtain approval for the marketing of the whole preparation. In contrast, TCM products are based on naturally occurring substances, predominately herbal and animal, and typically consist of mixtures of ingredients, the precise chemical composition of which has not been established in detail.

Standardization and quality control of Chinese medicinal materials are almost nonexistent. Primarily, standardization and quality control have been conducted through subjective means, such as visual examination and scent. These methods are not sufficient or acceptable if TCM products are to gain wider acceptance in the global market. Herbal materials bearing the same common name may be chemically different due to variations in growing conditions, environmental factors, age, and even time of harvest. Any variation in the chemical composition of a plant material may affect the therapeutic efficacy of the formulation and, thus, its medicinal quality and value. For these reasons, the establishment of strict standardization and quality control measures are necessary.

With the belief that the therapeutic effectiveness of TCM is based on the combination of active ingredients rather than on single, chemically defined substances, there appears to be a potential conflict between the requirements for the approval of TCM products in the framework of the international regulatory environment and the very nature of the practice of TCM. With the complex and variable nature of herbal formulas comes the

challenge of developing new methodologies and techniques that are suitable for probing such systems. Only recently has chemical fingerprinting been explored as a method of authentication for some TCM products. The present trend is to adopt the system used for Japanese *Kampos*, namely the HPLC profile of a reference standard for each registered product. Ideally, when deciding which of the many chemical ingredients are most important for the purposes of standardization, it is obvious that those producing major biological effects should be selected. Unfortunately, for most Chinese herbs, the active principles are not known. In such cases, the most abundant of the chemical constituents, which may or may not be proven to be the active ingredient of the product, will be used as the marker for analysis. Other methods of standardization have been introduced recently, including the DNA fingerprinting approach for the identification of plant species.[31]

Hong Kong TCM manufacturers are taking steps to improve their standards and quality control. TCM manufacturers in Hong Kong and China must upgrade their manufacturing facilities in order to register their products and sell them overseas. For example, they should strive to meet the Good Manufacturing Practices (GMP) guidelines of the countries where they seek approval for their products. A major Hong Kong TCM manufacturer has already succeeded in gaining approval from the GMP auditing officer from the Therapeutic Goods Administration of Australia. The government of Hong Kong is in the process of enforcing GMP for manufacturing Western drugs and guidelines for TCM manufacturing are expected to follow.

With the research institutions finding new methodologies to standardize herbal mixtures, the government implementing regulatory guidelines, and TCM manufacturers undergoing changes to meet both local and international standards, Hong Kong is taking steps toward the modernization of TCM products.

Safety

Safety is an important issue with regard to the use of TCM. In order to promote and develop herbal medicines, the safe use of the products must be fully investigated. Cases of inadvertent herbal poisoning following ingestion of TCM products that were contaminated with toxic plant species that resembled the prescribed medicine (e.g. *Clematis chinensis* and *Podophyllum*

emodi) have been reported repeatedly in Hong Kong and elsewhere. The herbal poisoning incidents have resulted in nausea, numbness of the limbs and even brain damage. In the worst cases, ingestion of the root of *Aconitum carmichaeli* and *Aconitum kusnezoffii* have resulted in death. In 1989, the Secretary of Health and Welfare appointed the Working Party of Chinese Medicine to make recommendations for TCM regulatory measures in Hong Kong.

The TCM Safety Information Center, at HKUST, has established a database of existing chemical and biological data on medicinal plants and other natural products from scientific literature. This database is useful to TCM industrialists, research scientists and regulatory agencies both locally and abroad.

The BRI TCM Center at HKUST is in the process of setting up chemical and biological assays for safety tests; developing and validating new methods for testing; and establishing TCM safety guidelines. Chemical assays are designed to test for: (a) marker compounds or active ingredients to ensure the correct identities of plant materials; (b) contamination by heavy metals; (c) contamination by microbial toxins; and (d) contamination by residual pesticides.

TCM biological assays for safety studies are required to supplement human experience in defining possible toxicity that may occur after short-term and prolonged exposure. WHO has published **Research Guidelines for Evaluating the Safety and Efficacy of Herbal Medicines** (1993), in which research criteria for evaluating the safety of herbal medicines are provided.[1] Safety tests include: (a) systemic toxicity tests for acute and chronic toxicity in animals, (b) local toxicity tests, such as skin irritation and allergy assays, and special toxicity tests, such as mutagenicity (Ames Test, chromosomal aberration, and micronucleus assays, etc.) carcinogenicity, teratogenicity and liver toxicity.

The current drug registration process in all developed countries requires a series of studies in laboratory animals to prove the safety of the experimental drug before clinical trials are performed on human subjects. The animal studies must be conducted in compliance with the Good Laboratory Practice (GLP) guidelines. China is now in the process of setting up GLP animal toxicology laboratories.[2] Hong Kong is well positioned to play a supporting role in providing modern analytical laboratories for the preclinical development of TCM products.

Reformulation and Packaging

Many new TCM preparations have appeared in the market in recent years. However, the formulation of most products remains relatively primitive and thus limits the medical application and market. With recent advances in pharmaceutical formulation technology, many traditional dosage forms can be reformulated to achieve wider applicability and customer acceptance. Reformulation, for instance, can mask the unpleasant odor of some TCM to improve customer acceptability. Transdermal technology can be applied to many TCM topical formulations, which are proven remedies for sports injuries. Tablet-making, in the form of liquid or solid encapsulation can be applied to TCM to develop new and improved dosage forms. For the consumer, reformulation will improve the taste, appearance and portability of such medicines. For the manufacturer, reformulation to new dosage forms would not only facilitate the shipping and transportation of TCM products but, more importantly, increase the products' market and expand their applicability. Furthermore, the stability of existing TCM formulations which can be affected by moisture, temperature and light can be improved through reformulation so that maximum shelf-life is achieved.

Hong Kong research institutes can foster these reformulation projects that will ultimately modernize TCM products. The BRI at HKUST has already established working relations with companies and research institutions to develop novel drug formulations. For example, BRI is currently working with a local TCM manufacturer to help it change its 100-year-old liquid formulation into a modern solid dosage form. BRI is also funding a project at HKUST to apply transdermal technology to health care products manufactured in Hong Kong.

New packaging processes and materials offer technological advantages by prolonging shelf-life, improving user-friendliness, and increasing cost-effectiveness.[2] Hong Kong manufacturers are market-driven and quick to respond to changes in customer taste. Thus, these manufacturers can assist Chinese TCM manufacturers in repackaging their products to meet market trends.

Conclusion

The international biotechnology industry is demonstrating unprecedented growth and promise brought on by innovative scientific advances, changing government policies and strategic

scientific advances, changing government policies and strategic research and business alliances. Hong Kong must quickly secure its place in this fast-growing industry. TCM has been identified as the sector of highest priority for biotechnological development in Hong Kong. Why select TCM? The trend in the herbal market has been toward greater awareness and acceptance of herbal products. The sales of herbal products have been increasing steadily over the last decade, with European countries taking a slight lead in accepting these alternative remedies. Because of regulations in both the U.S. and Europe, herbal products have largely been sold as health supplements. However, evolving attitudes and impending changes in law encourage the development of herb-derived drugs and present an opportunity to capture a portion of the lucrative pharmaceutical industry.

To respond to the global market and regulatory changes, Hong Kong must take advantage of its TCM history, strategic location and innovative business strategy to develop TCM products and TCM-derived drugs. Hong Kong's history as the largest trading center of TCM and TCM-based products, together with the strategic location to China, gives it an edge not shared by Western pharmaceutical companies. This closeness to China has fostered the establishment of networks and cooperative ventures with TCM institutions in China. Hong Kong's research institutions, which have had many years of research and development experience in TCM, have been generously supported by the local government to establish the infrastructure needed for the development of the TCM industry.

Several areas of TCM development need to be addressed by not only research institutions, but also the local government and TCM manufacturers. The areas include the scientific verification of the therapeutic actions of TCM products, the development of a new generation of herb-derived drugs, and the improvement of existing TCM products by focusing on standardization, quality, safety, and reformulation. The BRI TCM Center at HKUST is tackling these challenges with the goal of giving TCM products broader applicability and customer acceptance in the global market and, ultimately, to ensure continuous growth of the TCM industry.

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APPENDIX 1

Project Title
"A Database on Ethnobotanical Drug Discovery & Quality Assessment" (1995)

Funding Approved (HK$m): 0.992

Summary
The project aims to use modern biotechnological methodology and analytical instruments to conduct quality assessment and characterization of the major ingredients in various Chinese herbal medicines. Consultation services will also be provided to Chinese medicines manufacturers.

Project Title
"Laboratory for Quality Control of Chinese Medicines and Health Foods Based on Chemical Components" (1995)

Funding Approved (HK$m): 7.103

Summary
The project aims to establish a quality control laboratory to conduct definitive assessment and determination of various components of Chinese medicine or health food product. The center will also offer consulting services and assistance to manufacturers and other potential users in respect of quality control of Chinese medicines and health foods by examining their bioactive and chemical components.

Project Title
"Conference on Quality Assessment and Control of Herbal Products" (1996)

Funding Approved (HK$m): 0.1

Summary
The project aims to hold a conference which will serve as a forum to exchange views and experience on herbal products among manufacturers, professionals, scientists from China, Hong Kong and other countries.

Project Title
"A Safety Service Center to Enhance Credibility and Competitiveness of the Traditional Chinese Medicine Industry" (1996)

Funding Approved (HK$m): 2.352

Summary
The center aims to provide inquiry services on herbal safety issues to the general public and the TCM industry, and to assist the industry in filing foreign import approval for herbal products. In addition, a database of herbal safety documents will be set up and seminars on herbal safety issues will be organized.

Project Title
"Traditional Chinese Medicine and Database of China and Hong Kong" (1997)

Funding Approved (HK$m): 3.285

Summary
The project aims to establish a database which will provide information on TCM research and development (R&D) activities in Hong Kong and China. This database will be updated annually and its content will include R&D activities and results, supporting infrastructure, existing products and manufacturers, licensing and patent information, as well as investment opportunities.

Project Title
"The Establishment of a Traditional Chinese Medicine Center: Drug Development, Safety, Standardization and Reformulation." (1997)

Funding Approved (HK$m): 13.57

Summary
The project aims to establish a TCM center to:

(1) Provide supporting scientific documentation on TCM efficacy and safety;
(2) Explore new therapeutic potentials for existing TCM;
(3) Develop new drugs;

(4) Provide strategic planning and coordination for marketing TCM products; and
(5) Facilitate liaisons with pharmaceutical companies for joint ventures in TCM development.

Project Title
"Chemical Quality Control of Chinese Medicine as a Support for Export of Proprietary Chinese Medicines" (1997)

Funding Approved (HK$m): 2.448

Summary
The project aims to assist local TCM manufacturers to set up protocols and specifications for quality control of their products, and to help them seek approval for exporting their products to China and other countries. Workshops and laboratory demonstrations to quality control of TCM and health food will also be organized at least once every six months.

Project Title
"Development of Manufacturing Protocols for Improved Production of Standardized Quality Control for Mushroom Nutraceuticals from *Ganoderma lucidum*"

Funding Approved (HK$m): 1.112

Summary
The project aims to develop manufacturing process for the increased production and retrieval of bioactive polysaccharide / polysaccharide-peptide substances of reproducible quality from *Ganoderma lucidum*. Key physiological and nutritional parameters identified will be extrapolated for polysaccharide / polysaccharide-peptide materials with high yield. In addition, different downstream protocols will be examined to reduce adverse effects on the product quality and to maximize product retrieval.

Project Title
"A Preclinical and Clinical Validation of *Fructus Crataegi* and Green Tea in Lowering Blood Lipids" (1997)

Funding Approved (HK$m): 7.311

Summary
The project aims to develop a program in which *Fructus crataegi* and green tea can be validated under the new guidelines of the Dietary Supplement Health and Education Act. The project team will develop extracts from *Fructus crataegi* (commonly known as shanzha) and green tea, and will prove their effectiveness in lowering blood cholesterol.

Project Title
"Laboratory for the Modernization of Chinese Medicine - Standardization of Chinese Medicinal Materials" (1997)

Funding Approved (HK$m): 8.613

Summary
The project aims to:

(1) Establish standards of 10 selected materials for the U.S. dietary supplement market through chemical studies;
(2) Establish an information base of chemical components derived from TCM materials with health care and therapeutic value;
(3) Harmonize internationally the standards of those Chinese medicinal materials established in the project through a regional consortium; and
(4) Obtain novel pharmacologically active substances, single compounds or mixtures to further develop new drugs or dietary supplements.

Project Title
"Discovery of Traditional Chinese Medicine-Derived Saponins with Anti-Tumor and Cardiotonic Activities for Use as Health Food Supplements or Therapeutics" (1997)

Funding Approved (HK$m): 1.958

Summary
The project aims to utilize advanced screening techniques to search TCM-derived saponins with anti-tumor and cardiotonic activities. The deliverables of the project include:

(1) Development and transfer of the technology for efficient and

large-scale screening of TCM-derived saponins with anti-tumor and cardiotonic activities
(2) Discovery of novel pharmacologically active saponins or further development into health food supplements or therapeutics
(3) Organization of workshops and seminars, and
(4) Provision of technical consulting services in screening technology to the local industry

Project Title
"International Symposium on The Worldwide Herbal Industry: Present & Future" (1997)

Funding Approved (HK$m): 0.608

Summary
The project aims to organize an international symposium on the The Worldwide Herbal Industry: Present & Future on 15-17 July 1998. The tentative program includes the following topics:

(1) Drug discovery from herbal medicines,
(2) Gene and plant culture technology in herbal medicines,
(3) Quality control of herbal medicines,
(4) Clinical studies of herbal medicines,
(5) Regulation of herbal medicines and
(6) Manufacturing and marketing of herbal medicines.

Chapter 3

Development of a Chinese Medicine-Based Industry in Hong Kong

By

~ Kelvin Chan, Ph.D. ~
Research Director & Professor of Biomedical Sciences
Zayed Complex for Herbal Research & Traditional Medicine
Ministry of Health, Abu Dhabi, United Arab Emirates
&
On Secondment From
Liverpool John Moores University, United Kingdom

~ Donald Chia, Ph.D. ~
Pharmakon International Laboratory, Ltd.

~ Hin-Wing Yeung, Ph.D. ~
Director & Professor
Institute for the Advancement of Chinese Medicine
Hong Kong Baptist University



***Kelvin Chan, Ph.D., D.Sc.**, is research director, professor and head of Biomedical Sciences at Zayed Complex for Herbal Research & Traditional Medicine at the Ministry of Health in Abu Dhabi, United Arab Emirates. He is seconded to the present post from Liverpool John Moores University in the United Kingdom, where he is head of pharmaceutical research. Chan received his B.Sc. from the Liverpool School of Pharmacy in the U.K.; his MPS and FRPharmS from the Royal Pharmaceutical Society of Great Britain; his MIPharmM from the Institute of Pharmacy Management in the UK; his M.Sc. from the University of Aston in the U.K.; his Ph.D. and D.Sc. from the University of Birmingham in the U.K.; his CBiol/FIBiol from the Institute of Biology in the U.K.; and his FCP from the American College of Clinical Pharmacology. Chan is a visiting professor at the Medical School, University of Liverpool, U.K.; Faculty of Health Studies, Middlesex University in London; China Pharmaceutical University, Nanjing, China; Shenyang Pharmaceutical University, China; and Institute of Medicinal Plant Development, Chinese Academy of Medical Sciences, Beijing. He is on the editorial board of **Drug Metabolism & Drug Interactions**, **Pharmaceutical Sciences**, **European Journal of Drug Metabolism & Pharmacokinetics** and **Journal of Chinese Traditional Herbal Drugs**. Chan has published more than 300 articles in journals and books on drug disposition, and R&D and pattern recognition of herbal products on quality, safety and efficacy issues.*

The Growing Market for Herbal Products and Related Consequences

Medicinal plant products in various forms have been available for many hundreds of years for treatment of diseases in both the East and the West. A number of drugs used nowadays have their origin in natural sources, e.g., aspirin, morphine and Taxol. In fact, about one-quarter of the marketed orthodox pharmaceutical medicines is derived either from plant sources or from derivatives of secondary plant metabolites. **Table 1** summarizes some of the well-known pharmaceuticals originated from natural products. Yet the development of new drugs from natural sources is not very encouraging. Several factors are responsible for this observation. At present, of the approximately 2,000 varieties of minor illnesses and serious diseases, only 40% can be cured using conventional orthodox pharmaceuticals. Various chemicals and biotechnological products are being screened by pharmaceutical industries in the hope of discovering new cures. At the other end of the scale, the World Health Organization (WHO) in a recent survey observed that 80% of the world population, in particular those from developing countries with poor economies, depend on traditional (mainly herbal) medicine for primary healthcare.

Table 1. Some Examples of Pharmaceuticals Developed from Natural Products

DRUG	PLANTS	INDICATIONS
Aspirin	Willow Bark	Anti-inflammatory
Morphine, Codeine	Opium Poppy	Narcotic analgesic
Cocaine	Cocoa Leaf	Psychotic
Ephedrine	Mahuang	Sympathomimetic
Atropine and derivatives	Belladonna Leaf	Anticholinergic
Tubocurarine	Curare	Muscle relaxant
Vinblastine, Vincristine	Pink Periwinkle	Anti-cancer
Artemisinin (qinghaosu)	Qing Hao	Anti-malarial
Taxol	Pacific Yew Tree	Anti-cancer
Polysaccharide peptides (PSP)	Yun Zhi (fungus)	Immuno-active
Compound Q, GLQ233	Tian-hua-fen	Anti-AIDS

Failure of Conventional Research to Fully Use Medicinal Plants

A majority of the pharmaceutical industry has followed the conventional drug discovery paradigm that mainly concentrates on the identification of a target (a receptor, an enzyme or an in-

terfering microorganism) whose modulation is implicated in a particular disease. The screening of synthesized novel chemicals interacting with this target has been the conventional basis of new drug discovery. While many established pharmaceutical companies are involved in natural products discovery, their activities focus on identifying a single chemical active in these systems. Screening for new leads from plant extracts or other natural products using conventional extraction and approaches has not produced many new leads. One pharmaceutical company reported to WHO that it failed to isolate active compounds from Indian herbs after 15 years of research and development. One of the many reasons for this failure is that the research approach for orthodox screening and synthesis of compounds is not suitable for all medicinal plants which have demonstrated therapeutic activities when used according to the traditional way.[1] Nevertheless, the search for new leads for therapeutic agents from natural products has not stopped.[2] On the other hand, clinical trials on the efficacy of traditional herbal remedies have supported the introduction of some natural products. They are cranberry juice for urinary retention; garlic for reducing high blood pressure and cholesterol; ginger for motion sickness and postoperative emesis; Zemaphyte (a TCM herbal formula) for severe atopic eczema and related skin disorders that were resistant to orthodox treatments;[3] tea-tree oil for acne; valerian for treatment of anxiety; and feverfew for migraine prophylaxis. Many traditional medicines are used for severe conditions which are poorly treated by orthodox or conventional medications.

According to a survey in one publication, the top 25 best-selling herbs in 1996 were: Aloe, Coyenne, Danggui, Ephedra, Garlic, Ginkgo, Goldenseal, Hawthorn berry, Liquorice, Pau d'Arco, Red Clover, Siberian Ginseng, White Willow, Astragalus, Chamomile, Echinacea, Feverfew, Ginger, Ginseng, Gotu Kola, Hops, Milk Thistle, Peppermint, Saw Palmetto and Valerian.[4] More interestingly, the same publication noted that reputable companies have been acquiring smaller herbal manufacturers over the past few years.[5] A positive way of looking at this is that pharmaceutical companies would like to develop new treatment entities from herbal sources. A negative view might be that bigger pharmaceutical companies could hinder the development of herbal products because of their closed-shop point of view.

The Use of Traditional Chinese Medicinal (TCM) Herbs and Herbal Products in the West

In this era of advances in biomedical science and technology it is astonishing that consumers in rich, developed countries spent an enormous amount on over-the-counter (OTC) herbal products and related complementary therapies. Of these products, TCM received the most attention and recently has gained popularity in the West. Over the past 10 years several reviews have been written on the development of plant-derived drugs in China;[6] the contribution of TCM to modern pharmacology;[7] advances in natural product pharmacology in China;[8] the philosophical theory of Yin and Yang in the practice of TCM;[9] and the historical progress of TCM.[10] Increasing information on TCM has been published in English, and the debate about the efficacy of TCM products has begun.[11]

The recent popularity of Zemaphyte (a TCM composite prescription consisting of 10 different herbs in the form of an aqueous decoction) for the successful cure of atopic eczema that has been resistant to orthodox treatment has created greater interest in the use of TCM herbs and proprietary products.[3] Increasing concern and fear has also been expressed concerning the unsupervised use of TCM, the efficacy, toxicity and quality of these natural products, as well as the legal responsibilities of practitioners. Inclusion of orthodox medications such as antibiotics, non-steroidal drugs and steroids in TCM ready-made products was not considered a positive attribute of TCM in the West.[12] The use of fake or inappropriate herbs has contributed to a negative opinion about the safety and efficacy of TCM products.[13] Many popular and expensive TCM herbs are in short supply, and inferior substitutes or fake crude herbs have been found on the U.K. market.[14] Thus, the increasing popularity of herbal products as medications and food supplements has also produced fear about their quality, safety and efficacy and uncertainty about their active compounds.[15]

Tables 2 and **3** summarize our recent surveys on the use of TCM crude herbs and ready-made TCM products in the U.K.[16] These are supplied by importers of TCM materials based mainly in the U.K. The surveys indicate that the public and TCM practitioners demand better, cheaper herbs and herbal products, as well

as better control of imported herbal materials and products. There are at least 15 private schools of Chinese medicine in various parts of the U.K. offering part-time courses in acupuncture or TCM herbalism and producing TCM practitioners. The demand for high-quality TCM crude herbs and manufactured products in the areas of medications or health food has been increased in the European Union and in North America. This is the result of an increase in the number of Chinese clinics in these countries; however, there also has been concern about the proper training of TCM practitioners and the maintenance of acceptable levels of standards. The recent decision by the Chinese authorities to refuse admission of non-medically qualified persons for advanced training indicates[17] that improving the quality of TCM practice has been a concern. A unique Chinese hospital was set up in the early 1990s in a small town near Munich, Germany. It was run by qualified TCM clinicians from Beijing. High-quality TCM crude herbs and manufactured products have been certified according to German regulations that are one of the toughest in the E.U. Future regulations for licensing of imported herbal materials into EU countries most likely will be subjected to requirements set by the European Medicine Evaluation Agent. Healthcare which demands quality TCM practitioners and herbal products comparable to those set up for orthodox medicine will be the future direction in the practice of TCM.

Table 2. The Top 15 Most Widely Prescribed TCM Crude Herbs in the U.K. (Modified from Reference 16)

RANK	TCM HERBS	ENGLISH DESCRIPTION	PERCENT OF TOTAL
1	Danggui	Chinese Angelica Root	80
2	Gancao	Liquorice Root	64
3	Baishao	White Paeony Root	61
4	Fuling	Indian Bread	60
5	Huangqi	Astragalus Root	57
6	Shu Dihuang	Cooked Rehmannia	56
7	Baizhu	White Atractylodes Tuber	47
8	Sheng Dihuang	Raw Rehmannia Root	45
9	Dangshen	Codonopsis Root	37
10	Mudanpi	Tree Poeony Root	29
11	Chaihu	Chinese Thorowax Root	29
12	Chuanxiong	Lovage Tuber	26
13	Danshen	Red Sage Root	23
14	Banxia	Processed Pinellis Tuber	22
15	Fangfeng	Divaricate Saposhnikovia Root	21

Table 3. The Top 10 Most Widely Prescribed Ready-Made TCM Products in the U.K. (Modified from Reference 16)

Rank	Patent TCM Products	Percent of Total
1	Xiao Yao Wan	73
2	Ba Zhen Wan	45
3	Bu Zhong Yi Qi Wan	39
4	Yin Chiao Chieh Tu Pian	30
5	Liu Wei Di Huang Wan	30
6	Er Chen Wan	24
7	Gui Pi Wan	24
8	Qing Qi Hua Tan Wan	18
9	Bi Yan Pian	18
10	Gan Mao Lin	15

The above observations predict the demand for TCM crude herbs and ready-made herbal medications or health food will increase. What manufacturers should do is ensure the delivery of TCM herbal products with a guarantee of good quality, good price, safety, and efficacy. How this can be achieved is a complicated business. Recently, WHO published a survey[18] called "Regulatory Situation of Herbal Medicines: A Worldwide Review," which shares nations' experiences formulating policies for traditional medicinal products and registering and regulating herbal medicinal products. Regulatory issues will be the main concern for the future development of the herbal industry. The advantage that Chinese medicine has over other traditional therapies is the accumulation of good historical records of the successful use of natural products for treatment and prevention of diseases. Positive exploitation and expansion in these areas will create a new herbal industry.

Hong Kong Has the Right Ingredients for Herbal Manufacturers

The Significant Role of the Working Party on Chinese Medicine (WPCM)

The then-Secretary for Health & Welfare, in response to several mishaps of poisonous Chinese medicinal herbs in the early 1980s, appointed in 1989 the WPCM to review and make recommendations on the practice, treatment and use of TCM herbs and herbal products in Hong Kong. Over the past few years, WPCM has interviewed and consulted with many professional groups and held workshops and commissions for independent studies on

the actual practice and use of TCM. The eventual publication of the "Report of the Working Party on Chinese Medicine" has established guidelines for the development of TCM in healthcare based on the strength of its heritage with the Chinese people.

The Pharmacy and Poison Board of the then Department of Health & Welfare, which is a regulatory body on medicinal products, at present does not provide any regulatory or registration control on the import and export of materia medica from natural sources. This has been a historical arrangement, but legislation may change in the near future. The 1841 Treaty of Nanjing stated that, according to Chinese law and customs, Chinese materia medica and the practice of Chinese medicine would not be controlled by law in Hong Kong. Under the Pharmacy & Poison Regulations Ordinance (Cap 138) that requires all pharmaceutical products to be registered with the Pharmacy & Poison Board, Chinese materia medica, whether crude herbs or herbal products, are exempt from registration. In practice, the Department of Health officials purchased ready-made TCM products from the open market and conducted analyses to ensure that these ready-made TCM products were not adulterated with components of orthodox drugs. Imported raw or crude TCM materials are not inspected. More than 95% of Chinese materia medica used in Hong Kong is imported, mostly from China. These include 80% of ready-made medicines and 80% to 90% of crude TCM materials. There are very few official controls on the quality of TCM materials. There are no specific controls on TCM materials for the purposes of import and export, registration and sale, and dispensing and purchasing. Thus, over-the-counter sales of these materials without a prescription are not restricted. It is therefore not surprising to note self-regulatory approaches have failed to safeguard patients from poor-quality products. Fake materials and adulterated products have been identified in U.K. markets.

However, the spirit of self-regulation has been understandably followed. Circumstances have changed since 1841. Public awareness has increased and so have concerns and fear about TCM products and patient safety. Public demand for recognition of practitioner standards has increased in recent years. Having considered in detail the practice and use of TCM, the WPCM established several workable measures and made recommendations to improve the present situation and deliver a TCM system which should produce workable answers. A preparatory committee has been set up and registration of qualified TCM practitioners is underway. This is to be followed by licensing of import and export of TCM materials and related medicinal products.

Support From the Present Government

The Hong Kong Government's establishment up of the Preparatory Committee on Chinese Medicine (PCCM) in April 1995 represents a recognition of TCM in the development of the healthcare system in Hong Kong. It is envisioned that both the registration of TCM practitioners and the licensing of TCM materials and products can begin by the year 2000. The PCCM, consisting mainly of members of the TCM professions and related experts and supported by the Department of Health, will steer the implementation of recommendations made by the WPCM. A statutory body will eventually replace this committee. The overall approach has been to formalize and recognize the professionalism of TCM practice and the use of TCM herbalism in the prevention and treatment of diseases complementing well-established orthodox medicine. The public can then be reassured that a heritage that is thousands of years old will be delivered by a system with quality, safety, and efficacy.

Expert consultants from the Massachusetts Institute of Technology (MIT), upon invitation, did a detailed study of Hong Kong industry in 1996. They concluded their remarks with: "We see a future for Hong Kong as a world-class industrial power. To realize such an ambition, Hong Kong needs to strike out in a new direction, as a leader in the production of new generations of products. The high-valued-added goods of the 21st century will be service-enhanced products."[19] The MIT group recognized the potential strength and infrastructure that Hong Kong possesses in the manufacturing areas. Health service, in particular the maintenance of good health and disease prevention, will be an important direction. The development of TCM is perfectly in line with this direction. The MIT expert panel, as well as the chief executive of the Hong Kong Special Administrative Region of China, also identified and recently supported the development and manufacturing TCM products as "top priority" for Hong Kong.

Support from and Collaboration with Mainland China in Various TCM Fields

During the last 10 years, an enormous amount of interest and effort in both basic and applied TCM research has taken place in Hong Kong. Quite a lot of expertise has been acquired from colleagues in Mainland China via joint project schemes. Research funding from the University Grant Committee has given enormous encouragement to local scientists who would have been

extremely surprised to get grants for TCM-related projects in the early 1980s. The Hong Kong Jockey Club has always been extremely supportive of TCM research activities, and the Department of Industry in recent years has also been supportive. Without doubt, the intellectual resources in Hong Kong academia, with support from local universities and institutes, as well as support from academia on the Mainland and in Taiwan, will generate new ideas for future development of the new industry. A concise account of projects over the past three years is addressed in the chapter on Traditional Chinese Medicine in Hong Kong.

The Deliverable Model

The Mission Possible

Hong Kong provides some of the world's most reliable business, monetary, trading, and technology infrastructures. It provides a unique advantage for promoting and expanding Chinese medicine professionally and scientifically, and for establishing Chinese medicine in the global pharmaceutical market. Therefore, in order to maximize the usefulness of Chinese medicine for the prevention and treatment of disease, we propose a model that integrates education, research promotion, manufacturing and quality assurance for better healthcare. There is a big task ahead to put into practice the MIT recommendations on the development of manufacturing industry for TCM products. Various ingredients are there, what is needed is a workable and a deliverable model to set in motion this important mission. Hong Kong needs a proper and accountable organization to ensure the delivery of ideas from different sectors into products and goods with assurances of quality, reliability and brand reputation. The advanced countries in the West and the new consumers in China and other emerging economies demand these quality products. The following are some aspects of the mission that should be made a reality.

In line with the actions for national modernization of Chinese medicine, this model aims to coordinate closely with institutes in Mainland China. The ultimate common goal has been to create one of the national Centres of Excellence for promoting Chinese medicine globally. This national effort should address quality assurance of clinical and professional TCM practice; the launching of high quality, safe and effective TCM herbs and herbal products; and the promotion of a workable regulatory system to cope with international demands on quality, safety, and efficacy of crude TCM herbs and manufactured products.

The Model's Aims and Goals

The Model Organization (MO) should be responsible and be completely accountable to an independent board of trustees, which is formed to see that public funding for the execution of duties by the organization is used appropriately. After initial support over a defined period of time, subsequent development should be self-supported. Apart from generating capital via manufacturing of TCM products, joint venture projects and consultation income should be the logical sources of revenues. The model should strive to achieve the following goals:

- To develop for Hong Kong a global Centre of Excellence with a unique stand-alone identity for Chinese medicine in order to counteract misconceptions that TCM is a myth.
- To transform ideas from various Hong Kong and Mainland universities into basic and applied research in all aspects of Chinese medicine.
- To create an international center for coordinating the registration of TCM products and for registering TCM intellectual properties.
- To set up confidential troubleshooting facilities for Hong Kong's TCM manufacturing companies and small- and medium-sized industries which cannot afford such facilities.
- To set up training facilities for Hong Kong's professionals, technicians and dispensers and perhaps those of other countries. Trainees would learn skills required by the TCM industry, skills they cannot acquire in universities.
- To work in conjunction with experts at Hong Kong's universities and institutes as well as those in Mainland China to establish R&D programs which pursue new formulations, novel composite prescription products, and GMP manufacturing procedures.
- To provide facilities for small-scale pre-manufacturing production to small- and medium-sized industries.

Infrastructure of the Model Organization

The Model Organization should have premises large enough to house several Functional Units. **Scheme 1** illustrates the framework required. The board of trustees has the power to ensure a system of "checks and balances" for the organization. The overall executive role will be the responsibility of a team of directors which helps the managing director run the organization.

Development Strategy

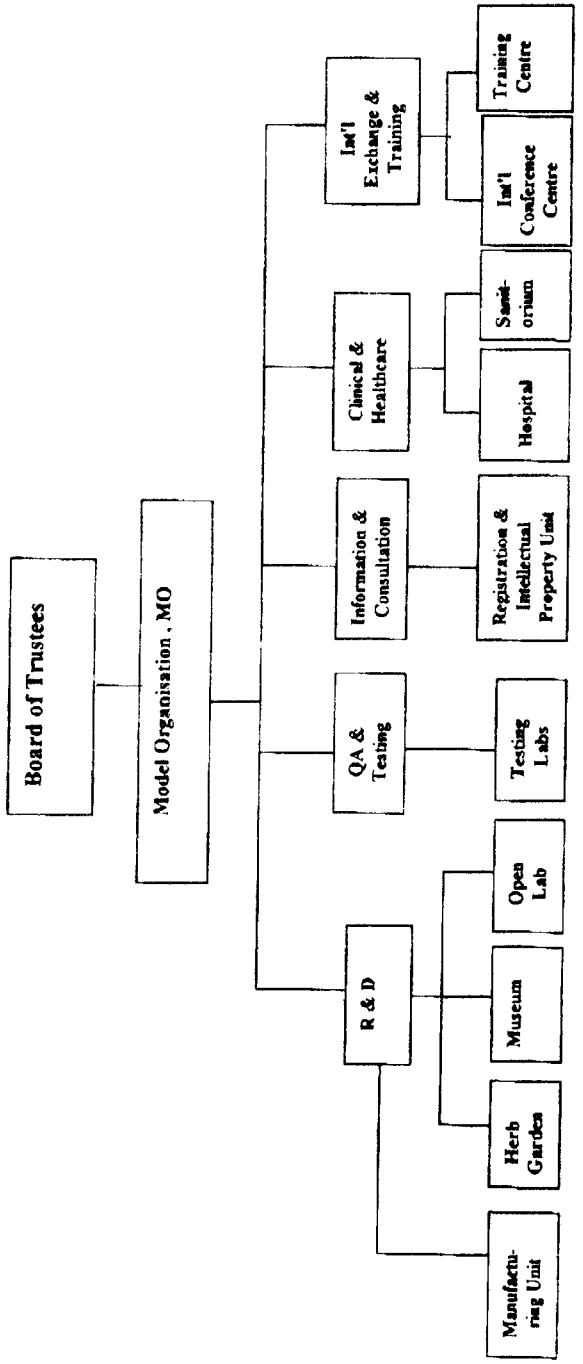
Innovative R&D Approaches for Market-Orientated TCM Products

Evidence of failure and difficulty isolating pure chemical entities from even a single medicinal plant as potential compounds for activity screening[20] indicate that conventional phytochemical screening should not be followed. Future R&D strategy should center on market-oriented research with the aim of manufacturing TCM products and coordinating development for small- and medium-size manufacturers.

The MO should identify and develop plant-based pharmaceutical products by undertaking pre-clinical and clinical research to meet Western regulatory standards, defining a standard formulation and dose, and confirming safety and efficacy. Many Chinese medicines, are based on composite prescriptions and are used for severe conditions which are poorly treated by conventional Western medicine. The MO's approach should be selective. Initially it should neither seek to identify a single target for activity, nor a single chemical entity from the prescription herbs. Based upon empirical clinical evidence of efficacy, the constituents of the herbal mixture can be standardized using developed quality control procedures to ensure reproducibility and the undergo controlled clinical trials. Where appropriate or feasible, the MO may seek to develop second-generation products through the identification and characterization of purified fractions or single chemicals derived from the original formulation using pattern recognition predictions.

Most TCM literature record a large number of preparations in use. Most TCM practitioners will use 200 to 300 herbs in a variety of combinations. The selection of successful formulas with input from expert TCM practitioners is a must when initiating R&D.

Scheme 1



The basis for product selection can be targeting chronic illnesses or disease prevention. They can be asthma, diabetes, skin diseases (including eczema, psoriasis), wound care, rheumatoid arthritis and senile dementia, such as Alzheimer's Disease. Products for improving immunological strength or the body's defense systems and reducing cardiovascular disorders and cancer are some other possibilities. Product development plans should be achievable, assuming the availability of resources, in the securing of development partners, where appropriate, a trouble-free program and prompt regulatory review.

Strategic Actions

This approach is unconventional, but controlled clinical trials have illustrated that it is possible to demonstrate safety and efficacy of the Chinese medicinal preparation Zemaphyte for treatment of atopic eczema[3] and the topical application of Tiger Balm for relieving tension headache.[21] The MO should progress TCM-based preparations through clinical trials. Guided by documented clinical use of the TCM composite formulary (Fu-Fang), a standard formulation can be reviewed and specified for R&D. The MO could develop quality control procedures to ensure that the pharmaceutical product can be produced in a repeatable manner and then safety and efficacy trials can be carried out. The R&D results can be used to secure a partner (a small- or medium-size herbal manufacturer) which will assume the majority of further development costs and be responsible for marketing. The MO will receive access and milestone payments and a royalty or margin on sales.

Various guidelines have been published addressing the registration of single-chemical entities of herbal origin, but there are no guidelines governing the pharmaceutical registration of complex mixtures of plant-based products. Evidently others have made such progress in the field.[22] It is possible that the Registration & Intellectual Property Unit (RIPU) of the MO, having satisfied the requirements within China's own regulatory body, can develop its approach with regulatory bodies in the U.K. and the United States. The RIPU will be pioneering a new area of drug development, and, together with the authorities, it is setting de facto standards. These include the demonstration of reproducible quality assurance of safety and measurable quality control procedures. There will, of course, be the usual uncertainties surrounding the regulatory bodies' evaluation of the clinical benefits against the risk of side effects, but these are common to all drugs.

Development of Appropriate Quality Control and Manufacturing Procedures

Initial approaches for dealing with these complicated problems should concentrate on developing procedures for procurement of crude medicinal plants and herbs using expert staff to authenticate source materials. This requires recruitment of experts from Mainland China. In the long run, training will be required in order to develop a dedicated staff.

The demonstration and recognition of combinational chemical analyses and pattern recognition for quality control of complicated decoction of multiple herbs has yielded a reliable means of QC for these products.[20] Industrial monographs for these crude materials should be prepared, validated as part of the references for standard operation procedures. These will be required to apply for the Product License Application (PLA). The MO has the important task of producing as many PLAs as required for all medicinal plants used. Eventually, a reference library will be produced for the use of the whole nation. Such difficult tasks can be shared by key centers and coordinated by the appropriate governing bodies in China.

The MO's main focus should be developing key products to the point of ensuring a sufficient supply to undertake clinical trials. Routine manufacturing strategy and supply considerations could be a secondary focus. The local manufacturing industries can do subsequent manufacturing of these products when R&D is complete. For example, locals can manufacture a TCM product from bulk decoction, with the resulting product being granules for oral administration. The decoction from herbal mixture and subsequent concentration and drying process are carried out in one location by a specialist industry, while the product is granulated, tableted and packaged at another. There could be capacity constraints in both the decoction and secondary manufacturing operation, depending on the scale of manufacturing by a particular partner. This can be coordinated by the MO.

Undoubtedly, after submission of the PLA, there might be changes in the approved methods and conditions of processing, and different facilities might be used. These changes will require further notification to the regulatory authorities. This will include a justification for the changes and a demonstration that the manufactured product is equivalent to that used in clinical trials. Given that the exact chemical composition of an herbal mixture is un-

known, it may be necessary to conduct clinical trials in support of the changes to demonstrate equivalence. However, the MO should develop QC procedures to deal with such changes and be able to represent the manufacturer in demonstrating to the satisfaction of the regulatory authorities that the product is equivalent without the need to conduct these trials.

There are risks associated with ensuring the quality of the plant material sourced from unreliable suppliers within and outside the country, with respect both to contaminant levels (particularly agrochemicals and heavy metals) and the possibility of deterioration of the material through incorrect storage. The MO should be able to install procedures to analyze batches of materials before processing to screen for contamination and deterioration and to develop a range of tests to confirm the identity of the materials used and their presence in the final products.

The MO should have regular contacts via meetings with international regulatory agencies such as EMEA (European Medicine Evaluation Agency) in Europe and the FDA in the U.S., or equivalent, regarding the data requirements for registration of their products both for clinical development and manufacturing and quality control. These meetings would indicate what steps must be followed to submit a PLA without unnecessary delays. In addition, the framework for product registration should be sought from these regulatory agents where possible to assure speedy consideration.

Advantages Outweigh Risks in the Present Approach

Ever since the advancement of synthetic drugs for treatment in orthodox medicine, orthodox doctors have viewed traditional medicines with skepticism. The majority of the public now believes that unequivocal evidence of clinical safety and efficacy would begin to overcome this natural conservatism. However, it is our opinion that the development of this market will require a considerable educational effort by the MO, which should set up supporting teams to help herbal manufacturers break into the existing and potential market dominated by orthodox drug manufacturers.

The pharmaceutical industry is highly competitive. A patent for the products will give product protection for a period of time. A patent can only be granted on an invention that is novel and not obvious. The MO should have competent experts looking after these areas. Robust patent protection on the use of the materials for their traditional indications is not possible in the first instance. Significant protection in the E.U. can be achieved by registering the first product in a therapeutic area and thereby obtaining six or 10 (depending on the country) years' exclusivity on the data used to support registration. These can be through formulation and process patents. Further protection can be achieved if the production of the herbal products is able to identify novel moieties that are patentable in the preparations which are responsible for the effects. With the number of plant-based remedies in use around the world, the risk is that a different mixture of plant materials could be developed by a competitor copying the development strategy pioneered by the original manufacturer. However it is believed that a generic competitor's threat to a plant-based medicine is low, as the imitator would have to generate new data, which would take several years, and pay an enormous amount of money or wait for the exclusion period to expire. Further, given the nature of the products, proving similarity to a generic product will be exceedingly difficult.

The Convention on Biological Diversity was signed in 1992 and has now been ratified by a number of nations, including the U.K., China, India, and the Russian Federation. The objectives of this convention include the maintenance of genetic diversity, the sustainable use of its components and the fair and equitable sharing of the benefits arising out of the utilization of genetic resources. The MO should work with China to address these areas and the issues arising from the convention. Development of research in botanical propagation to securing plant materials is an important task. Research initiative can be coordinated by the appropriate unit of the MO.

Assessment of the Potential Prior to Production

The MO should be able to give advice to herbal manufacturers before commencement of R&D and production of the TCM products. The expert from the appropriate unit of the MO should be able to identify project merits, risk factors, commercial potential and development plans for the potential products. This is an essential advisory role to ensure that only good products would be produced and to save money for development. A market search exercise should be conducted. Source materials should be secured. Steps could involve:

(1) Initial Proposal for a Product
For example if a Fu-Fang has been considered favorable for treatment of certain skin conditions,

a viable formulation can be designed. A standardized oral formulation, which allows defined doses to be used, avoids problems associated with the difficult preparation and poor taste characteristics of the TCM product and enables a specified product to be registered.

(2) Project Merits

Certain eczema are usually treated with an emollient, but current orthodox treatments for severe atopic eczema require an initial oral or topical administration of corticosteroids or immunosuppressants. These therapies may not be effective in all cases and may be accompanied by severe side effects. Evidence of some Fu-Fang prescriptions have been proven from TCM treatment. Such projects may be viable for further market research.

(3) Risk Factors

Manufactured Fu-Fang may be in capsule or granule form. After submission, the regulatory authorities make a judgement on the quality control procedures and on whether pre-clinical studies are adequate. It is possible that the review period will be protracted, that additional data will be requested, or that the dossier will be rejected on first submission. The effect of any of these outcomes will be a delay in the launch of the product and/or a decision by the regulatory agencies of some companies to restrict its use to only very seriously afflicted patients. Strategy and plans should be designed to recognize this possibility. Competitors could make use of the strategy pioneered by the present exercise in order to develop competing products.

(4) Commercial Potential

The prevalence of severe skin diseases has increased by perhaps two- or three-fold over the last three decades, and now affects 10% to 15% of the population at some point in their lifetime. The conditions are more prevalent in children (12%) than in older age groups (5%). Roughly 10% of cases in some developed countries may be described as severe, of which 10% are uncontrolled by current orthodox therapies. Total treatment

costs of treatment of severe skin diseases in the U.K. have recently been estimated at £288 million, of which about one-third are met by patients. This type of market research encourages further development of TCM products.

Cyclosporin, an immunosuppressant and anti-inflammatory agent marketed by Sandoz, is currently approved for the management of patients with severe atopic eczema. However, cyclosporin has a range of dose-related side effects, some of which are severe, and also is not effective in all patients. On the basis of clinical results to date, treatment with the TCM product doses has not brought about these side effects. Five other drugs are currently awaiting registration, and an additional six drugs are in the clinical stages of development for the treatment of atopic eczema.

(5) Development Plans

If the manufacturer has already carried out clinical studies on its trademarked product, a dossier should be prepared for submission to the regulatory agent and a launch in the near future should be planned. Discussions with regulatory authorities in other countries should be initiated. Other specific issues should be identified in the proposed development plan in order to cope with a revised framework for registration purposes, which could involve extensive additional data. Approval for registration can take as long as three years. Meanwhile, during the registration period, product development should be continued with clinical studies. It may be likely that an active fraction could be isolated from the complex mixture product of the TCM plant-based medicine.

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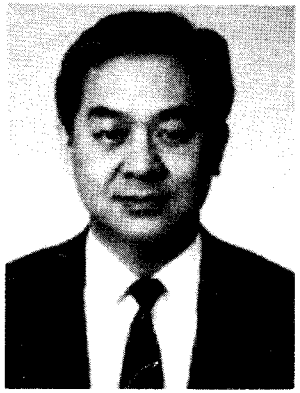
Chapter 4

Functional Genomics in Hong Kong

By

~ Albert Cheung-Hoi Yu, Ph.D. ~
Assistant Professor
Department of Biology
The Hong Kong University of Science and Technology

~ Yong Xie, Ph.D. ~
Assistant Professor
Department of Biology
The Hong Kong University of Science and Technology



***Albert Cheung-Hoi Yu, Ph.D.**, is an assistant professor in the Department of Biology at The Hong Kong University of Science and Technology. Yu received his Ph.D. in pharmacology at the University of Saskatchewan, Canada. Yu has edited two books and published 42 scientific manuscripts and 98 conference papers. He is a visiting professor at The First Military Medical University in China; project director at Shanghai Research Center of Life Sciences, The Chinese Academy of Sciences; adjunct professor at Beijing Medical University's Neuroscience Research Center; and visiting associate professor in the Department of Pathology at the Stanford University School of Medicine in Stanford, California. He is a member of the editorial board for **Neurochemical Research**, **Progress in Physiological Sciences**, and **Chinese Journal of Neuroscience**.*



***Yong Xie, Ph.D.**, is an assistant professor in the Department of Biology at The Hong Kong University of Science and Technology, where he is conducting research on antibody engineering and hepatocellular carcinoma. Xie received his M.S. in molecular genetics from Fudan University in Shanghai and his Ph.D. in biocehmistry, molecular and cell biology from Cornell University in Ithaca, New York.*

There exists a crusade to identify and characterize all human genetic material – the genome - that is rapidly changing the landscape of the biotechnology industry. Where there were once periods in this quest when the most talked about discovery was "the gene of the year," it may be soon when talk will surround "the gene of the day," says Harvard University Nobel laureate Walter Gilbert (*"The Genomic Gamble,"* **Science**, Vol. 275, Feb. 7, 1997, p. 767). This crusade is fueled by the Human Genome Project, an international research program that plans to sequence the three billion genes found in the 23 chromosomes of every human. Large pharmaceutical companies have seen the power that genomics holds in the process of discovering novel drugs and thus have played a vital role in the continuation of research and the provision of opportunity in this field. More than 80 percent of all the human genes that are going to be discovered will be because of pharmaceutical industry funding, says president of The Institute for Genomic Research (TIGR), Gaithersburg, MD, J. Craig Venter (*"Genome Investigator: Craig Benter Reflects on Turbulent Past and Future Ambition,"* **Scientist**, Vol. 19, No. 15, July 24, 1995, p. 1). The recent success of genomics companies such as Millennium Pharmaceuticals, Inc., Cambridge, MA; GENSET, Paris, France; and Affymetrix, Santa Clara, CA, in launching initial public offerings amounting to billions of dollars has had a deep impact on biotechnology and given genomics research a presence within the industry. This chapter is a discussion of what role Hong Kong will play in the further development and growth of the genomics industry within Asia and worldwide.

Underneath the expansive heading of biotechnology is the term "genomics;" which refers to the scientific discipline of mapping, sequencing and analyzing genomes. The term itself breaks down into "structural genomics" and "functional genomics." Structural genomics has as its goal the construction of high-resolution genetic, physical and transcript maps of an organism with its complete DNA sequence. Systematic structural genomic research on specific organisms includes: the Human Genome Project, Mouse Genome Project, E. Coli Genome Project and the Rice Genome Project. Functional genomics is a relatively new term only universally accepted within the past decade. It refers to the development and application of global (genome-wide or system-wide) experimental approaches in assessing gene function by utilizing the information and reagents provided by structural genomics. Thus,

whereas structural genomics is characterized by data management, functional genomics is characterized by its determination of the function of genes and their biological relevance. The gap that functional genomics bridges is essential in the transformation of static facts to circulating dollars.

In order to illustrate the immense importance of functional genomics to the discovery and commercializing process of novel drug development, let us look at a recent success story – the discovery of the obesity gene. Discovered in December 1994 by a team of researchers at The Rockefeller University in New York City, the exclusive license of the ob gene was granted to Amgen early in 1995 for an initial payment of US$20 million followed by clinical milestone payments several times that amount, plus specified royalties. Studies surrounding the function of the ob gene, suggest that it regulates the size of fat tissue mass. Fat cells containing ob genes were found to secrete a protein called leptin (from the Greek word for thin) that regulates food intake and metabolism. There are two other genes that have partaken in the fat-gene race: "tub," discovered by scientists at Millennium Pharmaceuticals, which triggered a major milestone payment from the company's corporate collaborator, F. Hoffman-La Roche, Inc., Basel, Switzerland, to the tune of up to US$70 million over five years; and the agouti gene, cloned in 1994 and under investigation by researchers at Oak Ridge National Laboratory and the University of Tennessee, Knoxville, TN, and Glaxo-Wellcome Research, Inc., Research Triangle Park, NC. The estimated market value for a prescription fat-reducing drug is US$1 billion, and an over-the-counter drug is US$10+ billion annually. The diet product market profits up to US$30 billion a year in the U.S. alone. In 1960, 24% of adults (ages 24-70) were considered obese in the U.S. (defined as 20% or more above ideal weight), compared with 33% in 1990. Under revised 1998 U.S. guidelines, which use the World Health Organization's definition of overweight persons, 55% of Americans are considered overweight. The discovery of the obesity gene is merely one gene discovery currently receiving commercial attention and gradual commercial success. The size of this emerging industry aside, competition between companies in the biotech and pharmaceutical fields is increasing, as these companies work to turn gene discoveries into innovative commercial application of the genes' function. Mere gene discovery is not valuable on its own; it is the discovery of how the gene works and what it means that ultimately commercializes the information. The move from "structural" to "functional" information is the goal. In this business, the stakes are high.

In the biotechnology industry, as in others, China is seen as the land of opportunity. The cooperation and collaboration between China and the rest of the world that is occurring as a result of this potential has affected the genomics industry as well. China has a richly diversified human genome pool with a population of 1.2 billion people representing 56 ethnic groups and with isolated areas of intermarriage within closed family groups over long periods of time. Collection and preservation of this genomic information is now an urgent priority as significant migration between the countryside and cities resulting from China's rapid economic development has taken place. The potential of China's rich and unique genomic resources has brought a heightened awareness of and commitment to human genomic research on the part of the Chinese. China has entered a joint venture in genomics research between the Chinese Academy of Medical Sciences (the largest medical institution in China with a network of more than 25 research institutes and hospitals) and GENSET (a publicly-owned biotech company specializing in genomics which has wholly-owned subsidiaries in the U.S. and Japan). In addition, the Chinese Human Genome Project was initiated in November 1993, sponsored initially by the National Natural Science Foundation and more recently by the Chinese High Tech Program. These are both prime examples of China's commitment to establishing and developing genomic biotechnology in the East. Furthermore, research centers dedicated to the Human Genome Project are being established in both Shanghai and Beijing. With regards to academia and genomics, The Chinese Academy of Sciences allocated 16 million RMB in the past three years to support functional genomics research. Central Government funding of approximately 50 million to 100 million RMB has been or will be allocated to the Human Genome Project. Further funding for post-genomic or proteime research projects (related to proteins expressed by a genome or tissue) is expected to be supported by both central and local governments as well as partially supported by venture capital.

Hong Kong has always been seen by international business as a gateway into China because of its geographic position and economic savvy. In terms of biotechnology and genomics, Hong Kong has a potential and a knowledge that is both unique and powerful. Biotechnology developments in the Hong Kong Special Administrative Region (HKSAR) have paralleled the commitment shown by China. Since 1994, HK$290 million has been awarded to 95 research projects under the Industrial Support Fund Scheme of the Industry Department in addition to support for the

Industrial Park Project. The body of students graduating from Hong Kong universities with specialized biotechnology-related skills and knowledge represent Hong Kong's investment in their biotech future. The end of 1997 marked the halfway point for the completion of the goal set by the Human Genome Project to sequence the genomes of humans and other selected model organisms, identify all genes and develop the technologies required to accomplish these objectives. Significant progress has been made in the processes of identifying and mapping genes, the development of stable DNA-sequencing technology, and the building of computational tools required for the analysis of sequence data. The need to handle, analyze, control and report the massive amounts of information being generated globally by biotechnology and its spinoff have created the field of bioinformatics. For Hong Kong, this need was met by forming the Hong Kong Bioinformatics Center (HKBIC), which was established in February 1998. With a grant of HK$1,627,830 from The Chinese University of Hong Kong and the award of an Industrial Support Fund of HK$4,983,000, its goals are to provide for the needs of biotechnology in Hong Kong and, thus, worldwide. The establishment of bioinformatics is a reflection of the growing needs of the evolving Hong Kong genomics industry. And yet, large-scale sequencing of the three billion base pairs of the human genome has barely begun: there have only been approximately 60 million base pairs analyzed to date. This is a reflection of the plethora of opportunities and success that is awaiting discovery and claim. Genomics research is being done in China – money is flowing in from various Chinese and Hong Kong government agencies and academic institutions, and there are well-educated researchers that represent the finest from all over the world collaborating and cooperating to further genomics discovery in China. However, the commercial value of this work has not yet been nurtured and thus its potential is unrealized. This is where Hong Kong comes in.

Hong Kong's biotechnology industry is already attracting the attention of functional genomics. The basis for the takeoff of functional genomics already exists in Hong Kong, all that is needed now is expertise on the part of financial players. Functional genomics is not only the hottest new field within the field of genomics, it is also Hong Kong's short cut to being a worldwide player in the genomics arena. Biotechnology itself has attracted the attention of large major pharmaceutical companies in the past, but the shift to watch for is new interest in genomics companies, especially since biotechs have also shifted their attention to this area over the past few years. In order to maintain a 10% annual growth rate, the pharmaceutical

industry's top 50 firms must more than triple their output of novel drugs, and genomics alone may make this feasible. The initial public offering of genome company Incyte Pharmaceuticals (INCY), Palo Alto, CA, on November 4, 1993, boosted the average stock value of the 12 publicly traded genome companies by roughly 130%, says Matthew Murray of Lehman Brothers; thus significantly out pacing 55 percent of the entire biotech sector in that period (*"I am pharma, hear me roar,"* http://europe.cnnfn.com/digitaljam/redherri.../index-txt.ht; San Francisco, **The Red Herring Online**, May 11, 1998, 4:12 p.m.). After this event, eight genomics leaders have posted average annual share price gains of more than 75%. Hong Kong investment players are accustomed to playing short-term return investment games that take a year or two and thus are playing the biotechnology game in the United States. Regardless of the history of Hong Kong investors, there is an anticipated shift from their short-term tradition to a long-term focus as a result of the handover of Hong Kong to China. Long-term investment is needed in China, and so it must be the focus of investors looking for opportunities in the Mainland.

The moneymaking area in Hong Kong biotechnology is functional genomics. The mere discovery of a gene is only the beginning of the process of utilizing biotechnology information to its utmost potential. Without knowing the function of this information, it is only a fact and not an application. What is needed is capital investment to give functional genomics commercial value and take it to the level where it is available to and effective for the public.

Financial development of functional genomics is Hong Kong's game. Money alone is structural, investment is functional. With the commitment of China and the HKSAR to the genomics industry, Hong Kong is in a position to play a key role in the nurturing and realization of the commercial potential of functional genomics. The strength of the knowledge and expertise represented by those involved in genomics development and the financial sophistication and focus on long-term investment in China contribute to solidifying this position. Once this opportunity in Hong Kong's genomics industry is missed, the parameters of the game will change. All who choose to seize this moment in Hong Kong's genomics evolution will triumph.

Acknowledgment

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Chapter 5

Transgenic Animal and Gene Targeting Technology in Hong Kong: Current Status and Future Prospects

By

~ Kathryn S.E. Cheah, Ph.D. ~
Chair of Biochemistry and Head of Department
The University of Hong Kong



***Kathryn S.E. Cheah, Ph.D.**, is chair of biochemistry and head of department at The University of Hong Kong. Cheah received her B.Sc. in biology from Queen Mary College, London University, University of London, her Ph.D. in plant molecular biology, Botany School and ARC Unit of Developmental Botany at Churchill College, Cambridge University, where she was also a Brooks Scholar. She did her postdoctoral fellowship in the Department of Biochemistry at the University of Manchester in the United Kingdom and was a research fellow at Imperial Cancer Research Fund in Lincoln's Inn Fields, London. Cheah referees research grant applications for the Arthritis and Rheumatism Council, United Kingdom; the Biotechnology and Biological Sciences Research Council, United Kingdom; the National Science Foundation, United States; the Anti-Cancer Foundation, Australia; and the Research Grants Council, Hong Kong.*

What is Transgenic Technology?

Transgenesis is the process by which new genetic material (DNA) is transferred into the chromosomes of plants and animals. For animals, the major milestone in transgenesis came in 1980 with the creation, by J.W. Gordon, of Yale University, and co-workers, of the first transgenic mouse by injecting DNA into the pronucleus of the fertilized egg. This development was made possible through significant advances in technology involving the combined application of developmental and molecular biology approaches. The next major experimental breakthrough was depicted on the cover of **Nature** in 1982, which showed a photograph of a giant transgenic mouse created by the overexpression of growth hormone. This result was significant because it was the first demonstration of inducible regulation of expression of a foreign gene in transgenic mice.

Transgenic techniques have also been applied to other species, such as sheep, goats, cows, chickens, and fish, but the greatest successes have been with mice, which, as a consequence, have become more widely used. A limitation of creating transgenic mice by pronuclear injection is the inability to control the site of integration of the transgene in the genome; therefore, the next major milestone was reached when it became possible to target DNA sequences precisely to their cognate position in the genome by homologous recombination in mouse embryonal stem (ES) cells. As a result it is now possible to tailor-make mice carrying specific mutations in any known gene by genetic targeting, popularly called "gene-knockout," and to transmit such mutations through the germ line of mice. Using this approach, genes whose functional impact is not fully known can be studied in an intact, in vivo integrated system. The next frontier in gene targeting is control and restriction of gene inactivation in time and place within the whole animal, i.e., tissue-specific (conditional) and inducible knockouts. Mice engineered in such a way will be most useful for studying gene function or for manipulating the action of particular genes/therapeutic proteins in specific tissues at particular times in life.

Applications

The applications of transgenic technology are multidisciplinary, of far-reaching significance and have been used in basic research as well as for the development of new and innovative approaches in medicine and biotechnology. A detailed de-

scription of the many ways in which transgenic animals have been and are being used, is beyond the scope of this article. To summarize however, applications of transgenic and gene-targeting technology have been in the following main areas:

- In basic research into how genes work;
- In biomedical research for the creation of animal models of human diseases and mechanisms of health and disease;
- In drug research, such as providing models for the testing of novel drugs for the treatment of many diseases such as cancer, AIDS etc.;
- For the development of DNA-based vaccines;
- For testing gene therapy protocols;
- In organ transplantation research;
- For use as bioreactors producing pharmaceutical and therapeutic proteins;
- For cloning valuable livestock as exemplified by the cloning of Dolly the sheep; and
- For engineering disease resistance in farm animals.

Genomics and Gene Function

The aim of the Human Genome Project (HGP) is to discover the genetic basis of human disease. As the HGP approaches completion, targeted to be 2003, new priorities in research have arisen. These areas have been variously described as "functional genomics" and "functional genetics" which have already become formidable forces for the discovery of disease genes, for the identification of drug targets and for the development of new therapeutic products. In functional genetics, analyses of transgenic and gene knockout mice are unveiling the functional role of many genes, helping us to understand the molecular basis of normal development and disease.

Bioinformatic tools which enable analysis of the sequence, protein motifs and structure databases arising from the various genome projects help us to make predictions about biological function, as well as to identify and design potential therapeutic targets. The use of mouse models created by gene targeting, transgenic technology and mutational screens enables testing of these predictions. A database of gene function is required to realize the benefits of gene sequence information in drug discovery. The massive amount of sequence information accumulating in public and commercial databases requires a systematic method for determining the function of each gene. The knockout mouse will be the common denominator by which all genes will be studied to determine their role in mammalian biology and disease. By studying the physiological, cellular and biochemical consequences of targeted mutations in mice, researchers will be able to determine the function of many genes as well as identify potential drug targets.

Transgenic Animal Models of Disease

Naturally occurring mutants with characteristics resembling those of inherited human disorders can be used for the discovery of disease genes. Conversely animal mutant models can be used to study the molecular mechanisms which underlie human disease and to validate predictions about the consequences of expressing candidate mutant genes. Of the available models, the mouse has become the most commonly used model system for human disease because of:

- The similarities in physiology and development between mouse and man;
- The wealth of detailed knowledge of mouse genetics;
- The large number of spontaneous mouse mutants which constitute a valuable genetic resource for the study of inherited diseases; and
- The ability to manipulate the mouse genome using transgenic and gene targeting technology.

By manipulating the mouse genome using "gene-knockout" technology, specific alterations which mimic human mutations can be targeted into the genes of mice. Genetically engineered mutant mice created in this way and which carry introduced foreign genes or targeted mutations provide a rich resource which can be used as models of human disease. The impact of the introduced genetic changes can be assessed at fetal, neonatal and adult stages in different generations, enabling insight to be gained into the mechanisms of disease.

Transgenics and Gene Discovery in the Post-Human Genome Era

The rapid advances in sequencing whole genomes and the HGP functional genomics research has led to the emergence of companies which specialize in marketing gene knockout expertise in programs targeted at the analysis of gene function and drug discovery on a commercial scale. One example is Lexicon Genetics (USA), which is using high-throughput gene targeting to define gene function on a commercial scale. Lexicon Genetics is marketing a mutant mouse gene database (OmniBank) which will be a library of novel mutant mouse embryonic stem cell clones created by gene targeting. The OmniBank database also uses bioinformatics software to create a functional genomics platform for use by pharmaceutical and biotechnology companies in drug discovery.

Drug target identification is a critical component in drug development and this is another area in which transgenic/knockout mice have a useful role. To identify drug targets, lines of mice that carry custom receptors, ion channels or other genetic alterations can be created and studied.

Of particular interest is the joint venture between Lexicon and the not-for-profit organization Merck Genome Research Institute, Inc. (MGRI). MGRI was established to promote and sponsor projects which enable scientists to develop assays and methodologies that can be applied broadly across genomics research to improve the accuracy and speed at which the function of new gene sequences can be determined. One of the Institute's broad objectives is to support development of high-throughput methods which create gene-targeted models for the purposes of studying gene function in specific models, including mice. MGRI has recently commissioned the creation of 150 mutant mouse lines in a five-year, US$8-million project with Lexicon. The purpose

of this joint project is to help researchers worldwide move from gene sequence to function at a faster rate. All mice produced in the project will be distributed on a not-for-profit basis to any requesting researcher.

Transgenics for Bioassays and Testing

Transgenic and knockout mice are also invaluable models for the testing of new therapeutic agents developed from pharmaceutical, traditional herbal medicine or gene therapy research. In October 1997, scientists at the National Institute of Environmental Health Sciences (USA) announced the Environmental Genome Project, which aims to discover genetic factors that modulate a person's susceptibility to environmental hazards (**Science** 278:569). Correlating variations in known genes which code for detoxifying enzymes such as paraoxonase, cytochrome P450, with disease susceptibility of individuals will require extensive testing in animal models. The various knockout and transgenic mice will be invaluable resources for such studies.

Transgenic Animals as Bioreactors

Transgenics can also be used for the production of human proteins for pharmaceutical, therapeutic and nutritional use. For certain protein drugs that require complex modifications to be functional or those which are needed in large amounts, production in transgenic animals is a very useful approach. There are many advantages to using transgenic farm animals as production facilities: the transgenic bioreactor can reproduce, it maintains its own fuel supply, and one can achieve a flexible production capacity through the number of animals bred. Best of all, by producing proteins in this way, the drug is delivered from the animal in a very convenient form – in the milk. In this new development, called "pharming," transgenic animals are created which express the human gene product (protein) in the mammary gland, allowing for its collection and purification during lactation.

However success in making an animal that can produce the drug is far from guaranteed. The success rate of producing transgenic mice varies from between 10% and 50%, but the transgenic rate for goats, sheep, or cows is less than 5%. Production of the drug is measured during lactation, after the animal is raised to maturity and bred. As a result of the long time periods involved and low success rates, developing transgenic farm ani-

mals is currently very expensive. Because of this expense, small litter sizes and long gestation times for farm animals, the production of therapeutics by transgenesis is typically tested using mice initially. The first mice to produce a human drug, tPA (tissue plasminogen activator, used to treat blood clots), was in 1987. Since then, the technology has advanced, and there are several companies which specialize in pharming therapeutics, using goats, sheep and cattle. Examples of therapeutics produced in transgenic farm animals, some of which are in Phase I/II clinical trials are: alpha-1-antitrypsin for the treatment of cystic fibrosis, fibrogen, Factor VII, human alpha lactalbumin (by PPL Therapeutics); recombinant antithrombin III (rhATIII), factor IX, growth hormone, beta interferon, HIV therapeutics, and a cancer vaccine (by Genzyme Transgenics).

Not all therapeutics are suited for production via milk. A notable exception is human hemoglobin that is being made in pig blood to provide a blood substitute for human transfusions. Because hemoglobin is naturally a blood protein, it is likely to be one of few exceptions to the usual method of production in milk. The economics of blood production are not ideal, however, because the animal producing the hemoglobin must be slaughtered to recover human hemoglobin.

Despite the problems, animal pharming, in general, is five-to-10 times more economical on a continuing basis and two-to-three times cheaper in start-up costs than cell culture production methods. A recent ground-breaking advance, the first cloning of an adult mammal ("Dolly") in 1997, has immense applications for the improved efficiency of pharming, for example, the cloning of transgenic animals proven to be good producers.

Transgenic Plants

Since the main focus of this chapter is transgenic animals, a detailed discussion of the application of transgenesis to create transgenic plants will not be made. In brief, a major focus of plant transgenesis is the production of plants with resistance to some pesticides, insects and diseases, thus reducing the amount of chemicals being used and released into the environment. Transgenesis can also be used to produce plants with improved nutritional qualities and greater yield to meet the food demand of an increasing world population.

Current Transgenesis Activities in Hong Kong

Basic Research

Transgenic technology is still new to Asia. In Hong Kong this technology has so far mainly been used in basic research programs in the universities. Projects focus on the areas of gene regulation and gene function as well as in creating transgenic models of disease. Transgenic mouse mutants generated from these projects could provide a valuable resource for the identification of new drug targets as well as act as models for bioassays and the testing of therapeutic compounds, drugs and compounds extracted from traditional herbal preparations. It would therefore be important and useful to establish a local database/registry for transgenic mouse lines and mutants which includes descriptions of phenotypes.

Building Infrastructure and Technology Transfer

Anticipating a growing demand for transgenic technology in Hong Kong and China, the Medical Faculty of The University of Hong Kong, and the Hong Kong Government Industrial Support Fund have established a Transgenic Technology Centre which is a core facility for providing high-quality transgenic technology training and consultation services.

The Transgenic Centre aims to provide a channel for technology transfer by introducing this state-of-the-art technology to the biotechnology industry in Hong Kong and in Mainland China. The initial emphasis is on training and technology transfer. The long-term aim is to develop the facility further to establish within Hong Kong a permanent center for the training of personnel and the production of transgenic animals in the region.

The Transgenic Centre has run two training workshops so far. In November 1996, Dr. M.H. Sham (an associate professor in the Department of Biochemistry at The University of Hong Kong), Professor Patrick Tam (the world expert on early embryo development, who is at Children's Medical Research Institute, Wentworthville, Sydney, Australia), Dr. Robin Lovell-Badge (co-discoverer of the sex determining gene, who is at MCR National Institute for Medical Research in London, U.K.), and myself organized and a three-week lecture and practical course entitled Molecular Embryology and Transgenic Technology (*http://*

www.hku.hk/biochem/tgcentre/course.html). This course provided the theoretical and technical knowledge in molecular embryology that is essential for any practitioner of transgenic technology. For investigators wishing to enter this field or learn more about the technology, the course provided the highest standards of instruction and a strong foundation in molecular embryology. The first course was oversubscribed, with applications exceeding four times the number of places. Twenty students from 10 countries enrolled, and feedback from questionnaires returned afterwards indicated that the course was a tremendous success. A second, shorter workshop, Current Advances in Gene Targeting: Theory & Practice, was held in February 1998, with Professor Richard Behringer (Department of Molecular Genetics, M.D. Anderson Cancer Institute, University of Texas in Houston) and myself as instructors.

The center is fully equipped for the production of transgenic and gene-knockout mice. It continues to offer consultancy and training to individual researchers as well as organize workshops. The activities of the Centre are coordinated by myself (principal coordinator) and Dr. Sham (co-coordinator). The Centre is located within the Department of Biochemistry at The University of Hong Kong and is staffed by scientists skilled in transgenic and embryo cryopreservation techniques and trained in animal husbandry.

Applied Research and Joint Ventures

Pharming in Hong Kong

Hong Kong Transgenic Limited is a joint venture between Asia Biotech Ltd. and the Applied Research Council of the Industry Department of the Hong Kong SAR Government, under the Cooperative Applied Research and Development Scheme (CARDS). It is currently engaged in the development of transgenic vegetables in collaboration with the Institute of Microbiology, Chinese Academy of Sciences. Transgenic anti-viral pepper and anti-softening tomatoes are presently being cultivated in Da Xing County near Beijing. Approval of these varieties for commercial production will be applied for in the near future. In collaboration with the Institute of Developmental Biology, Chinese Academy of Sciences, Hong Kong Transgenic Limited is also engaged in a feasibility study on the potential production of human blood proteins in transgenic pigs. In both instances, the transgenic products are scheduled for characterization and analysis in the Department of Biology, Hong Kong Baptist University. The establishment of Hong Kong Transgenic Limited provides a clear illustration of the value of the CARDS program in bringing together research and corporate resources of Hong Kong SAR and China for developing biotechnological products.

Also in the area of pharming, a joint project to produce an immunosuppressive therapeutic protein in transgenic animals has just started, as a collaboration between researchers at The University of Hong Kong, Imperial College London University (UK) and the Institute of Developmental Biology, Chinese Academy of Sciences.

Potential

The increasing wealth of expertise in basic research and teaching in Hong Kong in the areas of molecular embryology and transgenic technology will be a valuable and essential asset for the future development of applied research and development activities in Hong Kong. As more transgenic mouse mutants are produced in Hong Kong universities, it will be important to have a local registry/database of the different lines of mice and their phenotypes. The availability of such information will be useful for the identification of potential models needed for research and development in the areas of drug target discovery and drug/therapeutic testing.

The establishment of Hong Kong as a SAR of China brings increased opportunities for joint ventures with Mainland China in research and development involving transgenic animals. With the lack of land and extensive agriculture in Hong Kong, joint ventures with the Mainland are particularly appropriate in the area of pharming to produce therapeutics in transgenic farm animals.

It is very clear that at present great worldwide emphasis is being put on surveying genetic diversity for human disease genes and for studying regional patterns of disease. It is probable that this priority will continue to gain even more importance in coming years. Combined with the information explosion which will accompany the completion of the HGP, there will be rich resources for the gene and drug target hunter. There is no doubt that transgenic and gene targeting technology will be needed for any gene hunting endeavors to be carried out in the region.

Gene-knockout and transgenic projects require considerable molecular biology and micromanipulation skills, i.e., substantial research experience at a high level. In addition, problems encountered during a transgenic or knock out project are unpredictable and require substantial knowledge and considerable experience in the field. Projects producing knockouts therefore require highly skilled scientists and cannot be automated. Researchers in Hong Kong were the first in the region to knock out a gene, and there is a significant level of expertise in this area of research.

Given sufficient funding, Hong Kong's sound infrastructure and research talent position the SAR to make a significant impact in the application of transgenics in the area of gene and drug target discovery. The scale of success will depend on whether or not Hong Kong can interest the pharmaceutical industry in establishing research and development activities here or embarking on joint projects. So far the demand for the Transgenic Centre's services has been from the academic sector, reflecting the limited biotechnology and pharmaceutical research and development activities in this region, in contrast to the U.S., Europe and Australia. However, the Centre is poised for further development and has the capacity, for example, to undertake contract knockouts for the pharmaceutical industry. Collaborations in this area between Hong Kong and Mainland researchers will also be an important factor for the successful establishment of biotechnology research and development in Hong Kong.

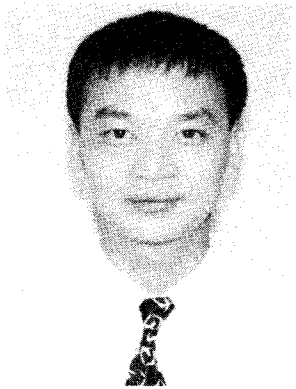
Chapter 6

Agricultural Biotechnology Taking Shape in Hong Kong

By

~ Simon S.H. Tang, Ph.D. ~
Research Manager
Kadoorie Farm and Botanic Garden, Hong Kong

~ Shain-Dow Kung, Ph.D. ~
Professor of Biology & Former Vice-President for Academic Affairs
The Hong Kong University of Science and Technology



Simon S.H. Tang, Ph.D. *is Research Manager at Kadoorie Farm and Botanic Garden in Hong Kong. He received his Ph.D. in parasitology from King's College London University, and he has first-hand experience in vegetable farming in Hong Kong and is interested in farm waste recycling and biological pest control.*



Shain-Dow Kung, Ph.D.*, is Professor of Biology and former Vice-President of Academic Affairs at The Hong Kong University of Science and Technology. Kung received his Ph.D. in plant physiology from the University of Toronto. He has extensive research, teaching and administrative experience in the University of Maryland system, where he was a professor of plant molecular biology, associate dean of Arts and Sciences, director of the Center for Agricultural Biotechnology Institute, and acting provost of the Maryland Biotechnology Institute. Kung is a Fulbright Scholar and is the author of more than 120 articles and the author/editor of more than a dozen books. His expertise is in agricultural biotechnology, and his research interests cover molecular evolution of chloroplast genomes; structure and fucntion of Rubisco; and analysis of regulatory sequences of UV-B radiation inducible genes.*

Introduction

It is only very recently that biotechnology found its way to the Hong Kong Special Administrative Region (HKSAR).[1] Thus, the authors cannot in this report offer much description beyond marking the birth of agricultural biotechnology in Hong Kong. By reputation and in reality, Hong Kong is a commercial city lacking farmland. As in all other metropolises, there is little agriculture, and food is mostly imported from neighboring regions. Given the fact that agricultural biotechnology has virtually been nonexistent, the background information as well as the description on the making of agricultural biotechnology in Hong Kong given below is more agricultural than biotechnology-oriented. However, it is encouraging that biotechnology has recently been recognized as an important discipline with a great future in Hong Kong. Agricultural biotechnology is inevitably becoming a part of this recognition, particularly in the academic sector.

Agriculture in Hong Kong

Agriculture is a relatively small sector in the Hong Kong economy. In 1994, agriculture and fisheries together represented only 0.2% of the annual GDP.[2] According to the 1991 census, the number of people classified as skilled agricultural and fishery workers was 20,455, or 0.75% of the workforce.[3]

Farmland in the SAR is limited. Out of a total area of 1,092 km^2, only 78.6 km^2 (7.2%) is devoted to farming and only around 23 km^2 (29% of the farmland) is actually cultivated.[4] **Figure 1** below shows the utilization of farmland in Hong Kong.

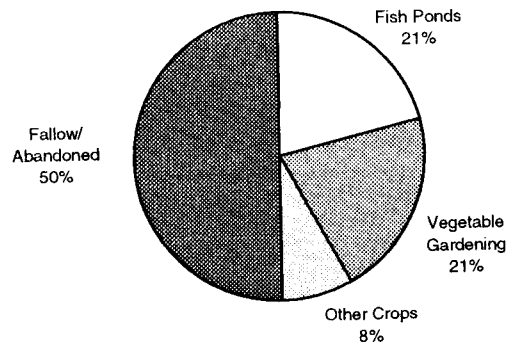


Figure 1. Farmland utilization in Hong Kong (adapted from Hong Kong Annual Digest of Statistics, 1995)

The limited supply of arable land and the phenomenal population rise in the postwar years instigated the change from traditional rice farming to small-scale and intensive vegetable and livestock farming.[5] The last recorded tonnage of locally produced rice was in 1991.[3] Crops most commonly cultivated now are leafy vegetables, flowers and ornamental plants (**Table 1**).

Table 1. Commonly grown crops in Hong Kong[6]

YEAR-ROUND VEGETABLES	SUMMER VEGETABLES	TEMPERATE VEGETABLES	FLOWERS
Chinese Kale	Chinese Gourd	Cabbage	Aster
Chives	Cucumber	Carrots	Carnations
Flowering Cabbage	Long Bean	Cauliflower	Chrysanthemum
Leaf Mustard	Water Spinach	Celery	Dahlia
Lettuce		Sweet Peppers	Ginger Lily
Radish		Tomatoes	Gladiolus
Spring Onion			Lotus Flower
Watercress			Peach Blossom
White Cabbage			Snapdragon
			Roses

As for the livestock industry, pig and poultry husbandry are the mainstays. There is very little cattle because of the lack of pasture. **Table 2** tabulates the local production of fresh vegetables, live pigs, poultry and fish in tons and the percentage of food consumed which is locally produced. Apart from live marine fish, all other local products constitute a small proportion of the foods consumed by Hong Kong people.

Table 2. Local food production in 1994 & 1995[6]

	1994		1995	
	local production	self-sufficiency ratio (%)	local production	self-sufficiency ratio (%)
Fresh Vegetables (tonne)	89,000	26	88,000	17
Live Pigs (number)	185,560	7	207,570	8
Live Poultry (tonne)	22,260	23	21,010	22
Marine Fish (tonne)	88,800	71	90,810	71
Freshwater Fish (tonne)	5,500	11	5,250	11

Agricultural Biotechnology

Background: Government Agriculture Support, Technical Services and Development Schemes

There is no monetary support or direct subsidies from the government for primary producers in Hong Kong, except for farms

suffering from natural disasters. In this case, grants from the Emergency Relief Fund are issued. However, there are four low-interest loan funds administered by the Agriculture and Fisheries Department (AFD).[7] They are the Kadoorie Agricultural Aid Loan Fund, the J. E. Joseph Trust Fund, the Vegetable Marketing Organization Loan Fund, and the World Refugee Year Loan Fund. A total of $15.3 million in loans was made to farmers in 1995/96.[7] Apart from the above-mentioned credit facilities, the AFD also runs a variety of technical services and development schemes which are discussed next.

The Fish Marketing Organization (FMO) and the Vegetable Marketing Organization (VMO) are two AFD partners which help support farmers. While the FMO and VMO provide much of the marketing services, technical services are provided via AFD Extension Offices. There are five Extension Offices located in various rural districts. Serving as links between the farming community and AFD specialist officers, these offices can provide farmers credit facilities, technological advice and development in local adaptive studies. New technologies are also transferred to local farmers through field demonstrations at AFD's experimental farm, farm visits, radio programs, various workshops and seminars (**Table 3**).

Table 3. AFD extension activity statistics for 1995-96[7]

	No.
Technical enquiries	20,044
Technical seminars & training courses	153
Meetings with agricultural co-operative societies	1,156
Radio programmes	52

Agricultural technical activities are focused on the introduction of exotic vegetables, promotion of mass seedling production, field application of integrated pest management, and evaluation of hydroponics systems. Agricultural biotechnology has been introduced in the field of integrated pest management, namely pheromone-based techniques and the biopesticide, *Bacillus thuringiensis*. In the livestock husbandry, some biotechnology-related applications and investigations have also been made. AFD has introduced the ELISA (enzyme-linked immunosorbent assay) test for Foot and Mouth Disease via the regional Foot and Mouth Disease control program for the livestock industry. Apart from these technical activities, there are

also agricultural development schemes. Currently AFD is overseeing only two major agricultural development schemes, the Agricultural Land Rehabilitation Scheme, which commenced in 1988, and the Accredited Farm Scheme, which began in 1994. The former is a scheme to recultivate fallow land not earmarked for other development, and 10 hectares of fallow land were rehabilitated in 1995/96. The latter is a voluntary scheme in which vegetable farms adopt an approved standard of production and practice safe use of pesticides. Products from farms which adopt the standard are monitored for pesticides and command a higher price in the market. A total of 112 farms covering 39 hectares have so far been accredited in Hong Kong. Interestingly, the scheme has been extended to the Chinese Mainland, and three farms there covering 392 hectares were accredited in 1995/96.[7]

The above reveals that there is little agricultural biotechnology within AFD. Perhaps this is not surprising given the government's general philosophy of free market and minimum intervention, plus the fact that the agricultural industry is a comparatively small sector of the economy. Furthermore, the Hong Kong biotechnology industry as a whole is still in its infancy. Nevertheless, the government does recognize the future importance of biotechnology and has moved to promote this industry.

Agricultural Biotechnology Projects in Hong Kong

Biotechnology is actively supported and promoted by the government through funding for research and development projects, manpower training and provision of physical infrastructure. In general, funding for research comes from the Research Grants Council (RGC). Support and funding for more applied and developmental projects operate under the auspices of the Technology Development Division of the Industry Department. There is a biotechnology internship program organized by the Biotechnology Committee. Moreover, two biotechnology research institutes have been established in Hong Kong, namely, the Hong Kong Institute of Biotechnology (HKIB), associated with The Chinese University of Hong Kong (CUHK), and the Biotechnology Research Institute (BRI) of The Hong Kong University of Science and Technology (HKUST).

The Research Grants Council (RGC)

The Research Grants Council (RGC) was established under the aegis of the University Grants Committee (UGC) in 1991. The role of the Council is to advise the government, through the UGC, on the needs of tertiary institutions in the field of academic research, with an aim toward developing a research base adequate to maintain the academic vigor and pertinence to the needs of Hong Kong. In a search of RGC's Internet database, the search term "bio" yielded 273 research projects funded by RGC since 1991.[8] After a subjective selection, 41 were determined to be directly related to agricultural biotechnology (**Table 4**).

Table 4. Agricultural biotechnology-related research funded by the Research Grants Council [8]

YEAR	NUMBER OF PROJECTS	NUMBER OF PRINCIPAL INVESTIGATORS	NUMBER OF INSTITUTIONS	FUNDING (HK$)
1997	11	11	3	7,492,240
1996	12	12	2	8,313,000
1995	9	9	3	5,708,000
1994	3	3	2	1,979,000
1993	3	3	2	2,093,000
1992	-	-	-	-
1991	3	3	2	1,220,000

Industry Department - Technology Development Division

The Technology Development Division of the Industry Department formulates and implements policies which are essential to the development and application of technology in the manufacturing industry. Programs related to biotechnology are the Industrial Support Fund, Applied R&D Scheme and Co-operative Applied R&D Scheme. Projects under funding from the Industrial Support Fund (ISF) are non-profit-making in nature and should be able to contribute to the overall technological or industrial development of Hong Kong. The other schemes encourage collaboration between the Mainland and Hong Kong by providing funding support as loans or equity participation to innovative projects which are product-oriented and have commercialization potential. No agricultural biotechnology projects were found in the latter schemes. The list of approved agricultural biotechnology related projects under ISF can be found in **Table 5**.

Table 5. Agriculture and horticulture-related projects approved under the Industrial Support Fund scheme during 1994-97. (Source: The Industry Department - Technology Development Division - Biotechnology *per com* Polly Kwok)

PROJECT TITLE	RECIPIENT ORGANIZATION	FUNDING APPROVED (HK$)
In Vitro Propagation of bulbous floriculture plants in a 2 litre bioreactor culture system	Hong Kong Institute of Biotechnology	990,000
Development of a high potency fish feed for the aquaculture industry	Hong Kong Baptist University	1,798,000
Development of infectious bursal disease virus (IBDV) vaccines for the poultry industries in Hong Kong and China	The University of Hong Kong	971,000
Expression of recombinant proteins in baculovirus and the applications of recombinant fish growth hormone in fish culture	Chinese University of Hong Kong	762,800
Application of modern biotechnologies to develop a gene bank for Chinese chicken pure line breeds	The University of Hong Kong	8,252,000
Vaccine biotechnology: Genetically engineered chimeric protein vaccine against foot and mouth disease	The Hong Kong University of Science and Technology	3,517,000
A spawning kit for induced reproduction in marine fishes using synthetic GnRH and receptor technology	The University of Hong Kong	3,037,000
Production of omega-3 polyunsaturated fatty acids by microalgae using conventional industrial fermentation facilities	The University of Hong Kong	2,118,000
Development of processes and products for an ornamental plant business in Hong Kong	Hong Kong Institute of Biotechnology	1,012,000

The Biotechnology Committee

The Biotechnology Committee was set up in 1995 under the auspices of the Industry and Technology Development Council with the aim of promoting the development of biotechnology in Hong Kong. As part of efforts to develop human resources for the local biotechnology industry in Hong Kong, the Committee has organized the Biotechnology Internship Programme with the help of the Industry Department. The program aims to enhance the quality of human resources by offering tertiary students in Hong Kong hands-on experience in this new and emerging industry. A total of 130 students from local tertiary institutions have joined the program and acquired invaluable research/industrial/commercial experience in both local and overseas biotechnology-related organizations in the past three years.[9]

Hong Kong Institute of Biotechnology (HKIB)

The Hong Kong Institute of Biotechnology (HKIB), located near the CUHK campus, was founded in June 1988. It received a donation of HK$170 million (approximately US$22 million) from the Hong Kong Jockey Club. Its mission is to promote the development of a successful biotechnology industry in Hong Kong, and its primary directives are to provide downstream R&D support and to serve as an incubator for commercialization of biotechnology-based innovations. The five-story R&D building has a total floor area of 75,000 square feet, of which the first two floors will accommodate a multipurpose bioprocessing facility with a pilot manufacturing plant for the production of biopharmaceuticals meeting the requirements of WHO's GMP.[10]

Biotechnology Research Institute (BRI)

The Biotechnology Research Institute was set up at HKUST in January 1990 with a grant of HK$130 million (around US$17 million) from the Hong Kong Jockey Club (HKJC). Similar to HKIB, its mission is to contribute to the development of a strong biotechnology industry in Hong Kong. At present, BRI operates as an association of scientists working in their laboratories and in centralized research facilities on the HKUST campus. Besides furnishing equipment for use in these laboratories, BRI sponsors specific facilities for: animal care, plant growth, cell culture, fermentation, a molecular structure laboratory, and a nuclear magnetic resonance laboratory. The BRI research areas are neuroproteins, protein engineering and design, plant biotechnology and Traditional Chinese Medicine (TCM). Several discoveries have generated new processes and products in drug delivery, in TCM and for use in diagnostic kits for diabetes.[11]

Joint Ventures

Though locally limited by various factors, the potential for development of agricultural biotechnology in Hong Kong could be increased through collaboration with research partners from the Chinese Mainland. The Life Science and Biotechnology Joint Laboratory of the Chinese Academy of Sciences (CAS) and HKUST is a good example. The Joint Laboratory, established in 1996, enables extensive research collaboration and academic exchanges in four major areas, one of which is plant biotechnology.

Active research on development of plant systems as bioreactors has been conducted at HKUST and at the , CAS. The Joint Laboratory also sponsored CAS scientists to visit HKUST and work on projects. Ongoing projects at the Joint Laboratory include the development of Tobacco Mosaic Virus (TMV) as a vector for the expression of foreign genes, gene expression in rice and tobacco and the establishment of algal transformation systems for the expression of exogenous genes.

To better meet the research needs of the Joint Laboratory, HKUST is now building an annex which will contain sufficient space to house a Biotechnology Resource Center and a Nuclear Magnetic Resonance (NMR) Center. The completion of the construction by the end of this year followed by an Asian Conference on applying NMR technology to biotechnology will certainly help generate more enthusiasm for agricultural biotechnology research among local researchers.

Prospects

The future of agricultural biotechnology in Hong Kong will largely be shaped by Hong Kong's geographical location, biotechnology research base, native agriculture condition, nascent local biotechnology companies, and government.

The geographical location of Hong Kong makes it a natural conduit for technology, knowledge and ideas between advanced nations and one of the world's greatest farming nations, China. Coupled with a solid base in world-class laboratories and researchers, Hong Kong holds much promise for the creation and development of an agricultural biotechnology industry. However, because of the limitations of local agricultural conditions, Hong Kong may only serve as a test bed for new products and processes or the production of very high value, agriculturally derived products, such as pharmaceuticals.

Companies which are knowledgeable about biotechnology, or newly formed biotechnology companies, must take up important roles in downstream activities such as the development, production and marketing of products and processes. From the biotechnology directory compiled by the Biotechnology Committee, there are 104 companies listed in the manufacturers/companies section of the directory. They are split into several groups: beverage, 6; equipment, 21; food products, 43; pharmaceutical, 33; and others, 1. None of these companies are directly involved in agricultural biotechnology, which appears to be confined to research institutes.[12]

Much of the research currently being undertaken is sponsored by the government, which does recognize the importance of biotechnology to Hong Kong's future. But, at present, there is no legislation concerning the release of genetically altered organisms into the environment. To ensure safe passage from the laboratory to the market and, ultimately, the consumer, the government will have to make laws and safety guidelines. Although these bureaucratic steps toward building an agricultural biotechnology industry are missing, and public acceptance is unknown, the foundations are in place, upon which a successful infrastructure/industry can be built.

Conclusion

It is clear that an agricultural biotechnology is in the making in Hong Kong but admittedly it is emerging at a very slow pace. Limited by the lack of science policy and land availability, it is unrealistic to expect agricultural biotechnology to develop into a strong industry.[13] Nevertheless, provided there is adequate support, the germ of research now being conducted at local institutes and institutions can be nurtured into a thriving industry, as strong as those in neighboring regions.

Acknowledgments

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Chapter 7

Pearl River Delta: A "Silicone Valley" of Technological Innovation?

By

~ M.H. Ng, Ph.D. ~
Professor, Department of Microbiology
The University of Hong Kong

~ Liang Yu Ning, Ph.D. ~
Guangdong Sciences and Technology Commission

~ S. Im, Ph.D. ~
Head, Department of Microbiology
The University of Hong Kong

[Report of a working group on technological cooperation between Hong Kong and Guangdong]

Preamble

Following the recent Hong Kong Technology Exhibition '97, the Guangdong Sciences and Technology Commission convened an informal working group to explore how Guangdong and Hong Kong may cooperate to vitalize Hong Kong's biotechnology industry. Membership of this group includes industry, government, R&D institutions, and businesses from both regions. Recognizing that most of the elements required for a sustainable and globally competitive industry are already in place, the group poses the question as to what is the most expedient means to make this a reality. This group chose to first focus its deliberation on diagnostics because, compared with, say, pharmaceuticals, diagnostics development entails a shorter lead time, lower developmental and marketing costs and more ready access to technologies.

Current Status of the Diagnostics Industry in China

The group finds that the diagnostics industry in China is in a stagnant state at present. The standard of manufacturing is generally poor; the products it produces are restricted to a few of the commonly used variety, e.g., diagnostics for hepatitis and AIDS; and the nation must depend on imports from the West to make up for the variety of diagnostics it lacks. Its link with R&D is not well established so that it is not able to produce new products to meet hitherto unmet needs and to anticipate emerging needs. The industry exclusively targets a limited segment of the domestic market at present. It has not been able to export the few diagnostics it produces, even though they are basically sound technologically. The import of the large variety of diagnostics needed is generally done in a haphazard fashion and is further hampered by cumbersome regulatory requirements. Consequently, this causes the cost of imported diagnostics to increase beyond market affordability.

Vitalizing the Diagnostics Industry

The group understands that a plan is already afoot for Hong Kong and Guangdong to join forces to develop and expand R&D. It puts forward a market-oriented product development plan to dovetail this joint R&D effort and links it to the industry and market. Capitalizing on Hong Kong as the shop window and Guangdong as the industrial base, this plan aims first to capture from the West a significant share of the existing diagnostics mar-

ket and then to compete with it on equal terms for markets which are expected to emerge in the near future.

Having analyzed its feasibility, the group concludes that this plan can provide an expedient means to vitalize the domestic diagnostic industry making it competitive on a global scale. The group believes that a sustainable diagnostics industry can create an investment climate which can avail the capital markets for financing further development of not only the diagnostics industry itself, but also other areas of technology. On a wider scope, therefore, the working group sees its plan as a role model for technology development which synergizes our combined strength in intellectual resources, a large manufacturing base, an intimate knowhow of and access to the domestic and global market and one of the largest capital markets in the world. Hence, it does not consider inconceivable that the Pearl River Delta should become a "Silicone Valley" of innovative technology. The following outlines some of the features of this plan.

Market-Oriented Product Development

In its deliberation, the working group on technological cooperation between Guangdong and Hong Kong concluded that the absence of an infrastructure for market-oriented product development is the major deterrent to the development of a sustainable diagnostics industry. The product development plan it put forward is intended to reverse this deficit. In general, it aims to transform prototype diagnostics from R&D and modify existing products into value-added products which comply with specific market and regulatory requirements. The plan also involves producing these products in sufficiently large quantities for the purpose of promotion and market penetration.

Partnership. The market-oriented product development proposed represents a transition in the commercialization of technology. The potential benefits conceived from basic research and subsequently confirmed by R&D are then scrutinized for their commercial potential. A plan is then devised to realize the goals by the most expedient means. The decision to undertake product development is primarily a commercial one, but a sound decision would depend on good scientific advice. Scientific input would also help ensure that the product being developed is technically sound. In addition, marketing and regulatory requirements are incorporated into the design of the products. The subsequent

scaling up of production would require the support of a suitable manufacturing facility and industry expertise to ensure product quality. The entire effort must be backed by aggressive marketing and adequate financing. In light of its multi-faceted nature, the working group considers product development best organized as a joint venture, the partnership of which is determined on the basis of the type of expertise and resources required for such an undertaking.

Products. The products developed are targeted at specific markets. It involves, for example, improving the quality of China-made products so that they meet the requirements of overseas markets, and modifying overseas products in such a way that they meet the requirements of domestic markets. For the purpose of the present discussion, China-made products are referred to as Category 1 products and overseas products are referred to as Category 2 products. Recognizing that the success of the program depends on developing products that can meet hitherto unmet needs, create new needs and anticipate emerging needs, the plan emphasizes the development of prototype products from R&D and the transformation of these products into new and unique products, referred to here as Star Products. While Category 1 & 2 products are intended to capture a share of the existing overseas and domestic markets, respectively, Star Products are intended to create and dominate new markets, enabling domestic industry to compete with major industries on equal terms.

Product lines. The plan's long-term strategy is to develop a comprehensive range of related diagnostics in all three categories with an eye toward becoming "One-Stop Shops" supplying the needs of substantial existing or emerging target market segments. This strategy serves not only to enhance marketing but also to minimize developmental and marketing costs because of the relatedness of product lines. The One-Stop Shop strategy which aims both at existing markets and emerging markets is an integral part of the plan proposed by the group.

Financing. The plan proposed by the working group will be implemented in stages. The first will be focused mainly on Category 1 and 2 products, because the lead time required is relatively short. Revenue generated from sales of these products can then be used to finance the development of several product lines designed to enhance the global competitiveness for our industry. The establishment of a sustainable and competitive diagnostic industry is expected to create a favorable investment climate here, which not only will allow the industry increasing access to the

capital markets. It will also facilitate development of other areas of technology in this region.

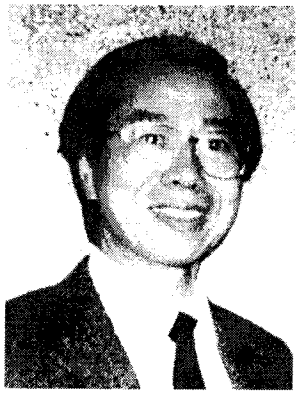
The business objective is to generate revenue to finance a limited product development initially and gradually expand its scope to a larger variety of diagnostic products. Accordingly, the initial effort will be focused on a limited number of Category 1 and 2 diagnostics, which are relatively simple to do and can be accomplished in a relatively short period. The revenue generated from sales of these products can then be used to develop special lines of related products to enable the industry to compete favorably with major companies in the West. Its success may be expected to create a favorable investment climate, availing the capital markets to finance further development not only in diagnostics, but also in other areas of technology.

Chapter 8

Recent Advances in DNA Diagnostic Technology and Current Development in Hong Kong

By

~ Joseph Wing On Tam, Ph.D. ~
Associate Professor
Department of Biochemistry
The University of Hong Kong



***Joseph W.O. Tam, Ph.D.**, is an associate professor in the Department of Biochemistry at The University of Hong Kong. Tam received his B.Sc. from The Chinese University of Hong Kong and his Ph.D. from The University of California, Davis. He has been involved in research and teaching in Hong Kong and the United States. Tam was a visiting scientist at the National Institutes on Health in Washington, D.C., and a visiting professor at Baylor College of Medicine in Houston, and The University of California, San Francisco. He has also worked in the private sector, as R&D Director at E-Y Laboratories in San Mateo, California. Tam was one of the first to apply chemical modifications as a treatment for genetic disease in 1973 while in Northwestern University and again first to introduce the recombinant DNA technology into Hong Kong in 1979. His current activities include the functional studies of insulin receptor and fast DNA detection method. He holds a U.S. Patent for "Rapid Flow Through Method for DNA Hybridisation Process."*

Introduction

DNA analysis is the center of activities in basic biological scientific research, from molecular biology, ecology, phylogenetic to medicine. Its potentials for industrial, agricultural, forensic and clinical applications have been well recognized worldwide and some of which have already been realized. In the healthcare discipline, it provides a totally new direction from preventive care through early diagnosis to disease management and recombinant pharmaceutical development. This review only focuses on the diagnosis aspects of DNA analyses.

Molecular diagnosis has been used for routine diagnosis in clinical laboratories and point of care for decades *(Price & Newman, 1997)*. Because of the low cost, high throughput format immunodiagnostic assays have been dominating the market. However there are intrinsic drawbacks for most of these tests because they are focused on the gene products or metabolites of the target which will only give indirect information and therefore could lead to possible misdiagnosis. DNA-based detection, on the other hand is well recognized as the only kind of test that will give direct and definitive diagnosis for disease-causing genes such as genetic disease, viral, bacterial and parasitic infections *(Tang et al., 1997)*. Recent evidences suggested that many of the metabolic diseases are genetic basis. For this reason DNA-based analysis is bound to be the method of choice for future disease diagnosis, forensics and many other fields of application. Due to the recent advances in DNA technology, DNA direct detection is developing very rapidly. However the number of assays available for routine laboratory test is still rather limited because of the expensive and time-consuming nature of the present formats. Nevertheless many of these are already in use in research laboratories and will soon be available for routine application.

DNA diagnosis, including forensics, for target identification can be classified as follows: (1) The presence or absence of the target DNA sequence which include partial and complete deletion, (2) mutation of the target sequence, point mutation and short insertion or deletion, and (3) polymorphism. The general scheme for successful diagnosis strongly depends on the efficiency of the methods used in (a) sampling (b) amplification and (c) detection and these are the focus of discussion. Because of limited space only the most recent relevant references are cited here; readers interested in original details can refer to earlier articles cited therein.

Sampling

DNA sample can be obtained by different methods depending on the sampling sources and the amplification procedures used. In general direct sampling is the preferred method if they are readily available as long as they are nucleated cells or nucleic acid containing organism such as species identification of plants, bacteria, viruses etc. For human samples, blood, hair fallacies, urine, saliva, stool or any other infected target cells can be used for genetic identification or diagnosis of the infectious agents. For prenatal diagnosis, chorionic villi biopsy is preferable to the amniotic fluid or fetal blood sampling because it is less invasive and can be done at the earliest stage of conception.[1] Most recently, maternal plasma has been used successfully for the amplification of fetal DNA for prenatal diagnosis of sex *(Lo, Y.M. et al., 1997)*. It is still not yet certain about the reproducibility, the success rate and how early do fetal cells start circulating in the maternal blood for successful prenatal diagnosis. If indeed these factors can be proven reliable for routine use, maternal plasma would be an important sampling source because it is the least invasive method neither imposing risk to the mother nor to the fetus. Another important factor affecting the ultimate outcome of any test is sample processing. In general it involves effective lysis of the cell to release its nucleic acid content without degradation. Conventional methods include centrifugation, chaotropic or proteinase inactivation and extraction. Other assay techniques may require elaborate purification scheme. For most eukaryotic cells or viral particles boiling under hypotonic conditions may suffice. Bacterial or plant cells may require specific treatment to break down the cell walls. Therefore, the sample-processing scheme must be designed for its specific application.

Amplification

In the early eighties most analyses were done with purified DNA samples which required micrograms quantities, very time consuming isolation processes and techniques like molecular cloning, restriction mapping and Southern Blotting. This is not only very time-consuming but also expensive and often produced false negative results. With the discovery of Polymerase Chain Reaction (PCR) and other amplification methods, DNA analysis has become readily applied for routine use. The amplification can be categorized into (a) target sequence amplification whereby the specific sample sequence(s) is being amplified (e.g. PCR, LCR, SDA and TMA etc.) and (b) signal amplification whereby the

amplification is directed toward the primary signal rather than the sample sequences (e.g. bDNA, DNA-DSE and HTA etc.). The former methods are superior in detecting very low copy number of the target sequences whereas the latter methods are more dependable if quantitative information is preferred. The following are some of the most frequently used amplification techniques used nowadays:

Target Sequence Amplification

Polymerase Chain Reaction (PCR)

Ever since its discovery, PCR (even before the isolation of the thermally stable enzyme Taq polymerase) was immediately used for genetic disease diagnosis *(Rolfs et al., 1992)*. The method uses a pair of specific 15-30 bases single-strand oligonucleotides complementary to the two DNA strands of the target sequences as primers and the thermally stable Taq polymerase to carry out 20-40 cycling polymerization reactions. In general this can provide 105 to 107 amplification in one hour in an automatic thermal cycler. Although in most cases, amplifications of relatively short fragments a few hundred base pairs are preferred, amplifications of over 20kb are readily attainable. With the use of multiple pairs of primer (multiplex amplification), different sequences of the sample genome and/or target contaminants can be amplified simultaneously. Other amplifications such as the ASA, COP, ARMS and RG-PCR are methods of choice for specific mutational analyses. PCR-RFLP has been used widely in DNA fingerprinting for inherit traits and phylogenetic identifications. In the cases of forensic identifications by DNA fingerprints, PCR-RFLP, based on short tandem repeat (STR) polymorphisms or multiple gene loci polymorphisms, is the most dependable, frequently used and accepted as the gold standard internationally. The technique is now extended to RNA fingerprinting through the used of RT-PCR or RAP-PCR. The most significant advantage of PCR is its sensitivity and specificity. With stringent and straight controlled conditions such as increase in annealing temperature and use of a second set of gene specific primer known as nest PCR, the method can detect single copy of the target sequence. In general, 10-50 copies are routinely detected with certainty. However, because of its extreme sensitivity, ultimate care must be obeyed to avoid contamination. The only drawback is its inability to make quantitative measurements with acceptable accuracy and reproducibility without very elaborate design and

operation scheme. For a known sequence such as HIV, accurate quantitation has been achieved by co-amplification with the addition of an internal standard which is a hybrid construct of similar length flanked with the same primer sequence but of different inserts as internal calibration. Other attempts have been less accurate.

Ligase Chain Reaction (LCR)

LCR was developed after the isolation of the thermally stable Taq ligase. The principle is similar to PCR. In this case two pairs of complementary oligonucleotides probes, within the adjacent known target sequences, are used in the reactions. These probes are allowed to hybridized with the target DNA and if the sequences match perfectly, the two probes will be in juxtaposition enabling the ligation to occur. In the additional cycling reactions the ligated probes serve as target template to give exponential amplification similar to PCR, therefore having similar intrinsic advantages and limitations. The distinct difference between the two processes is that in the LCR reactions, exact nucleotide sequence information must be known for the design of detection probes. Whereas in PCR reactions, degenerate primers distal from the target sequences can still be used and hence in the PCR reactions allelic sequences can be identified and characterized. The recent introduction of the Gap-LCR by Abbott Laboratories (Abravaya, 1995) has expanded the LCR application limit. This method has been applied for routine clinical diagnoses in ELISA format for genetic diseases, parasitic and other infectious agents.

Strand Displacement Amplification (SDA)

This is a relatively new development similar to the LCR which was developed by Becton Dickinson Research Center in 1992 *(Walter et al., 1992a & 1992b)*. The SDA utilizes the displacement characteristic of the DNA polymerase, an exonuclease deficient klenow (exo-klenow). In addition, a restriction nuclease (e.g. HincII) is added to the amplification cocktail containing dS-ATP instead of dATP. Hence during the extension processes the restriction enzyme (e.g. HincII) will nick the unmodified strand of a hemiphosphorothioate form of its recognition site after polymerization and therefore creating the new template for further extension. With the use of hybrid oligonucleotide primer pair(s) carrying the target specific sequence at the 3' end and a 5' restriction enzyme cleavable sequence, exponential amplification

of the target DNA sequence can be achieved at constant temperature without the use of expensive thermal cycler. Consequently, the amplification time can be reduced to 10-15 minutes at optimal conditions. When single strand binding protein from T4 bacteriophage (t4gp32) is added to stabilize the single strand DNA, amplification can be extended from 100 to 2000 nucleotides in length. With the appropriate assay system as discussed later this technique can detect 10 molecules in 30 minutes *(Spears et al., 1997)*. Furthermore the recent isolation of the thermally stable enzyme contributes to further improvement on specificity of the method.

Transcription Mediated Amplification (TMA)

Transcription-based amplification system (TAS) was first reported by Kwoh el. al. in 1989 *(Kwoh, 1989)*. This method is best applied for the detection of RNAs but can also be used for DNA samples. First, during the reverse transcription reaction an oligonucleotide sequence recognized by a DNA-dependent RNA polymerase is inserted into the target sequence to be amplified. This modified sequence is then capable of initiating transcription producing multiple copies of RNA for analysis. The TAS is in fact utilizing both the reverse transcriptase as well as the RNA polymerase to amplify the target sequence. Using the phage T7 promoter and the corresponding RNA polymerase each cycle is capable of generating about 40-fold of amplification. This is another isothermal amplification technique that does not require the use of thermal cycler resulting in a simpler, faster and less expensive assay system with equal sensitivity and specificity *(Goessens et al., 1997)*. The technique has been improved and is also known as transcription-mediated amplification (TMA), that is available commercially for routine qualitative as well as quantitative diagnostic assays for viral and parasitic agents *(Pasternack et al., 1997)*.

Qß Replicase Amplification (QßRA)

The amplification of Qß replicase is different from that of the PCR because it amplifies the specific template molecule hybridized to the target RNA sequence. It is similar to the transcription-based assay described above. Qß replicase is an RNA-dependent RNA polymerase isolated from bacteriophage Qß that specifically recognizes a unique folded RNA structure of the Qß genome replication origin such as the midivariant (MDV-1) RNA

sequences. *(Tyagi et al., 1996)*. The technique uses a recombinant hybridization oligoribonucleotide probe having the replication sequence at the 5' end and the specific sequence downstream from it. After hybridization, the Qß replicase synthesizes the single stranded RNA product that complements the parent target template followed by exponential amplification. Because each cycle of replication takes only ~20 seconds at constant 37°C, a 10^{12}-fold amplification takes less than 15 minutes, an order of magnitude faster than that of the PCR process.

Endonuclease Mismatch Amplification (NMA)

Isothermal cycling amplifications such the SDA, TMA and QßRA have one of the common intrinsic drawbacks: lower specificity. This is due to nonspecific hybridization of the detecting probe at a relatively low temperature ~37°C process. For SDA and TMA doing a nest amplification can effectively solve this problem. In the case of SDA a second primer pair is used after initial amplification. For TMA a second set of RNA polymerase and promoter-gene specific oligonucleotide primer must be used to carry out the nest TMA. For QßRA because of the lack of alternate form of RNA replicase, a very efficient target sequence purification scheme must be used to reduce the background noise *(Lawrence et al., 1990)*. Recently new amplification systems emerged by taking the advantage of the ability of the mismatch repair endonuclease to cleave these mismatched double strand probe/target hybrid sequences. Mismatch Identification DNA Analysis System (MIDAS) is an isothermal process using the labeled oligonucleotides as the detection probe for mutation diagnosis. The nucleotides are labeled at both ends as in the case of LCR, which may be symmetrically or asymmetrically dependent on the detection systems used. Excess amount of oligonucleotide probe of 20-50 bases long, are incubated at the appropriate temperature both for efficient hybridization and enzymatic cleavage. After hybridization the mismatched repair enzyme will cleave the mutation probe at the point of mismatch and dissociate from the target sequence, allowing the excess probe to anneal again. This isothermal cycling process called Oscillating Cleavage Amplification Reaction (OsCAR) is the basis for signal amplification. A similar system called Enzymatic Mutation Detection (EMD) uses the T4 Endonuclease VII, a resolvase isolated from T4 phage capable of cleaving many types of mismatch DNA structures such single-base mis-pairs, Holiday structure, Y junctions and heteroduplex loops. Although EMA is still in its early stage

of development, it is already been applied for the successful detection of a wide variety of point mutations with close to 100% sensitivity. Evidently the applicability of this method is limited to single or multiple point mutation(s) and is therefore less useful compared to all the other methods described above. However, it is potentially far superior to many of the existing methods directed towards mutational analyses such as SSCP, CSGE, DGGE, CCM and other equivalent techniques.

Signal amplification

Branched-DNA (bDNA)

Horn and Urdea *(1989)* developed the first real success for direct quantitation of genomic DNA without target amplification. The principle is based on the Christmas tree like formation of synthetic branched DNA over the target sequence by direct hybridization without amplification *(Chiron Patent #WO9202526; US-558897)*. The detection oligonucleotide consists of a hybrid sequence: at one end is a target specific sequence and at the other a sequence complementary to the root of the synthetic bDNA tree immobilized with a signal reporter of various kinds for signal amplification. The signal increases in direct proportion to the stacking number of the bDNA tree and the number of target specific detection probe designed along the target sequence. The number of probe varies with the length and specificity of the target sequence. This method is most suitable for the high throughput ELISA formats. The recent bDNA HIV 3.0 assay kit produced by Chiron can detect 50 HIV RNA copies/ml with over 95% specificity and is able to quantify genetic variant subtypes *(Collins et al., 1997)*. With the recent development of PNA, a peptide-link nucleic acid, the stability of the probe is further increased.

DNA Dendrimer Signal Enhancement (DNA-DSE)

The principle is similar to bDNA, but instead of using bDNA it uses sequence specific dentritic DNA with multiple single strand binding sites for molecular association to form molecular aggregates, thereby providing signal amplification. The method can be used on the conventional Southern, dot blot and reversed dot blot or ELISA assay formats. After the target nucleic acid is immobilized, target sequence specific DNA dendrimers are allowed to hybridize to the denatured target, followed by further molecu-

lar scaffolding which generates signal amplification. This amplification occurs independent of the label used in the final step in the assay, which can produce two to three orders of enhancement over the conventional assay system. Although it is of inferior sensitivity compared with b-DNA, it provides potentially a workable alternative *(Nilson, et al., 1996)*.

Transcription/translation coupled Assay (TTCA)

This is a relatively new development based on new concept of enzymatic signal amplification used for nucleic acid hybridization assays *(Chiu & Christopolous 1996)*. The disadvantage of conventional enzyme link assay system is the partial inactivation of enzyme through the cross-linking process. Instead of cross-linking the enzyme to the reporter probe, TTCA utilizes the in vitro transcription/translation processes to produce the fully active enzyme molecule within the assay system. In doing this Chiu and Christopoulos created a new label signal reporter, an expressible enzyme-coding DNA fragment, for nucleic acid hybridization assays. This DNA fragment contains a firefly luciferase coding sequence; the T7 RNA polymerase promoter sequence upstream for driving the in vitro transcription; and a streptavidin at the 5' end for affinity capture onto the hybridized detection probe. The target DNA, preferably in relatively short ~200bp fragment, which may be the amplified product, is denatured and allowed to hybridize simultaneously with two target specific oligonucleotide probes. One of these is either immobilized or labeled with an affinity ligand such as dioxgygnin for immobilization onto the microtiter wells via antigen/antibody interaction; and the second is labeled with biotin. The captured hybridized DNA complex is then allowed to react with the expressible DNA fragment followed by in vitro transcription/translation to generate the enzyme luciferase for chemiluminescence signal production. Although the hybridization is carried out in 37°C, a low stringency condition, the double labeling probes in principle should reduce the background due to nonspecific hybridization compared to TMA, QßRA or SDA. This is another isothermal amplification system that can produce quantitative measurement and is best suited for the high throughput, low cost format that deserves further development.

Analytical Method

The general approaches for analyzing the amplified product for final identification include sequences and fragment analysis,

hybridization analysis, DNA sequencing. In most cases a combination of these methods are often employed. Methods for detecting the presence or absence of the known target DNA sequence include restriction endonuclease mappings and PCR amplification techniques. For relatively long deletion(s) restriction endonuclease mapping analyses, including allele specific RFLP, have be used successfully. For the detection of point mutation or very short insertion or deletion sequence specific detection methods must be used. In general, methods will either involve (i) DNA fragments analyses by electrophoresis or/and (ii) DNA annealing by hybridization. **Table I** lists some of the common examples and their methods for detection. It is clear that the majority requires the use of stringent hybridization procedures. In recent years, as a consequence of the Human Genome Project (HUGO), technological development for analytical procedures have certain breakthrough in terms of cost, time saving, accuracy and dependability. In order to maximize the cost effectiveness of this development we must develop: (1) low-cost automation of high-throughput DNA diagnostic methods; (2) simple, rapid, low-cost individual tests that can be applied for bedside, point of care and rural area where laboratory facilities are lacking. Recent development in miniaturization such as the microchip, in situ amplification is the candidate for the former. However very few available techniques have been developed for the latter. I would like to review some of these developments with an emphasis on the latter and those currently in active research and development in Hong Kong.

Electrophoresis

Conventional gel electrophoresis is still the most widely used method for much applications in fragment identification and sequencing. This includes the RFLP, ASA, COP and conformational DNA analyses such as the SSCP, CSGE, DGGE and the chemical and enzymatic cleavage for point mutation analyses e.g. CCM and NMAs. Although substantial improvement has been made using the precasted ultra thin gel, the method is still rather time consuming and requires substantial manpower. For this reason many of the conventional gel electrophoresis analyses have been successfully replaced with the capillary electrophoresis (CE) apparatus such as CAGE, CDGE, PFCE etc. The development of the capillary-array-based CE reduces the cost as well as provides the rapid and cost effective automating analysis for fragment separation and identification. DNA sequencing CE-based equipment is also available on the market. With the recent development of low-viscosity, replaceable gel matrices *(Quesada, 1997)* to improve the reproducibility, CE may soon replace the conventional

techniques. Detailed review of the technique and its potential applications can be found elsewhere *(Mitchelson et al., 1997)*. Recently high-throughput electrophoresis methods have been developed in the forms of diagnal-gel *(Day et al, 1998)* and microfabricated capillary array *(Simpson et al., 1998)* that are capable of analyzing 96 samples compatible to ELISA microplate format. These methods combine with the microplate reader and conventional gel electrophoresis will enable one to analyze thousands of lane/day at minimal cost for the detection genetic variants down to single-base mutation. With the addition of temporal-thermal-ramp control Day and co-workers *(1998)*, reported that the apparatus can used for de novo scanning of unknown mutations and achieved similar accuracy.

Hybridization Based detection

As shown in **Table I** hybridization is still the major means for nucleic acid detection and identification. Before describing the most recent rapid hybridization processes developed in our laboratory a brief review of the recent advances in Microfabrication and micromachinary that utilizes hybridization process is described below. A number of recent reviews can be found for detailed information and for other biological applications *(Liu et al., 1997; O'Donnell-Maloney et al., 1996)*.

DNA Microchip technology

The concept has been mentioned for many years but Affymetrix using the photochemically synthesized oligonucleotides microdots on the silica surface in situ for detection probes first implemented it. The ink-jet printing technique is successfully used to deposit oligo-arrays onto printable surfaces *(Brennan 1995 US patent 5,474,796 and Baldeschwieler et al., PCT WO95/25116)*. Current technology has enabled the synthesis of ~105 probe sites per cm^2. Similarly Shalon and co-workers *(1995)* also developed mechanical microspotting. In addition, the novel peptide nucleotide analogs (PNA) provide more stable probes that are capable of forming the same double helical structure by hybridization has also been used to improve performance. This technology is fully reviewed by Hoheisel *(1997)*. Although microchip technology is still unavailable for routine application, a number of prototypes have already been developed and applied for almost all the possible ways of DNA analyses including known

or unknown point mutations, direct hybridization-based sequencing and DNA fingerprinting. Undoubtedly the potential application can be extended for rapid search of otherwise unknown candidate genes.

Micromachining Techniques

The Microfabrication technology has advanced to a new dimension by the combination of various disciplines of electronics, chemistry and molecular biology. Recently researchers of Nanogen Inc. have developed a microscopic system that contains an electronically addressable electrode micro-array that provides direct electric field capable of controlling a variety of biomolecular reactions. The incorporation of electric field can control various interactions: (1) facilitating the transport of charged molecules to selected microlocations which can then selectively control the concentration of reactants over the immobilized probe and; (2) the reversal of the electric field may be used to selectively remove the molecules with lower affinity away from the reaction to achieve absolute specificity. The stringency of the nucleic acid hybridization can therefore be carefully controlled to achieve exact homologous annealing with nearly no background. *(Sosnowski et al., 1997)*. The microelectromechanical systems (MEMS) developed by Microtechnology Laboratory of University of Minnesota have developed a micromachinings for DNA extraction, PCR thermal cycler and detection system (e.g. 1mm lateral dimensions) that can perform the various analysis *(McGlennen, R.C., paper presented in the NMHCC Bio/Technology Conference on Advances in DNA Diagnostics, Washington DC October 27-28, 1997)*. These are just two of the many examples of microfabrication devices. Evidently, the potential for cost-efficient high throughput such as pocket-sized apparatus for routine applications is imminent.

Hybridization Assays in Homogenous Solutions

Homogeneous DNA hybridization has been the basis of molecular biology research activities and details of the annealing process and kinetics have been well characterized. The advantages of this homogeneous system cannot be utilized for developing diagnosis assays because of the difficulty of assaying multiple analytes simultaneously without first being separated and the latter is often the limiting factor. However, with the recent advances in multiple reporter group technology this assay sys-

tem has gained much momentum. The Hybridization Protection Assay (HPA) is perhaps the first mature homogeneous format successfully applied for multiple analytes in a single tube without separation. It utilizes short oligonucleotide probes covalently labeled with the time resolvable chemiluminescent acridinium esters (AE-probes) and their distinct hydrolysis profile between the DNA/probe hybrids. Discrimination is possible because the unhybridized single strand AE-probe is rapidly hydrolyzed to the permanently non-chemiluminescent AE product. Some of the other assay systems (e.g. SPA, CPT, CRCA, etc.) use similar concept and the fluorescence probes.

Signal Generating Reporter

Many DNA test kits on the market use the simple and conventional radioactive labeled probe such as 35S and 32P for direct visualization on x-ray film by autoradiography. Current development emphasizes on the use non-radioactivity probes. Enzyme-link probe coupled with immunoassays provides the necessary enhancement through light or color production. These signals can be amplified further by the sandwich or molecular matrixes scaffolding. Significant advances in the reporter groups development have been achieved which include a number of light producing fluorescent, infrared and energy-transfer dyes *(Glazer et al., 1997)*. With the recent development of fluorophores having different emission wavelengths and time resolvable emission, multiple detection assay systems in a homogeneous solution without the need of separation or purification are now possible. In the microchip and other solid phase formats, confocal microscopy *(Lipshutz et al., 1995)* is used to measure the emission of dyes to provide the sensitive detection. This technique is particularly effective for in situ hybridization. However the complexity and cost of the system is inhibitory for use as general diagnostic assay. Other reporters utilizing the electronic properties for direct detection are being investigated. Deamer has recently developed the unique analytical system for the analysis of single DNA molecules by the electronic signal generated while moving through a narrow transmembrane pore of the hemolysin channel complex *(Deamer, 1997)*. Direct electronic signal in situ detection is now possible through the use of covalently bound transition metal DNA probe, when hybridized with the target DNA activate the electron transfer reactions *(Barton al el.,1997; Meade, T.L., 1996 and 1997)*. DNA biosensors based on electrochemical oxidation have also been developed *(Thorp, 1998; Hall et al., 1996)*.

Activities in Hong Kong

Due to financial constraint active research in Hong Kong was neither encouraged nor supported until the mid eighties with the formation of the Research Grant Committee (RGC). Nevertheless, we started the limited recombinant research activities in Hong Kong in 1980 concentrating on the identification of molecular defects in hemoglobinopathies. The first positive diagnosis was done by direct Southern Blotting for deletions and RFLPs and/or ASO for non-deletion mutations *(Tam et al., 1983 and Chan et al., 1984)*. Using the newly discovered PCR method and direct sequencing, point mutations at four different codons in the beta globin gene were unveiled two in our laboratory and two from the Department of Medicine, HKU. Currently most DNA diagnoses are still confined to research laboratories. Yet there are already fairly widespread establishments among the many institutions including hospitals in Hong Kong for prenatal, postnatal diagnosis of genetic diseases, bacterial, viral or even parasitic infections. The DNA fingerprinting are mainly done in a government laboratory. Basic research activity in molecular biology has increased exponentially and is now expanded to all areas of Bioscience research since the formation of RGC in the late eighties. Research output from this area have increased by hundreds of folds in recent years. Activities include many areas of research, from plant phylogeny to human development, through the use of conventional molecular biology techniques such as PCR, AP-PCR, DD-PCR and transgenics to instrumental-based technologies e.g. confocal microscopy or biosensors, which are out of the scope of this review. In diagnostic technology development, among the many, microchip-based is being carried out in The City University in collaboration with The University of Science and Technology. ASO-PCR and sequencing have been applied in the Prenatal Diagnosis Unit in HKU and associated hospitals. DNA vaccines and immunodiagnostics developments are also very active and are supported by the Industrial Support Fund established since 1994. The maternal serum and plasma sampling technique developed in UK by Dr. Dannis Lo et al., *(1997)*. is now being used in The Chinese University of Hong Kong by Dr. Lo himself. Thus we have passed the threshold in critical mass for basic and applied Biotechnology development in Hong Kong. However significant advances depend upon the efficient use of resources. Other than funding, thorough communication and collaboration between biological scientists, engineers and others is the key for success.

To date most of the DNA diagnostic techniques in development emphasize on the high throughput format, which requires expensive and sophisticated instrumentation and therefore must be center oriented. Effective diagnostics should be people oriented and the majority who need low cost testing are away from well-established metropolitan centers. Hence immuno-testing kits like test-strips are still most useful despite its limitations. Our laboratory is concentrating on developing fast diagnostic techniques that can complement the immunoassays and the machine-based DNA diagnoses. The ideal formats like that of the immunodiagnostic test-strips would be those that can be applied anywhere at low cost. For this reason I would like to elaborate on two of the concepts we developed both of which are on the basis of direct nucleic acid hybridization.

Direct Flow-through Hybridization

This patented concept and devices spun out of the well-established properties of solution nucleic acid annealing kinetics in the sixties. The fundamental problems that are not achievable in the frequently used solid phase hybridization (e.g. membrane-based or the newly developed microchip on silica glass plates) to give efficient and rapid annealing process are: (1) the low effective concentrations of the probe and the target sequence allowed to make contact with each other to achieve the double-strand formation and (2) the accurate control of stringent conditions for specific hybridization. In the Flow-Through Hybridization process, the probe molecules or the target sequences, in the case of reversed-blot hybridization, are directed towards the complements thereby increasing the speed of diffusion, making all the reagents into close contact with each other for fast and effective interaction possible. (Similar idea has just been reported for use in the DNA microchip technology using electric force, see *Sosnowski et al., 1997.)*. The specificity is controlled by the use of the hybridization device and the media of the assay system. Further details have been disclosed in U.S. Patent #5,741,647. **Figure I** shows the simple arrangement of the flow through hybridization device. The main components consist of the temperature regulated thermal block and the membrane assembly. Automation can be added. The membrane assembly unit can vary to give different forms of testing need, from multiple strips to a single membrane to achieve the microdots formats for high throughput assays. The membrane can be any material that is capable of immobilizing nucleic acid and the detecting probes e.g. nitrocellulose, nylon or their modified forms. For reversed dot blots we used the Biodyne C and the EDC for oligonucleotides probes immobilization. The gasket is made of thermally conducting material for efficient heat conduction and accurate temperature control of the membrane assembly. The temperature block is powered by the Pelter element and is capable of maintaining +0.5 °C. Using the appropriate reaction media and exact conditions the required stringency can be optimized and maintained for very specific hybridization to eliminate non-specific false positive results. The method has versatility to be used for qualitative as well as quantitative measurements and therefore can be applied in the research laboratories and field diagnoses. We have evaluated the method for population screening using the ApoE genotypes as examples. 22 DNA samples isolated randomly from Chinese in Hong Kong were studied. The DNA fragments encoding the ApoE are amplified by PCR. For direct comparison we used the same gene specific primer pair as reported in the literature. The amplified samples were subjected to the conventional restriction analyses and our Reversed-Dot Blot hybridization assays in parallel. The restriction analyses involved first restriction endonuclease digestion followed by gel electrophoresis for the identification of respective retraction fragments for each genotype. In the RDB, four oligonucleotides were designed to detect the two variant sites of the ApoE, and were immobilized onto the membrane in separate dots for capturing the amplified target DNA. The target DNA samples were each amplified with biotin-labeled nucleotide. The hybridization was done on the device as follows: The membrane assembly was maintained at 42°C throughout hybridization process, which included hybridization solutions. (1) Drop 0.5ml of prehybridization solution to block the membrane from nonspecific annealing, (2). 2ml of the denatured DNA samples were allowed to flow though the membrane for specific hybridization to the immobilized probe followed by 3x 0.5ml washing solution. (3) Color development was carried out at 37°C using the streptavidin-HRP system from Sigma. Our data *(Liu and Tam, 1997)* confirmed that the fast hybridization protocol produced exactly the same results as that obtained by the much more costly and time consuming restriction endonuclease digestion followed by gel electrophoresis saparation analysis procedures *(Mak, Y.T. et al., 1996)*. **Figure II** shows the typical hybridization scheme and results. As shown in the inserts we were able to achieve absolute specificity at sub-fmole quantity and simultaneous detection of multiple samples and/or multiple probes by hybridization in a single membrane. Using the reversed dot-blot format, detection of single or multiple point mutations were readily achiev-

able. This method can be easily modified to adapt to the microchip format when the ink-jet technology is used for oligonucleotide immobilization. Evidently this is a general hybridization process that can achieve absolute specificity and sensitivities comparable to or better than the other conventional procedures but requires much less time and reagents. A typical comparison is given in **Table III**, which include data for the Single-step nucleic acids assay described below.

The Single-Step Hybridization Assay

Agglutination assays have been very widely used since it was first discovered in 1901 for blood typing. Most recently rapid agglutination assays for HIV, HBV, H5N1 et. have been developed for routine tests. These tests are gaining in popularity because they are simple, fast and inexpensive. Furthermore single or multiple assay formats can be readily prepared and therefore can be adopted in testing laboratories, point of care or anywhere that is needed without many facilities. However these tests are still confined to the immunochemical formats and therefore results are less informative (e.g. for most infectious diseases) if further confirmation is required. This current limitation has drastically reduced the significance of the advantages of these tests. We have developed the agglutination assay and applied it to testing the analytes of nucleic acids. We used latex particles for the agglutinin because they are well characterized and prepared in relatively uniform and reproducibly. The most crucial factors for successful development of this assay include the design of the oligo, and the immobilization procedures and the reaction medium. The sequence of the oligo-probes together with appropriate reaction medium would ensure specificity. On the other hand, the result of immobilization determines the number and the charges of the immobilized latex probes that will directly affect the stability of the colloidal particles and influence the agglutination process. The reaction principle and the result are illustrated in **Figure III**. Indeed this is a very simple test and our preliminary results indicated that it could be applied to the detection of nucleic acids *(Yan et al., Clinical Chemistry, 1997)*. However in the case of latex colloids the stabilization process still needs to be improved. The most serious limitation is that it may be difficult to differentiate between sequences of high homology. Hence it is ideal for detecting foreign sequences such as infectious agents in the host but not for isogenes or variant mutants. Nonetheless it will certainly be a valuable assay system that should be developed further. Latex or other large particles such as the RBC are most ideal for agglutination assay by visual inspection but the reagents are less stable. Other soluble form (not colloid) of agglutinating probes such as the dextran can be considered for development with suitable monitoring system that can detect the aggregation of smaller particles formed e.g. the aggregometer. With the help such instrument quantitative measurements would be attainable.

Conclusion

DNA diagnostic methods are developing very rapidly. The worldwide attention is mostly focused on the high throughput multiple assay systems and the Microfabrication such as the DNA microchips and the MEMS. Undoubtedly these are the ideal assays for the future because of their capacity and versatility. However, because of the expensive nature of the instrumentation and sophistication they are center oriented and will probably be less useful as point of care or over the counter assays. The electron transfer assay developed by Meade *(1997)* may be the potential candidate for the latter. It is important, however, that simple and rapid and inexpensive diagnostics be developed for bedside, over-the-counter formats so that efficient diagnosis is possible in underdeveloped area where most of our human population reside. For this reason, the two rapid DNA diagnostic methods described above warrant further development. It is clear that they have different applicability and specificity because of their difference in underlining principle and working conditions. The Agglutination assay is most simple and inexpensive but is limited to the detection of distinctly different sequences from the pool e.g. foreign genes. On the other hand, the Flow-through Assay can be made much more specific and is able to differentiate many analytes simultaneously among highly homologous sequences in the same test strip. Potentially, this can be adopted for the Microdot formats similar to Microchip, with the ink-jet technology, to perform in situ dideoxyl-sequencing by hybridization/polymerase reaction. Conceptually, the flow-through hybridization process should produce better signal to noise as well as lower background. This remains to be investigated.

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FIG. 1

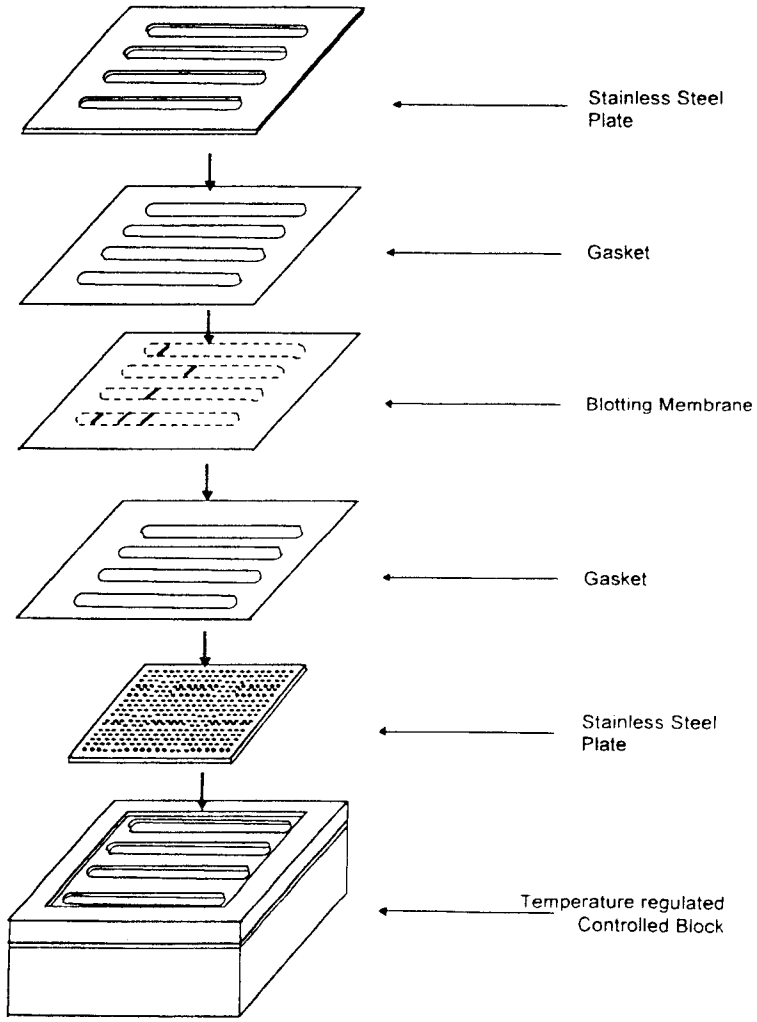


Figure I: This a typical assembly scheme of the Direct Flow-through Hybridization Device. The flow direction can be modified for quantitation and to adopt for microdot format. The device can be upgraded for automation.

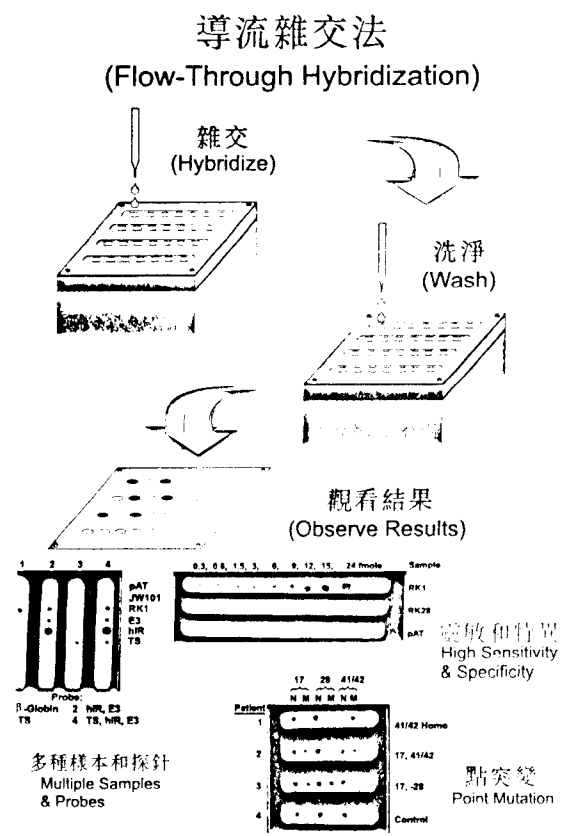


Figure II: The Flow-through Hybridization Process and typical procedures. Typical results shown: (a) upper inserts illustrate the Southern Hybridization format using the Flow-through procedures. DNAs of different sequences were dotted into the membrane, biotinated probe(s) was allowed to flow through the membrane for hybridization followed by color development for visual inspection. DNA sequences used: pAT= plasmid DNA; JW101= human alpha-Globin; RK1= human beta-Globin; E3= human beta-Globin exon-3; hIR= human Insulin Receptor; TS= parasitic Thymidylate synthase; RK28= human beta like Globin sequence. (b) The lower insert shows the Reversed Dot Blot (RDB) format for the detection of single point mutation(s) of Hong Kong Chinese beta-Thalassemic patients. One microliter of 20nt normal (N) and mutated (M) ologonucleotides were immobilized onto the membrane. Patient samples were PCR amplified with biotinated dUTP and allowed to hybridized by Flow-through process followed by color development.

Table I Hybridization Process Used for DNA Analysis

Mutation analysis	Electrophoresis	Microchip	Single-tube assay	Hybridization@ Process
RFLPs				
small and large fragments analysis by Southern etc.	yes	n/a	n/a	required
Sequenceing analysis	yes	*in situ* extension	no	needed for Microchip
HPA and SSCP	yes	may be	yes	required
Microsatellite-repeat or Short-tandem repeat (STR)	yes	n/a	n/a	may required
Complex DNA mixes:				
Randomly amplified Polymorphic DNA	yes	yes	limited*	required
Multiplex amplification	yes	yes	limited*	required
Detecting single-base mutations: (amplified by PCR etc)				
Known mutation				
Single point	yes	yes	yes	not required
Multiple points	yes	yes	yes	may required
Unknown mutations	yes	yes	n/a	required
Allele specific amplification (ASA)	yes	yes	yes	not required
Real time PCR- ASA#	-	-	yes	not required

@ This column represent whether Hybridization is needed for the method used to achieve the final analysis. In the microchip and the single-tube assays and all amplification processes, hybridization is always required.

* In the homogenous solution assays the number of target sequences that can be analyzed simultaneously depends upon the number of chromophores that can be effectively monitored either by differences in wavelength of absorption/emission or difference in kinetic parameters.

Table II: Comparison of the Conventional Hybridisation with the Fast DNA Detection Methods

	Conventional Hybridization	Fast DNA Detection Methods	
	Southern Blot	Direct Flow-through	Single-step
Hybridization Time:	2-12 hrs.	1-5 min.	<0.5 min.
Reagents Used:	100s ml	<10 ml	<0.1 ml
Equipment:	Hybridisation Oven	Special designed Thermal Block	Glass Slide
Cost:	Very high	low	very low
Specificity:	Single Base Mutation	Single base	Nonhomologous Sequences
Capability:	Single probe Multiple probes (RDB)	Multiple genes or probes	Single gene per assay
Sensitivity:	Similar	Similar	Similar
Area of Application:	Research & Diagnosis	Research & Diagnosis	Diagnosis

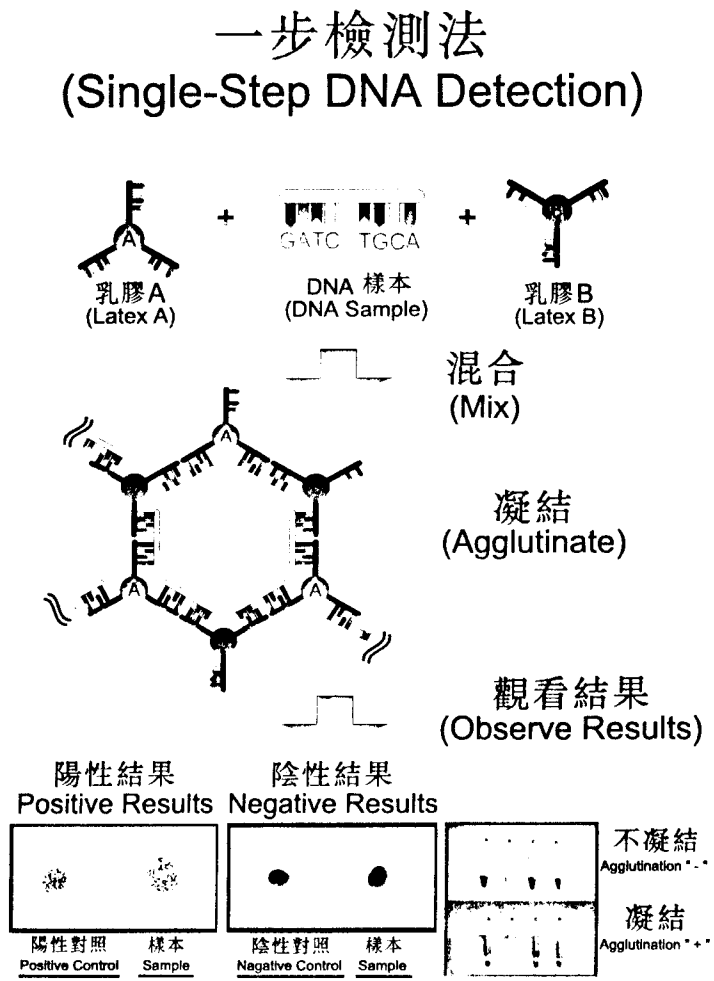


Figure III: The principle and test results of the DNA Single-step Agglutination Assay. Again human -globin DNA sequences were used as examples.

The Private Sector

Chapter 9

The Business of Developing Health Products from Traditional Chinese Medicine: A Private Company's Perspective

By

~ Duncan Mak ~
Scientific Officer
Hong Kong Traditional Chinese Medicine Research Center

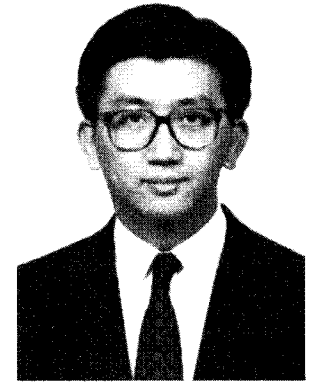
~ Harry Yeung ~
Managing Director
Hong Kong Traditional Chinese Medicine Research Center

~ Cheok Y. Lee, Ph.D. ~
Senior Manager, Human Resources
LLK Health Products Group Limited

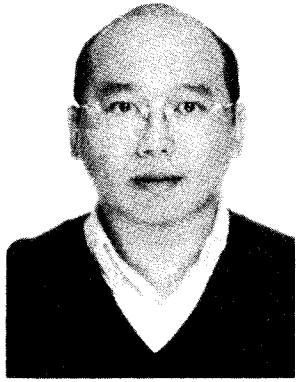
~ Sammy Lee ~
Chairman
Hong Kong Traditional Chinese Medicine Research Center
&
LLK Health Products Group Limited



Duncan H.F. Mak *is scientific officer at the Hong Kong Traditional Chinese Medicine Research Center, and he is involved in the technology transfer of R&D findings to the manufacturing of Traditional Chinese Medicine-based health food products. He holds an M.Phil. in biochemistry from The Hong Kong University of Science & Technology and has been researching the antioxidant properties of Chinese herbs. He has authored a number of scientific papers on this subject.*



Harry K. C. Yeung *is the managing director of the Hong Kong Traditional Chinese Medicine Research Center and general manager of Caring International Group Limited. Yeung has an MBA from The Hong Kong Polytechnic University. He has 16 years of pharmaceutical sales and marketing experience with Glaxo Hong Kong Limited and was general manager there from 1990 to 1994. Yeung is also one of the founding members of The Hong Kong Asthma Society and has been an active executive committee member since 1989.*



***Cheok Y. Lee, Ph.D.**, is senior manager of human resources for LKK Health Products Group Limited in Hong Kong. He also serves on the research committee of the Hong Kong Institute of Human Resource Management. Lee is a graduate of Tulane University. He served as a naval officer in the Republic of Singapore Navy and was an assistant professor at Pepperdine University. Lee has publications in the **Journal of Aging and Physical Activity**, **Physiology and Behavior**, **Neuropsychology**, and **Violence Against Women**, as well as in various abstracts of professional meetings.*



***Sammy W. S. Lee** is chairman of both the Hong Kong Traditional Chinese Medicine Research Center and LKK Health Products Group Limited. The Hong Kong SAR Government appointed him to the Biotechnology Committee to help steer biotechnology development in Hong Kong. Lee is also an executive director of LKK Group Limited, a Hong Kong-based multinational company known for its Chinese sauces and condiments. Lee is a graduate of the University of Southern California.*

Overview of the Global Herbal Market

The competence of Western medicine has substantially prolonged life. However, according to a report by the World Health Organization, cancer, heart disease, and other chronic illnesses are killing more than 24 million people a year.[1] Western medicine alone cannot alleviate the suffering and death caused by poor health.

In many developed countries, the use of alternative approaches to improve general health are on the increase because of the insufficiencies of Western medicine. Among the many alternative therapies, herbal remedies in the form of medicines and health products are becoming increasingly popular.

The worldwide market for natural foods, dietary supplements, herbal medicines and natural-care products was US$46 billion in 1996, with the United States of America and Western Europe each occupying one-third of the marketshare. The Japanese market has an 18% of marketshare, and all developing countries account for less than 15% of the world marketshare.[2] Market growth of 10-15% a year is expected in the United Kingdom and 20-30% in the USA.[3,4] In addition, WHO recognized Japan as having the highest per capita consumption of herbal medicine in the world.[5]

Traditional Chinese Medicine (TCM) has always been well accepted among the Chinese, and its influence is also strong in Europe and Southern Asia, particularly Japan. From 1974 to 1989, there was a 15-fold increase in sales of Chinese medicinal preparations in Japan while the increase in mainstream pharmaceutical products was only 2.6-fold.[5] Similarly, more than 60% of respondents to a Hong Kong survey take TCM for health maintenance or to treat sicknesses; moreover, over 94% of the respondents believe in the curative effects of TCM.[6] Yet, the TCM's variety and its lack of standardization has hindered its acceptance by the educated public. Generally speaking, TCM comes in two forms: prescribed formula and patented medicine. The former refers to loose medicinal materials prescribed by practitioners, whereas the latter refers to finished packaged drugs that make claims. Since the 1980s, patented medicine started to dominate the market and accounted for more than 65% of TCM sales in China.[7] The trend towards packaged drugs or functional food will surely prevail as China's economy continues to boom. With an annual growth rate of some 15%, the expansion of China's drug and health products marketplace has outperformed its overall 10% annual economic growth since 1985.[8]

In 1996, TCM accounted for 40% of the worldwide healthcare market, and there is an increase in the use of herbal medicine in Asia, the U.S. and Western Europe.[7] Businesses in Hong Kong cannot ignore the strong signal for investment in this area. As a matter of fact, Western businesses have already sniffed out the profit opportunities in the Chinese herbal medicine business. Companies such as Nestlé, Vevey, Switzerland; Quaker Oats Co., Chicago; and Unilever N.V., Rotterdam, Netherlands, are actively researching Chinese herbs.[9]

Hong Kong as the Choice Base of TCM Development

From our business point of view, Hong Kong, not China, is the choice base for the modernization and development of TCM.

China, having a population of 1.2 billion (20% of the world population), possesses the largest market as well as unparalleled resources in herbal materials and thousands of years of practical experience in TCM.[1] The development of TCM-based products is only a matter of renovation or modernization, not invention, according to Dr. Robert Ko, Research and Development Director of Hong Kong Traditional Chinese Medicine Research Center.

But there are barriers to modernization. First, there is an important difference in paradigms between the practices of TCM and Western medicine. For example, to treat cancer, Chinese doctors use a complex combination of herbs to combat cancer cells as well as to fortify a patient's immune system, whereas Western doctors focus on applying synthetic compounds that can single-handedly kill cancer cells.[10] Thus, in order to modernize TCM, there is an urgent need to build a scientific basis for TCM and to modernize the manufacturing technology of TCM products.

Another barrier to the modernization of TCM is that much of the critical information used in diagnosis is communicated verbally from teacher to student. The ability to extract and record knowledge from this human-to-human interaction is especially important for TCM growth. Language and cultural differences in teaching, negotiation and conflict resolution are the major obstacles for Western businesses attempting to modernize TCM. The Chinese-based, multicultural nature of Hong Kong (now a Special Administration Region of China) allows it to serve as a bridge between Western technology and TCM knowledge. Because of Hong Kong's proximity to the Chinese hinterland, Hong

Kong can utilize Mainland China's intellectual power in TCM to develop products. In addition, Hong Kong is equipped with the labor and technology know-how for product manufacture.[11]

According to Jing-jie Yu, a consultant with the U.S. National Cancer Institute and associate professor of Beijing Union Medical College, other factors that prohibit China from expanding the TCM market include the lack of funding and facilities to do technologically sophisticated modern studies and its deficiency in the area of commercialization.[10] Hong Kong – Asia's capital of unrepentant capitalism and the gateway to China, with its business and technology know-how, can fill that bill.

Status of TCM Development in Hong Kong

Hong Kong's advantageous geographical location, cultural uniqueness and business environment provide a great advantage for the modernization of the TCM industry. Success, however, would depend heavily on the availability of infrastructure and support from the scientific community, industries and the government.

The emergence of Hong Kong as a base for the modernization of TCM began in 1979, when the Chinese Medicinal Materials Research Center (CMMRC) was established at The Chinese University of Hong Kong. While CMMRC has focused on the basic research of Chinese herbs, it was not until 1988, following the opening of the Hong Kong Institute of Biotechnology, that TCM was recognized as one of the industries that can flourish in Hong Kong. The pace of TCM development progressed even further in April 1995 when the Preparatory Committee on Chinese Medicine advised the government on the statutory framework for the promotion, development and regulation of TCM. Abetted by the active support of the government in recent years, more and more TCM-related institutions have been set up *(See* **Table 1***.)*.

Barriers to TCM-Based Pharmaceutical Entry Into Major Western Markets

In a report on Hong Kong's biotechnology industry, Wang et al. recommend that Hong Kong should place TCM in the position of highest priority among all other categories of biotechnology in order to be competitive.[12] However, they also report that most of the TCM companies currently chose to market their goods

Table 1. Institutions in Hong Kong that Support or Participate in TCM Research

NAME OF INSTITUTION	STARTUP YEAR	MAJOR SOURCE OF FUNDING	MISSION AND OBJECTIVES
Chinese Medicinal Material Research Center (CMMRC) (at Chinese University of Hong Kong)	1979	University Grants Committee (UGC), Hong Kong Jockey Club, Croucher Foundation Hong Kong Government Industry Department	- to document and evaluate the efficacy of TCM - to explore better application of TCM - to upgrade the scientific contents of TCM
Hong Kong Institute of Biotechnology (HKIB)	1988	Hong Kong Jockey Club	- to provide the essential infrastructure and to act as a catalyst for the emergence of biotechnology industry in Hong Kong - to generate proprietary downstream processing technologies and transfer them to the commercial sector
Biotechnology Research Institute (BRI) (at Hong Kong University of Science and Technology)	1990	Hong Kong Jockey Club	- to support and co-ordinate basic and applied research in biotechnology - to facilitate research collaboration among Asia-Pacific countries and overseas institutions
Hong Kong Traditional Chinese Medicine Research Center (HKTCMRC) (at Hong Kong University of Science and Technology)	1996	A collaborative research venture between Lee Kum Kee Group Ltd. and HKUST	- to promoting research on Chinese herbal medicine particularly those used for safeguarding health - to establish the efficacy of proprietary Chinese herbal medicine products by scientific methods - to safeguard consumers' interests by standardizing the efficacy and safety of proprietary Chinese herbal medicine products
Traditional Chinese Medicine Safety Information Center (TCMSIC) (at Hong Kong University of Science and Technology)	1996	Industrial Support Fund	- to disseminate safety information and requirements - to furnish scientific data from the literature on TCM products and their ingredients - to analyze the available data and advise on safety issues - to coordinate the acquisition of new test data through referral to appropriate laboratory facilities - to conduct seminars and forum to promote safety awareness and scientific development of TCM products
Hong Kong Pharmaceutical Technology Center (HKPTC) (at HKIB)	1997	Industrial Support Fund	- to assist the local pharmaceutical industry in meeting existing Good Manufacturing Practice (GMP) requirements in manufacturing according to the HKSAR Government - to serve local industry to develop and upgrade pharmaceutical technologies in Hong Kong
Institute for the Advancement of Chinese Medicine (IACM) (at Hong Kong Baptist University)	1997		- to facilitate the basic, applied, and clinical research of Chinese medicine (CM) - modernization of CM-based industry through collaboration with the industrial and business organizations

as food products because of the great resources required to surmount the stringent regulatory requirements in major markets.

The many barriers to entry given by Wang et al. include: stringent regulatory environment; huge financial investment; 5-to-10-year lead time in the development cycle; and the lack of financial reimbursement by U.S. and European health care systems.

TCM-Based Health Products Versus Pharmaceuticals

From our business perspective, we agree that the pharmaceutical business is very lucrative; however, we wish to point out that the potential earnings from marketing health food products is as good, perhaps even better. Specifically, we think Hong Kong companies wishing to exploit the full market potential of TCM can instead concentrate on the development of TCM-based health products.

Pharmaceutical products must achieve very high quality standards for safety and efficacy in order to pass stringent regulatory requirements before they can be sold in Western markets. The 5-to-10-year lead time required for pharmaceutical research means that return on investment can only be realized much later. On the other hand, health food's short cycle from development to marketable product is a definite plus. Furthermore, investing in health food instead of pharmaceutical can lead to faster financial returns. The cumulated amount of investment also is significantly smaller for health food product development than for pharmaceutical development.

The West's restrictions on sales of over-the-counter drugs and prescription medications are no help to smaller TCM companies. If drug development is not successful, the potential losses are huge.

This is not so with health food products because health products undergo less-stringent regulatory controls. Moreover, many companies have been very successful in using direct-selling methods to market their health products. Given direct-selling's high potential for explosive growth, TCM-based health products can clearly benefit. Companies in Hong Kong, such as LKK Health Products Group Limited, have applied this technique to marketing and sales. So far, the outcome is encouraging.

Since reliance on TCM or herbal medicine is learned through socialization, there is a vast existing market of Chinese, Japa-

nese, and some European (such as German and French) consumers. The penetration of TCM-based health food products into these cultures and markets will be much easier than marketing to highly regulated Western countries.

In the next millennium, the concept of health will perpetuate a market trend toward preventive means such as regular exercise and the consumption of health products. We can see this happening as more and more people buy exercise gear, eat health foods and take dietary supplements.

The climate is ripe for TCM health food products to be marketed in force. Disease prevention from the regular consumption of TCM health food products has always been accepted by the Chinese and Japanese. Now the Germans, French and Americans are also buying into alternative therapies and herbal medicine for disease prevention and treatment. Furthermore, the variety of health food products that can be manufactured from a single TCM prescription can hardly be matched by pharmaceuticals.

The Role of Lee Kum Kee in the Research, Development and Commercialization of TCM

Founded in 1888, Lee Kum Kee has since been renown for quality sauces and condiments as part of its mission to promote Chinese cuisine and culture around the world. Recent business diversification by Lee Kum Kee has resulted in the formation of LKK Health Products Group Limited.

The LKK Health Products Group Limited is involved in research and development, manufacturing, and the marketing and sales of health products. The business aims to promote the international acceptance and wider use of TCM remedies and natural health food supplements. According to Mr. Lee Man Tat, Group Chairman of LKK Group Limited, LKK Group's corporate vision is to become one of the top 10 multinational conglomerates in Hong Kong by the year 2000, promoting Chinese gourmet to people around the world, and transforming traditional health products through scientific methods.

TCM Activities in Mainland China

Guangdong Nanfang Lee Kum Kee Health Products Company Limited, a joint venture between Lee Kum Kee and the First Military Medical University of the People's Republic of China was the first member of the LKK Health Products Group Limited. Both joint venture partners have their unique expertise: The First Military Medical University has extensive experience in TCM research, and Lee Kum Kee has a solid foundation in manufacturing and the distributing food products globally. The joint venture created a company with strong research and development, as well as manufacturing and marketing ability. Given the aging population and the increasing consciousness of Chinese toward maintaining health and preventing illness, the company has identified TCM-based health products as its research and development direction.

The first product developed by the joint venture was Infinitus Health Tonic. The product was launched in China in late 1994. The test marketing of Infinitus through conventional methods (newspaper advertisements and drug store promotions) was, however, not successful. However, Infinitus Health Tonic was highly commended by consumers who took it regularly. The unsuccessful initial product launch was due to a failure to promote its benefits to consumers through conventional advertising efforts.

To tackle this challenge, the company discontinued distribution through drug stores and introduced a direct-selling mechanism. Product knowledge seminars and self-education reading materials were offered to direct-selling members who were users themselves. Coupled with an attractive reward scheme and effective training program, the business has since enjoyed unprecedented growth in sales and membership.

Currently, the company is building its second manufacturing plant, implementing Total Quality Management and aggressively preparing itself for ISO 9002 International Quality Accreditation. The company is committed to further investing in research and development to expand its health product line.

Guangdong Elite Elegance Consumable & Health Products Company Limited, based in Cong Hua City, China, is another member of LKK Health Products Group Limited. Elite Elegance is responsible for research, development, manufacturing and sales of health and personal care products.

TCM Activities in Hong Kong

Inspired by early success in the commercialization of TCM research, Lee Kum Kee is enthusiastic in considering new projects relating to TCM research. At the Hong Kong University of Science and Technology, the Biotechnology Research Institute has supported research by Dr. Robert Ko to isolate the active ingredient in a Chinese herb believed to provide protection against coronary heart disease and possibly to retard the aging process. In May 1996, Lee Kum Kee reached an agreement with The Hong Kong University of Science and Technology to establish the Hong Kong Traditional Chinese Medicine Research Center (HKTCMRC) on the HKUST campus.

The HKTCMRC collaborative research venture is the first of its kind in Hong Kong between industry and academia in the development of TCM. Its aim, according to the Center's Research & Development Director, Dr. Ko, is to modernize TCM by establishing the efficacy and safety standards of herbal formula used for safeguarding health. Eventually, the stringent research & development roadmap will confer upon health food supplements developed from TCM a high level of quality assurance. This, in turn, will enable such products to meet international regulatory requirements. The Center has appointed prominent Mainland experts as consultants, giving it access to the vast source of TCM knowledge in China.

NDA, Newly Discovered Antioxidant, and Bio-Sports are the two products developed by Hong Kong Traditional Chinese Medicine Research Center and they are now being sold. Currently, the Center publishes a biannual TCM Net and is creating a website to promote TCM worldwide.

Caring International Group Limited is yet another member of LKK Health Products Group Limited. It handles worldwide business development. Another company, Caring International (Hong Kong) Limited, was formed in 1996 to launch NDA and Bio-Sports through direct selling.

Advancing TCM from Hong Kong to the Global Market

Although the development of standardized TCM-based health products is still in the early stages, a niche market for a new generation of TCM health products is emerging and this offers great business opportunities for the TCM industry. As indicated in China's ninth five-year economic plan (1996-2000), biotechnology is a key element in the country's economic development.[13] Researchers at the Massachusetts Institute of Technology also consider TCM to be an area in which Hong Kong could be a major player.[12] Another competitive advantage Hong Kong has over its rivals is its proximity to China, where a vast source of TCM knowledge is available. Under the S.A.R. Government, there are plans to regulate TCM practitioners and products and to turn Hong Kong into an export center for Mainland TCM products. Local companies are encouraged to draw resources from their Mainland counterparts.[13] Credit should be given to the Hong Kong Industry Department for steering the development of biotechnology through a Biotechnology Committee and offering monetary support through the Industry Support Fund, the Applied Research and Development Scheme, and the Cooperative Applied Research and Development Scheme. However, Hong Kong is lagging far behind Taiwan, Japan and Korea in the value-added processes of TCM. If Hong Kong wants to succeed in the TCM industry, there should be more government support and collaboration between researchers and industrialists in Hong Kong and across the Mainland border. The existing Hong Kong industrial players, including Lee Kum Kee, should carefully consider expanding their research investment in upgrading TCM-based health products to patented medicine. This will allow investors to tap into yet another segment of the global TCM market.

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Chapter 10

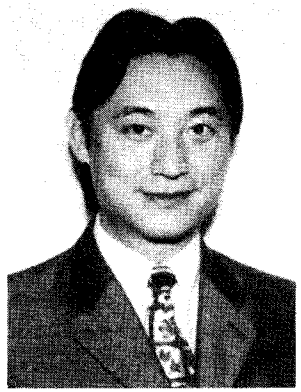
The LifeTech Group and Its Vision of Biotechnology in Hong Kong and China

By

~ Dominic Man-Kit Lam, Ph.D. ~
Chairman & CEO
LifeTech Group of Healthcare Companies, Hong Kong

With
~ Olivia Yee-Yee Lam ~
LifeTech Group of Healthcare Companies, Hong Kong

~ Wilson Fong Lam ~
LifeTech Group of Healthcare Companies, Hong Kong



***Dominic Man-Kit Lam**, Ph.D. is chairman and ceo of LifeTech Enterprises, Inc. in Hong Kong. His company selects and brings Eastern and Western medicines together and markets them first in China and, subsequently, worldwide. Lam received a B.Sc. in mathematics from Lakehead, an M.Sc. in physics from UBC, his a Ph.D. in medical biophysics, and did postdoctoral training at Harvard Medical School in Cambridge, Massachucetts. Lam was the founding director of the Hong Kong Institute of Biotechnology. He received an Medal of Merit from U.S. President George Bush in 1989 and was invited to be on the President's Inner Circle, and advisory group the the President. Lam has been an assistant professor at Harvard Medical School; a professor of biotechnology, cell biology and ophthalmology at Baylor College of Medicine in Houston, Texas; and an honorary professor at the Chinese Academy of Science. Lam also helped bring Project Orbis, the Flying Eye Hospital, to China.*

***Olivia Yee-Yee Lam** graduated from The University of Texas in Austin with a B.S. in biology and English.*

***Wilson Fong Lam** is majoring in pre-medicine at The University of Texas in Austin.*

Introduction

Although I grew up in Hong Kong during the '50s and '60s, my first exposure to Hong Kong's life sciences programs did not occur until 1970, when I was invited by Professor Joseph Hwang, then Chairman of the Department of Physiology at the University of Hong Kong to give a lecture on my ophthalmic and neurobiological research. In the late seventies, Professor Y.C. Kong of The Chinese University of Hong Kong and I collaborated on a series of studies regarding the development of the vertebrate retina.[1-5] In October 1982, the founder of Project Orbis, Dr. David Paton, and I brought the now well-known international flying eye hospital to Hong Kong and then to Guangzhou during Orbis' first year of operation.

In 1988, at the invitation of Professor Yang Chen Ning and Professor Charles Kao, then Vice Chancellor of The Chinese University of Hong Kong, I became the founding director of the Hong Kong Institute of Biotechnology (HKIB), a non-profit organization aimed at developing a biotechnology industry in Hong Kong. In this effort, Professor Sir Harry Fang played a vital role in helping to secure a HK$170 million grant from the Hong Kong Jockey Club for the establishment of HKIB. Dr. Albert Chang, whose excellent article about the current status and future goals of HKIB is described elsewhere in this book, now directs the institute in a most capable and successful manner.

Although I began visiting and giving lectures in China in 1980 and became Honorary Professor of the Chinese Academy of Science in Shanghai in 1985 as well as Visiting Professor of Dr. Sun Yat Sen Medical University in Guangzhou in 1986, it was not until my tenure as director of HKIB (from 1988 to 1992) that I began visiting and analyzing China's academic and commercial organizations of life sciences in a more systematic manner. A result of these visits was the formation of a joint venture on drug discovery which included HKIB, Institute of Organic Chemistry in Shanghai, the Institute of Microbiology in Beijing and Syntex Corporation of Palo Alto, California (since acquired by Roche). I also gained considerable insight on the strengths and weaknesses of China's biotechnology projects and its commercialization efforts. It was then that my hope of helping China build a strong biotechnology industry began to germinate.

The Birth of LifeTech

Accordingly, in 1992, I decided to resign as HKIB's director. The institute was fortunate to recruit Professor K.P. Wong from California as the next director. In 1993, I started LifeTech Enterprises Ltd., a healthcare company incorporated in Bermuda, with technologies and products we developed or acquired in the U.S. The initial investment of US$1 million came from the Hong Kong Concord Enterprises Co., Ltd., a corporation owned by Canadian Eastern Finance Investments Ltd., Cheung Kong (Holdings) Ltd., Hutchison Whampoa Ltd., and several entities from Mainland China. LifeTech went public in 1997 by acquiring a U.S. public company through the investment banking firm of Laidlaw Southwest in Houston. LifeTech has a distinguished board of scientific advisers chaired by Professor Torsten Wiesel, president of Rockefeller University and a Nobel laureate in medicine. The other board members include Dr. Jere Goyan, former commissioner of the U.S. Food and Drug Administration, and Mr. Luc Tissot, former president of the Swiss Academy of Engineering.

The mission of LifeTech was to select and bring the best of Eastern and Western medicines together and to market them first in China and, subsequently, worldwide. LifeTech's operations were divided into the following sections: (1) research and development, (2) manufacturing and (3) marketing.

In order to achieve these objectives efficiently with limited LifeTech human resources, the company first formed a number of majority-owned joint venture operations or partnerships in key regions of China, including Tianjin and Beijing in the north, Kunming in the west, Guangzhou and Shenzhen in the south and Shanghai in the east. In addition, besides its in-house R&D projects, LifeTech also established collaborations with multinational pharmaceutical and biotechnology companies, such as Schering-Plough of New Jersey, Boehringer Mannheim of Germany and Tularik of California, on drug discovery programs using extracts from plants indigenous to China.

LifeTech's initial product lines include nutraceuticals (health foods) such as herbal lozenges; phytopharmaceuticals (herbal medicines) such as respiratory, gastric and gynecological products; Western pharmaceuticals such as ophthalmic solutions; and antibiotics and home diagnostic devices. These products are either manufactured by LifeTech in China, or manufactured for LifeTech by leading healthcare companies such as Boehringer Mannheim.

LifeTech's products are sold in China by the company's joint venture partners there. LifeTech began marketing its products outside China in 1997 under agreements with two leading Asian companies, the A.S. Watson Group, which is owned by Hutchison Whampoa (a LifeTech shareholder) and has about 600 stores in Asia, and Eu Yan Seng (a LifeTech shareholder and a herbal medicine company), under the "Watson's" and "Eu Yan Seng" brand names, respectively.

Immediate Future of LifeTech

For 1998 and the foreseeable future, LifeTech plans to expand the aforesaid operations in R&D, manufacturing and marketing. For R&D, the company is considering the establishment of several new programs in China, including (1) the identification and commercial development of a series of "anti-aging" nutraceuticals and pharmaceuticals targeted for the ever-increasing over-40 population; (2) the identification of natural products and their active ingredients as novel medicines or as better substitutes for existing pharmaceuticals; and (3) the use of recombinant DNA technology to produce edible transgenic plants for the manufacture and oral delivery of medicines to for humans and animals. [6-8]

In the area of manufacturing and new product identifications, LifeTech has established a manufacturing company in Hong Kong and plans to have some of its products manufactured here in the next year or so, especially for territories like Taiwan, which does not permit the importation of products made in Mainland China. Additionally, for some of LifeTech's anticipated bestsellers, the company intends to retain full control of its production and quality by managing its own manufacturing facilities.

In the area of marketing, which is currently of paramount importance to LifeTech's commercial success, the company intends to create its own brand-name products, initially concentrating on two product lines: (1) respiratory and (2) immune-enhancing and/or anti-aging. The LifeTech respiratory series is based on a combination of Chinese and western medicines. The company anticipates that, besides the launch of LifeTech's herbal lozenges in spring 1998, initially in Hong Kong and, subsequently, in Mainland China, at least two other products will be introduced later this year. Similarly, two or three natural and well-proven (but little known in China) "immuno-enhancing and anti-aging"

products will be launched under LifeTech's brand name in May 1998. LifeTech believes that both could be important product lines for Hong Kong and China, especially in view of the recent concerns associated with diseases such as the so-called "H5N1 chicken flu" in this part of the world. In our effort to successfully launch LifeTech's own brand-name products, the company is working closely with Bates Hong Kong Ltd., a major advertising company in Hong Kong and China, to better develop the company's image and to position LifeTech's products in the marketplace.

LifeTech and Biotechnology in China

It is well recognized that biotechnology and life sciences will be one of the most important global industries in the 21st Century. This is especially true for China because (1) China has a huge agricultural industry and population; (2) the per capita spending on healthcare in China is still a fraction of that in developed countries but is increasing rapidly; (3) China probably has the greatest human and natural (e.g. herbal) resources in the world to support a first-rate biotechnology industry; (4) the governments and major corporations in Hong Kong and China certainly have the financial resources to support the establishment of such an industry; (5) the commercialization of novel biotech-based technologies and products is still in its infancy in China; (6) being home to a quarter of the world's population, China certainly has the market for the successful commercialization of its own home-grown biotech products. Thus, China is in an excellent position to become a major power in biotechnology.

However, serious obstacles and concerns also need to be addressed in order to facilitate the commercialization of biotechnology in China. First, although the Chinese Government, through its numerous agencies, such as the Academy of Science, Ministries of Public Health and Agriculture, Science Council etc., provides a large number of research grants to bioscientists and their academic institutes, as well as for the commercialization of certain biotech projects (e.g. the Star Fire Plan), support for the latter has been rather insignificant. It is recommended that the government, at both the central and municipal levels, consider the establishment of grants, contracts, loans or other means specifically targeted for the commercialization of important biotechnology projects, especially those that could potentially be patented internationally. Such grants and awards play an important

role in the success of the biotechnology industry in the U.S. For instance, at the federal level both the National Institutes of Health and the National Science Foundation have many peer-reviewed small business innovative research (SBIR) grants of between US$50,000 to US$1 million given directly to biotechnology companies for the commercialization of their projects. Likewise, the Department of Commerce and the U.S. Armed Forces also give million dollar grants to institutions and companies for developing biotech projects. At the state level, many states have similar award programs. For instance, Texas supports biotech commercialization by giving advanced technology grants to university – corporation partnerships. While it is recognized that the Chinese Government may not have similar financial resources or priorities for aiding in the commercialization of its biotech projects, even modest programs for this purpose would be an important boost to the Chinese biotech industry. In this regard, the Chinese government might also consider the establishment of matching grants programs in which the government and a Chinese or foreign company each invest in the commercialization of a biotechnology project in China.

Secondly, the biotechnology industry in the U.S. has also benefitted greatly from the availability of billions of dollars of venture capital and other investment vehicles to fund the establishment and growth of biotech companies. In addition, many multinational pharmaceutical companies also support or invest in biotech companies. In contrast, there are relatively few such financial resources in China. The advancement of venture capital and other funds targeted for biotechnology in China would therefore be another significant step towards the establishment of China's biotech industry.

Thirdly, the development and commercialization of a novel biotech product is often a very expensive and time-consuming process. Extreme caution must therefore be taken to assure that the intellectual property of such a product and its associated technologies are well protected, most preferably through patents, but also with proprietary trade secrets and knowhow. If possible, such protection must apply to as many countries as possible. In this regard, it is especially important that the inventors pay particular attention not to jeopardize the patentability of their product or technology, for instance, by prematurely publishing or disclosing their inventions. It is therefore preferable that, at the earliest opportunity, China-based biotech companies and institutions that intend to develop a novel biotech product for the worldwide mar-

ket obtain legal counsel from attorneys familiar with international patent and trademark laws.

Finally, the communication of biotech projects requires a strong management team familiar with the many disciplines that must come together for the successful marketing of a biotech product. These include knowledge of intellectual property protection, business and commercial development, regulatory affairs, and commercial-scale GMP manufacturing, as well as distribution and marketing strategies.

The most important lesson for doing biotech business in China and the Far East is to identify the correct business partner in each venture, one that is honest, dedicated, knowledgeable in the business and in the political environment, and well-enough connected to ensure that the project proceeds without excessive bureaucratic obstacles.

In conclusion, the development of a major-league biotechnology industry in China and Hong Kong is a very exciting and realistic opportunity. LifeTech hopes to be a part of such an establishment.

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The Role of Government

Chapter 11

Government Support for the Biotechnology Industry in Hong Kong

By

~ Francis Ho ~
Director-General of Industry
Government of the Hong Kong Special Administrative Region



Francis Ho *is Director-General of Industry of the Hong Kong SAR Government. He is responsible for Hong Kong's industrial development. Since 1976, he has also held senior administrative posts in constitutional affairs, social services, environmental protection, and trade policy. Ho has a bachelor's degree in science, and has pursued advanced studies in public administration at Oxford University in the United Kingdom.*

Introduction

Only some 10 years ago, biotechnology as an industrial sector was almost unheard of in Hong Kong. It is not an exaggeration to describe biotechnology as an academic discipline then, without much relevance to Hong Kong's economic development. In the past, we only had the food and beverage industry and a small pharmaceutical and Traditional Chinese Medicine (TCM) industry. Many of the establishments in these sectors were small, and they were mostly family-owned businesses. Diagnostics, vaccines and biopharmaceutical manufacturing never came into the community's mind as commercial propositions.

However, with the growing awareness that Hong Kong must move toward higher value-added and knowledge-intensive economic activities, people are beginning to realize that biotechnology is likely to be a niche area for Hong Kong. Given that it is neither labor-intensive nor land intensive, biotechnology ties in with Hong Kong's own strengths and avoids Hong Kong's physical constraints. Biotechnology thus embraces Hong Kong's own competitive advantages. Recent years have witnessed a continuous effort on the part of all parties concerned to focus on the development of biotechnology and related industries in Hong Kong.

Our Fundamental Principle

The Hong Kong Special Administrative Region (HKSAR) Government's industrial policy is to create, within the framework of a free market, an environment that is most conducive to the development and prosperity of businesses. We are committed to providing the necessary physical, human and technological infrastructures, to supporting applied research and development, to facilitating technology transfer and upgrading, and to maintaining the most business-friendly environment. In short, we assume the role of a support service provider and facilitator.

Infrastructural Support

The most significant biotechnology development in Hong Kong took place in 1988 with the establishment of the Hong Kong Institute of Biotechnology.[1] Its mission is to provide the catalyst and support for the emergence of a local biotechnology industry and to provide downstream research and development support for the commercialization of biotechnology products. It is now

engaged in a whole range of industrial support activities, such as assisting researchers in commercializing their research results, transferring technologies involved in the manufacturing of vaccines and biopharmaceuticals, and providing technical support for local pharmaceutical firms to comply with Good Manufacturing Practice (GMP) requirements. It also runs an incubation program which assists biotechnology start-ups with reduced rents, communal laboratory facilities and other business or technical support, including arranging liaisons with prospective business partners in Mainland China and overseas.[2]

In addition, the Biotechnology Research Institute was established in 1990.[3] Its mission is to assist Hong Kong in its economic development and, in so doing, contribute to the economic well-being of the Asia-Pacific region through research, development and training of specialists in biotechnology. This is done by initiating research projects, encouraging cooperation among government, academia and industry, and attracting world-class scientists, hence creating the capital and reservoir of human resources necessary to spawn progress in this new area. Its major activities include research in neuro-proteins, protein engineering and design, plant biotechnology and TCM.

Another example of infrastructural support is the establishment of industrial estates for use by all types of industry. The Hong Kong Industrial Estates Corporation is a statutory body set up in 1977 to develop and manage industrial estates in Hong Kong. It offers developed land at cost on its industrial estates to industries with new or improved technology and processes which cannot operate in multi-story factory buildings. In this way, the corporation facilitates industrial development by broadening its base and upgrading technology levels. The corporation currently has three industrial estates, the total area of which is 210 hectares.[4] To ensure we will be able to meet the continuing demand for special industrial land, we are now planning a fourth industrial estate. There are currently only a few biotechnology companies in these industrial estates, and most of them are pharmaceutical companies.

We are also actively planning to develop a science park in Hong Kong. By bringing together local and overseas companies with technological competence, the science park will help nurture indigenous, technology-based companies, promote technology transfer and enhance regional cooperation in technological development. We envisage that the science park will take up some 22 hectares of land, and that it will be developed in phases over a period of 15 years.[5]

Other infrastructural support facilities which we have put in place in recent years are the Drug Delivery Technology Centre; the Laboratory for the Quality Control of Chinese Medicine and Health Food; the Manufacturing Technology Centre for Human Vaccines and Biopharmaceuticals; the Traditional Chinese Medicine Centre for Drug Development, Safety Standardization and Reformulation; the Laboratory for Chinese Material Medica Standardization; and the Hong Kong Pharmaceutical Technology Centre.

The Drug Delivery Technology Centre's mission is to introduce advanced drug-delivery manufacturing techniques that would enable local pharmaceutical manufacturers to introduce proprietary products with special delivery properties at an affordable price. It is located at the Hong Kong University of Science and Technology (HKUST), Clear Water Bay, Kowloon, Hong Kong, Tel: (852) 2358-7288, Fax: (852) 2358-3978.

The Laboratory for the Quality Control of Chinese Medicine and Health Food is equipped with state-of-the-art equipment to conduct definitive assessment and determination of various components of TCM or health food products. It is located at the Chinese Medicinal Material Research Centre of The Chinese University of Hong Kong (CUHK), Shatin, New Territories, Hong Kong, Tel: (852) 2609-6140, Fax: (852) 2603-5248.

The Manufacturing Technology Centre for Human Vaccines and Biopharmaceuticals is the only GMP pilot manufacturing facility for human vaccines and biopharmaceuticals, and it has the capability to manufacture clinical-grade, bio-engineered materials for Phase I, II and III clinical trials in Hong Kong. The primary functions of the center include developing pre-GMP production and GMP pilot manufacturing technologies of microbial products; developing quality-control tests for bioengineered products; and providing GMP contract manufacturing services to local and overseas clients. The center is managed by the Hong Kong Institute of Biotechnology, Ltd., 2 Biotechnology Avenue, 12 Miles, Tai Po Road, Shatin, New Territories, Hong Kong, Tel: (852) 2603-5111, Fax: (852) 2603-5012, e-mail: enquiry@hkib.org.hk.

The Traditional Chinese Medicine Centre for Drug Development, Safety, Standardisation and Reformulation provides supporting scientific documentation on TCM efficacy and safety and explores new therapeutic potential of existing TCM. It develops new TCM drugs and provides strategic planning and coordina-

tion for marketing TCM products. Another major task of the center is to liaise with pharmaceutical companies for joint ventures in the development of TCM products. The center is operated under the Biotechnology Research Institute of the Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong, Tel: (852) 2358-7290, Fax: (852) 2358-1552.

Chinese Material Medica Standardisation is a project to establish standards of 10 selected materials through chemical studies as well as an information base of chemical components derived from TCM materials with healthcare and therapeutic value. It also harmonizes internationally the standards of those TCM materials through a regional consortium and seeks to obtain novel pharmacologically active substances, single compounds or mixtures to further develop new drugs or dietary supplements. The project is being carried out by the Department of Chemistry at Hong Kong Baptist University, Kowloon Tong, Hong Kong, Tel: (852) 2339-7066, Fax: (852) 2339-7347.

Hong Kong Pharmaceutical Technology Center provides local manufacturers with information on means to comply with GMP guidelines. Technical services and GMP training workshops will also be provided to the Hong Kong pharmaceutical industry. The center is managed by the Hong Kong Institute of Biotechnology, Ltd., 2 Biotechnology Avenue, 12 Miles, Tai Po Road, Shatin, New Territories, Hong Kong, Tel: (852) 2603-5111, Fax: (852) 2603-5012, e-mail: enquiry@hkib.org.hk.

Human Resources Development

For technology development, the most important factor is the quality and capability of the people. Well-trained and technologically competent human resources are vital for the development of a healthy biotechnology industry. Hong Kong is therefore committed to providing a comprehensive system of education and vocational training to help develop the full potential of our young people and to equip our workforce with the necessary knowledge and skills.

We have made substantial investments in education over the past few years. The 1990s witnessed a significant expansion of our higher education program. In the early 1980s, less than 5% of 17-to-20-year-olds had the opportunity to receive tertiary education. The proportion has increased to 18%. The eight institutions funded by the University Grants Committee (UGC) are now offering 15,000

first-year first-degree places each year. Of these, over 1,000 belong to biotechnology and related disciplines. The well-educated young graduates of these institutions are the future leaders of our economy. They are receptive to new ideas and are prepared to work in new technological environments.

As for training at the technician and craftsman level, the Vocational Training Council provides a wide range of full-time and part-time technical education and industrial training programs in different disciplines.[6] Both full-time and part-time biotechnology-related training courses at High Diploma, Diploma and Certificate levels are offered by the Vocational Training Council. Subjects include applied biology, pharmaceutical technology, environmental technology, waste management, and food and science technology. In addition, the New Technology Training Scheme was established in 1992 with a funding injection of HK$105 million from the government. Its objective is to provide assistance to local companies which intend to train their staff in new technologies or new production processes. The New Technology Training Scheme supports training in aquaculture technology, bioelectronics technology, biofertilizer technology, biopesticide technology, biosensor technology, fermentation technology, floriculture technology, food technology, horticulture technology, instrumentation engineering, medical diagnostics technology, pharmaceutical technology, tissue technology, and transgenic technology.

Support for Research and Development

Research and development is obviously one of the most essential elements if we wish to encourage scientific development and build a biotechnology industry in Hong Kong. To this end, the HKSAR Government has made substantial investments in both academic and applied research. Academic research is important because we firmly believe a strong research base in our tertiary institutions will help provide new knowledge and ideas which will eventually be turned into applied technology.

For this reason, the Research Grants Council (RGC) was established in 1991 under the aegis of the UGC.[7] The role of RGC is to advise the government, through the UGC, of the needs of tertiary institutions in the field of academic research, with an aim toward developing a research base adequate to maintain academic vigor pertinent to the needs of Hong Kong. It helps universities develop their research cultures through various ways, such as al-

locating funds for research projects, acquiring major facilities which they could not otherwise afford, and encouraging collaboration between institutions in Hong Kong and overseas.[8]

While academic research plays an important role in the development of science and technology, it is equally important to ensure that the economy will be able to benefit from its application and commercialization. Various funding schemes have therefore been set up to help local industry support bodies and private companies carry out research and development programs.

In 1994 the Industrial Support Fund (ISF) was set up to support projects which are beneficial to the industrial and technological development of Hong Kong. To date, more than HK$1.3 billion has been committed for some 371 projects.[9] Of these projects, 101 are biotechnology related. The funding commitment for these 101 projects is over HK$310 million. This actually accounts for almost a quarter of the total approved funding under the ISF, and has grossly outnumbered other industrial sectors, whether in the number of applications, number of approved projects or in terms of the total funding commitment.[10]

Furthermore, we run a venture capital scheme called the Applied Research Fund.[11] The Fund provides funding support, in the form of loan or equity participation, to local companies to carry out technology ventures, applied research or product development projects. The Fund has so far supported 26 projects, of which five are biotechnology projects. We believe the scheme will induce more companies to engage in applied research activities and nurture and upgrade the technological capabilities of our workforce. The biotechnology industry will again benefit from this initiative.

Intellectual Property Rights Protection

Another essential element for the promotion of research and development in biotechnology is intellectual property protection. To promote the spirit of invention, innovation and technological development, we need to ensure that there is a robust regime for the protection of intellectual property rights so that inventors and researchers can protect and exploit economically the results of their endeavors. We have recently enacted new legislation for the protection of patents, industrial designs and copyrights to ensure that our regulatory regime is in accordance with the prevailing international standards for intellectual property rights protection, including the Trade-Related Aspects of Intellectual Property Rights (TRIPS) under the World Trade Organization. Prior to July 1997, patents, copyrights and industrial designs were protected by extension of the relevant United Kingdom legislation to Hong Kong. In June 1997, the Legislative Council enacted the first fully localized and independent legislation on patents, copyright and registered designs in Hong Kong. Hong Kong now has its own local legislation for the protection of patents, copyrights, trademarks, registered designs, and layout designs of integrated circuits, while other intellectual property rights, such as trade secrets, are adequately protected under common law. The relevant intellectual property laws of Hong Kong and their features are as follows:

Patent Ordinance. This ordinance enables the granting of an independent patent in Hong Kong based on patents granted by the Chinese Patent Office, the U.K. Patent Office or the European Patent Office. The patent will be capable of being tested for validity, rectified, amended, revoked, and enforced in Hong Kong courts in accordance with the laws of the HKSAR. The ordinance provides for the establishment of an independent Patents Registry, and enables the granting of short-term patents of up to eight years for the protection of inventions with short commercial lives.

Copyright Ordinance. This ordinance provides comprehensive protection for recognized categories of literary, dramatic, musical and artistic works, as well as for films, television broadcasts and cable diffusion, and works made available to the public on the Internet. It extends copyright protection to works of authors from any place in the world, or works first published anywhere in the world. It also provides Hong Kong customs officers with sweeping powers against copyright pirates and makes it easier for customs officers to seize suspected pirated goods.

Registered Designs Ordinance. This ordinance provides for the set up of a Designs Registry to provide the Hong Kong design profession with a user-friendly and inexpensive registration system. Designs which are new in Hong Kong can apply for registration.

Protection of Layout Design of Integrated Circuits. Hong Kong has special legislation to protect original layout design for incorporation into an integrated circuit. Subject to certain exceptions, the owner is able to take civil action to prohibit others from reproducing or distributing his layout design without his consent

or without payment of royalties. There is no need to register the layout-design right because protection is automatic.

Cooperation with Mainland China

Being a Special Administrative Region of China, we are in a good position to take advantage of opportunities to cooperate with academic and research institutions on the Mainland, many of which are on the leading edge in the field of science and technology, which includes biotechnology. Local universities have initiated a number of biotechnology-based research projects in collaboration with academic and research institutes on the Mainland. A number of these projects have been provided with funding support from ISF. One example is the Laboratory for the Quality Control of Chinese Medicine and Health Food set up at CUHK, where a formal collaborative agreement has been made with the National Institute for the Control of Pharmaceutical and Biological Products, Ministry of Health of The People's Republic of China. Another example is the Traditional Chinese Medicine Center in the Biotechnology Research Institute at HKUST, where there is collaborative research jointly conducted with the Chinese Academy of Sciences' Shanghai Institute of Materia Medica, the Shanghai Medical University, and the Shanghai Institute of Pharmaceutical Industry. We will continue to explore means to encourage more cooperation with the Mainland. I am sure that our industrial and business leaders will see similar collaborative opportunities as an effective means to enhance their competitiveness.

The Way Ahead

Although biotechnology-related industries have a short history in Hong Kong, they play an important role in the future development of Hong Kong's economy. For instance, for the food and beverage sector, biotechnology could help modernize existing production processes and develop new products. TCM should also have a high potential for success because of our knowledge base in this area and the growing acceptance of TCM as a health supplement or an alternative medicine in Western countries. Other biotech areas that exhibit potential for development in Hong Kong include diagnostic kits and biopharmaceutical products. We fully understand that biotechnology is very much science based, and much must be done in the areas of research and development, technological support and market analysis. We believe that to bring about the development of higher value-added and higher

technology industries in Hong Kong, more collaborations between the government, academia and business are required.

The chief executive of the Hong Kong Special Administrative Region has set forth a vision to make Hong Kong an innovation center for the region. In March 1998, he appointed a special body, known as the Commission on Innovation and Technology, to identify ways to move Hong Kong towards higher value-added industries and to make Hong Kong the region's innovation center. The commission published its first report in September 1998. It has recommended a series of measures to realize the above vision. In his policy address delivered in October 1998, the chief executive announced the acceptance of the commission's recommendations, including the setting up of a $5-billion Innovation and Technology Fund and the establishment of an Applied Science and Technology Research Institute to strengthen midstream R&D in Hong Kong. Other recommendations contained in the commission's first report include measures to enhance technological collaboration with China and to foster more university-industry collaboration. The Government of the HKSAR is taking forward these recommendations. The commission shall continue its study in the coming months and will publish its final report in mid-1999.

We are well aware of these issues and are fully committed to providing the necessary infrastructural support and human resources to facilitate the development of a biotechnology industry in Hong Kong in the years to come.

Footnotes

1. The Hong Kong Institute of Biotechnology was established with a donation of HK$170 million from the Hong Kong Jockey Club Charities Trust. It is located within The Chinese University of Hong Kong.

2. There are now six incubatees and five tenants at the Institute.

3. The Biotechnology Research Institute was established with a donation of HK$130 million from the Hong Kong Jockey Club Charities Trust. Its establishment is part and parcel of the Hong Kong University of Science and Technology.

4. They are in Tai Po, Yuen Long and Tseung Kwan O. There are 124 companies operating in these three estates.

5. A site at Pak Shek Kok has been identified for the Park, and reclamation is now in progress. It is expected that services available would include (a) multi-tenant low rise premises with high-quality servicing for rent to technology-businesses; (b) land plots on long leasehold to technology-based firms to purpose-build their own premises; and (c) essential services (such as meeting rooms, a library, exhibition hall, parking spaces, amenity facilities, banks, shops, and restaurants) to facilitate technology transfer and the application of advanced technology.

6. The Vocational Training Council is a statutory body established in 1982. In 1996, the Council provided technical training to 43,100 full-time and 61,800 part-time students.

7. The Council comprises local and overseas academics, as well as local lay persons. It has four specialist panels, namely, the Physical Sciences Panel, Engineering Panel, Biology and Medicine Panel and Humanities, Social Sciences and Business Studies Panel.

8. The funding available through the Research Grants Council in the past five years is: HK$156 million (1993), HK$261 million (1994), HK$277 million (1995), HK$345 million (1996), HK$423 million (1997).

9. All industry-support bodies, trade and industry associations, higher education institutions, professional bodies, research institutes and locally incorporated companies are eligible to apply. Examples of projects are those which aim to provide a communal infrastructural support service, introduce new manufacturing techniques, increase productivity, or develop new technologies.

10.

	1994		1995		1996		1997	
	all sectors	biotech	all sectors	biotech	all sectors	biotech	all sectors	biotech
no of applications	267	44	212	51	200	62	341	132
no of approved projects	81	18	71	18	61	20	84	28

11. The Scheme was set up in 1993. It aims to encourage technology ventures and applied research and development activities in the private sector by providing funding support as a catalyst.

Chapter 12

Role of Research Grants Council in Developing Biotechnology in Hong Kong

By

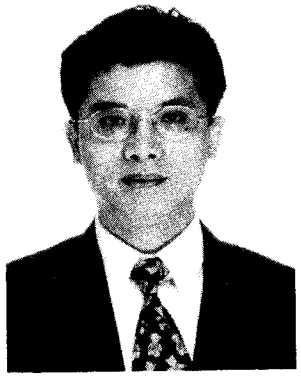
~ Lap-Chee Tsui, Ph.D. ~
Geneticist-in-Chief
The Hospital for Sick Children, Ontario, Canada

Professor
The University of Toronto, Ontario, Canada

Chairman, Biology & Medicine Panel
Hong Kong Research Grants Council

~ Marcus Tsui ~
Deputy Secretary
Hong Kong Research Grants Council
&
Assistant Secretary-General for Research
University Grants Committee of Hong Kong

***Lap-Chee Tsui, Ph.D.**, is geneticist-in-chief at The Hospital for Sick Children and university professor at The University of Toronto, Ontario, Canada. He is a member of the Hong Kong Research Grants Council and chairman of its Biology Medicine Panel.*



***Marcus Tsui** is deputy secretary of the Hong Kong Research Grants Council and assistant secretary-general for research of the University Grants Committee of Hong Kong.*

Introduction

The development of biotechnology in Hong Kong has a relatively short history. There are probably two main reasons: first, even now, Hong Kong does not have any significant biotechnology industry; second, the Hong Kong Government has only in recent years started to improve the infrastructure for basic and applied research in Hong Kong. As such, much of the research activities related to biotechnology have been supported by the Research Grants Council (RGC) through its support of basic research in biology and medicine. In this chapter, we attempt to provide an overview on the background of RGC, how its operates, and how it contributes to the development of biotechnology in Hong Kong.

Basic Research in Hong Kong

For many years, basic research in biological and life sciences was mainly carried out by two academic institutions: The University of Hong Kong (HKU) and The Chinese University of Hong Kong (CUHK). Following a rapid expansion of Hong Kong higher education in the 1980s, there are now eight institutions which are funded by the University Grants Committee (UGC), of which only two do not offer laboratory-related programs. Besides HKU and CUHK, the other six UGC-funded institutions are: City University of Hong Kong (CityU), Hong Kong Baptist University (HKBU), Lingnan College (LC), The Hong Kong Institute of Education (HKIEd), The Hong Kong Polytechnic University (PolyU), and The Hong Kong University of Science & Technology (HKUST).

Despite the UGC's mandate to advance higher education in Hong Kong, separate funding for research from the government was only made available by the Committee in 1983. During the period 1985-88, HK$45 million, equivalent to 1% of the recurrent grants, were allocated to fund research projects. The funds were disbursed by a research subcommittee of the UGC. In 1986, the Government recognized the need to increase the research capabilities of the institutions with enhanced funding from 1988 onward and that, in principle, the broad thrust of these research activities should be geared to educational needs. At the same time it was accepted that Hong Kong industry required an improved research base in order to remain competitive and that the tertiary institutions could, and indeed should, play a major role in this respect. Government's specific funding for academic research

(entitled "Earmarked Research Grant" starting from 1991 and administered by the RGC) is highlighted in **Table 1**.

Currently, Hong Kong operates a dual-funding system for government-supported basic research. Under this system, the research infrastructure, staff time, standard equipment, consumables, and minor administrative expenses are to be provided by the institutions, largely through funding from the UGC. The RGC uses a competitive process to award research grants for the acquisition of essential equipment, the hiring of research support staff, the payment of non-standard general expenses, and attendance at international conferences.

The Hong Kong Research Grants Council

The RGC was formally established in January 1991, with the following goals:

(1) To advise the Government, through the UGC, on needs of institutions of higher education in Hong Kong. This includes the identifying priority areas in order to develop a research base adequate for the maintenance of academic vigor and pertinent to the needs of Hong Kong; and

(2) To invite and receive, through institutions of higher education, research grant applications from academic staff and applications for the award of studentships, or stipends, and postdoctoral fellowships; to approve research awards and other disbursements from government funds; to monitor the implementation of such grants and to report at least annually to the Government through the UGC.

The RGC's members are primarily eminent researchers or individuals drawn from the local academic and business sectors. The Council also includes expert academics from outside Hong Kong. For the purposes of its principal activity, the consideration of applications for research grants, the Council operates on the basis of peer review through subject panels comprising mainly local academics and an international network of expert referees. Currently, there are four subject panels: Engineering, Physical Sciences, Biology & Medicine, and Humanities, Social Sciences & Business Studies. Panel members are appointed on the basis of their expertise in a particular field as well as perceived possession of a fair mind and breadth of vision.

RGC Funding

In 1988, the Government for the first time agreed to provide a sum of HK$120 million earmarked for research activities from 1988-91. In 1989, the Government realized that it would be necessary to put in place permanent machinery in the form of a Research Grants Council to examine and approve competitive bids for research grants, in addition to monitoring and advising on research matters. In 1991 the RGC was formally established, and the Hong Kong Legislature approved an allocation of HK$510 million for Earmarked Research Grants (ERG) for 1991/92 to 1994/95. The actual amount of ERG allocated by the RGC per year has subsequently increased significantly, at an annual rate of about 20% since 1991, thanks to the UGC supplements:

Table 1: Size of Earmarked Research Grant Since 1991

Year	HK$million
1991-92	$100 m
1992-93	$122 m
1993-94	$144 m
1994-95	$144 m
1995-96	$275.7 m
1996-97	$331 m
1997-98	$369.3 (later increased to $423.3 m)

The steady increase in research funding for academic research probably reflects the Government's conscious decision to upgrade and enhance higher education in Hong Kong. It is estimated that between 1991 and 1996, Hong Kong recruited some 3,500 new academic staff from the international community. In order to attract highly motivated overseas academics to teach in Hong Kong's institutions of higher education, the additional research funding was obviously required. It is of interest to note that, even as recently as 1997, only about 70% of the academic staff in Hong Kong institutions held an M.Phil. or a Ph.D. degree (the relative figure for 1991 was even lower, at 50%). In addition, there has been a significant increase in the demand for funding in recent years. We believe that the increase does not only reflect the steady expansion of research capabilities among the UGC-funded institutions but

also a maturing research culture among the academic staff at all levels, accelerated by a natural and healthy dose of competition.

A research culture is now firmly established in Hong Kong. This appears to have been brought about by the efforts of the Hong Kong higher education institutions, and the competitive grant and peer-review system administered by the RGC. Since its establishment in 1991, the RGC has allowed the institutions and academics to pursue their own research directions and apply for investigator-driven grant supports. Through the peer-review system (which is further explained below), only those research proposals with very sound scientific merit would receive RGC funding through the annual competition. In order to raise the quality of research in Hong Kong, the RGC has gradually modified its policy from funding as many proposals as possible to funding more fully a smaller number of high-quality proposals. The overall success rate of the annual competitive grant exercise has been gradually reduced from 67% in 1991 to 43% in 1997. Although the latest success rate is still high by international standards, it should be noted that the RGC is the only funding body in Hong Kong that provides support for academic research, and that Hong Kong has a relatively short history in research. Nevertheless, according to the overseas members of the RGC, about 10-15% of the Hong Kong research proposals are definitely internationally competitive.

In order to assist new faculty members and to permit the generation of new research ideas, the RGC also provides a small sum of Direct Allocation (18% of the RGC funding in 1997) to individual institutions to support smaller projects and provide seed funding for new projects. In addition, each year the RGC also disburses a central allocation on a competitive basis to support the acquisition of major research facilities or equipment and library collections for collaborative research projects involving more than one institutions. In 1996, the RGC agreed to extend the scope of central allocation to support group research in an attempt to foster collaboration across disciplines and/or institutions so that they may take on larger and longer-term projects. The total amount of grants distributed by the RGC by way of central allocation in 1997 was over HK$28 million. The continuation of this scheme to enable the purchase of major research equipment and facilities and collaborative research across disciplines and/or institutions may also allow the UGC and RGC, as well as the institutions to identify their existing areas of strength that have the potential to be further developed into strategic "Areas of Excellence" in Hong Kong. The UGC has formally invited

UGC-funded institutions to submit bids for funding to develop existing areas of strength into Areas of Excellence. We have not so far conferred an AoE title to any particular area, although certain institutions have, in anticipation of the UGC AoE scheme, declared their own identified "Areas of Excellence" or "potential areas of excellence."

The Peer-Review Process

The success of the RGC is primarily due to its rigorous peer-review system. Project grant applications are selected for funding on the basis of a set of criteria, including academic quality, institution's commitment, contribution to academic/professional development, potential for social, cultural or economic application, and availability of and potential for non-RGC-funding. Nevertheless, the primary determining factor for successful bidding of a research grant is its overall academic quality, which covers the scientific and scholarly merit of the proposal, qualifications and track record of the investigators, originality and feasibility within the time scale of the proposal.

The RGC subject panels, formed by local academics and experts from outside Hong Kong are in turn assisted by independent external reviewers. External reviewers are selected by RGC subject panel members from their own contacts or peer groups, nominations by grant applicants, and from the RGC's register of subject specialists. Throughout the years, the register has accumulated over 6,000 names of international experts, of which 1,700 are in the biology and medicine disciplines.

To enable applicants to improve their research objectives and experimental design, all comments and suggestions from their peers in the international community are disclosed to applicants. This feedback policy also allows the applicants to respond to the criticism and improve their applications on resubmission.

The Biology & Medicine Panel

The Biology & Medicine subject panel advises the RGC on matters relating to research in biology and medicine and selects grant applications for funding in these subject areas. The size of the Biology & Medicine Panel has doubled, from seven (including one overseas member) in 1991 to 14 (including four overseas

members) in 1997. Its growth in membership reflects not only the increase in the number of research proposals but also the breadth of applications received in recent years. The type of research projects ranges from studies of the behavior of specific organisms in local geographic areas to the cloning of pharmaceutically important or disease-related genes to the characterization of the three-dimensional structures of medically relevant proteins.

The number of research applications in the Biology & Medicine stream has increased four-fold, from 73 in 1991 to 310 in 1997. The increase in terms of funding sought is more significant, from HK$58 million in 1991 to HK$344 million in 1997. The number of applications and average amount sought per proposal in the biology and medicine stream as compared with other science streams are as follows:

Table 2: Number of applications and average amount sought per proposal

	1991		1997	
	No.	HK$'000	No.	HK$'000
Biology & Medicine	73	796	310	1,110
Engineering	96	871	517	951
Physical Sciences (*)	-	-	182	957

(*The Engineering and Physical Sciences Panel was spilt into the Engineering Panel and Physical Sciences Panel in December 1993.)

The average size of competitive project grants awarded by the RGC to research proposals in the Biology & Medicine stream as compared with other sciences streams is as follows:

Table 3: Average size of awarded ERG project grants (Numbers in HK$'000)

	1991	1997	
Biology & Medicine	498	750	(+ 51%)
Engineering	447	580	(30%)
Physical Sciences	(447)	477	(7%)

As the research culture becomes more firmly established in Hong Kong, academics there are gradually developing more ambitious long-term research goals. Although the majority of the current grants are funded for two years, an increasing number of proposals are seeking larger grants for three-year of funding. The Biology & Medicine panel has recommended that the RGC consider five-year funding for exceptionally meritorious proposals. A majority of members of the panel believe that long-term, sustained funding would promote excellence in research, encourage the development of long-term research goals and novel research ideas, and increase opportunities for discoveries.

Important Developments in Hong Kong's Applied Research

The Hong Kong Government has also substantially improved the infrastructure for applied research in Hong Kong in recent years. Since these subjects are topics of discussion in other chapters, we only attempt to provide an overview from our perspective here.

In 1993, an Applied Research & Development Scheme was launched with start-up capital of HK$200 million. The primary objective of the scheme is to increase applied R&D activities and to foster an R&D culture in Hong Kong with Government funding as a catalyst to invest in applied research initiatives with industrial support. In response to an initiative to facilitate local industries to leverage technical and research expertise in Mainland China, a Co-operative Applied R&D Scheme was launched in 1995. In 1994, the Industry Technology Development Council (ITDC) also launched an Industrial Support Fund (ISF) to provide support for industrial projects which are beneficial to the industrial or technological development of Hong Kong.

In addition, the Government has established the Hong Kong Industrial Technology Centre Corporation (HKITCC) to promote industrial technology and to act as incubators for start-up companies. To promote the biotechnology industry in Hong Kong, two institutes of biotechnology have also been established with close support from two local universities: the Hong Kong Institute of Biotechnology (HKIB) at CUHK, and the Biotechnology Research Institute (BRI) at The Hong Kong University of Science & Technology. The former is engaged in mainly downstream development of biotechnology products while the latter is mainly involved in upstream discovery research. As a long term strategy to further the development of a research base in Hong Kong, the Government is constructing a science park. The proposed site of the science park is in close proximity to the "research belt" comprising a number of universities, HKITCC and HKIB.

Concluding Remarks

While biotechnology is generally perceived to be an applied science or an industry, much of its forefront in research and development is led by basic research in biology and medicine. Besides academic institutions' involvement in biotechnology discoveries which can be turned into new industry, these institutions also train qualified research personnel. Moreover, the gap between basic and applied research in biology and medicine has also been narrowed over the years: Many investigators in RGC-funded institutions have already attracted industrial funding support for their research projects, some of which were previously RGC-funded. Therefore, although precise statistics are lacking, the RGC has clearly contributed both directly and indirectly to the development of biotechnology in Hong Kong.

Ideally, the outcome of all basic research should eventually be applied in the development of industry. On the other hand, the direction of basic research should not be dictated by the perceived future of a particular industrial or commercial product. This point is best expressed by Mr. Nigel French, Secretary-General of the UGC, in his paper entitled "The Hong Kong Research Grants Council – The First Seven Years," which was presented at the RGC Retreat in December 1997:

> *"I would hope that RGC will adhere to its mission of principally supporting academic research. Suggestions that the Council should shift its emphasis more towards applied research and that university research should be brought into closer alignment with the need of local industry (**Made by Hong Kong,** Berger & Lester, 1997) are, in my mind, misplaced. The value of much university research is surely mainly at a level of where relevance to 'the needs of local industry' cannot be determined, because that industry is not yet born. Moreover, as indicated earlier, there are many other avenues for the support of applied research now than there were seven years ago."*

In other words, without a sound base of basic research, there will be no future in applied research.

As all the necessary foundations for excellent research in biology and medicine in Hong Kong have been laid, we have full

confidence that through the collective efforts of higher education institutions, research institutes, government and industry, and their respective international networks, biotechnology in Hong Kong and in the region has a very bright future.

Chapter 13

The Case for Establishing a Biotechnology Product Testing and Inspection Infrastructure in Hong Kong

By

~ Sherman Kwok-Wing Fung, Ph.D. ~
Divisional General Manager, Bio-Science Division
SGS Hong Kong Ltd.



***Sherman Kwok-Wing Fung, Ph.D.**, is founder and the division head of the SGS Hong Kong Bio-Sciences Division, focusing on the development services of biotechnology, pharmaceutical and Traditional Chinese Medicine. Previous to founding the Bio-Sciences Division, Fung served as a laboratory manager at SGS Hong Kong, in the Chemical Services Laboratory. He holds a B.Sc. in chemistry from Imperial College, London University, and a Ph.D. in molecular sciences, with the thesis titled "Models and Mimics of Isopenicillin N Synthase," from Oxford University. Fung has extensive exposure to and experience in Hong Kong's commercial, government and academic biotechnology circles. He is a council member of Hong Kong Chemical Society and an editor of **Chemistry in Hong Kong**. Fung has been elected chartered chemist and registered analytical chemist of the U.K. Royal Society of Chemistry, and also approved chemist of the U.S. American Oil Chemists' Society.*

Introduction

Hong Kong has experienced tremendous economic growth in the past 20 years and, at the same time, it has experienced a transformation as the territory's manufacturers began to move their labor-intensive production operations across the border into Mainland China. This transformation has shifted the attention of the Hong Kong Government, academics and local industrialists to retaining Hong Kong's manufacturing industry; attracting external investors to open factories in Hong Kong, developing high value-added business. All these initiatives are part of an urgent agenda.

"As Hong Kong considers the direction of its future industrial development to safeguard and build upon the economic growth and prosperity it has achieved to date, technology is widely being hailed as the key to long-term success," asserted Dr. Otto Lin, vice president for R&D at the Hong Kong University of Science and Technology (HKUST).[1] According to the Massachusetts Institute of Technology (MIT) Made by Hong Kong report, there are a number of industries in which Hong Kong could become a major player.[2] One such area is biotechnology.

Now we may need to ask this question: "Does Hong Kong have the requirements to establish a biotech industry?" To answer it, we need to identify what we have already achieved and what we are capable of achieving.

Technology. Hong Kong has seven publicly funded tertiary institutions carrying out academic and applied research. According to the **Biotechnology Directory 1997**, published by the Hong Kong Government Industry Department, there are 19 research centers dedicated to biotechnology research, among them the Biotechnology Research Institute (BRI), founded in 1990 at HKUST; the Biotechnology Laboratory, founded in 1986 at The Chinese University of Hong Kong (CUHK); the Institute of Molecular Biology, founded in 1989 at The University of Hong Kong (HKU); and the Hong Kong Institute of Biotechnology (HKIB), founded in 1989 for downstream biotechnology developmental research.

Infrastructure. Hong Kong has steady and reliable electric and water supplies to sustain the high-demand R&D activities required for developing biotechnology products. In terms of information technology and telecommunication, Hong Kong has excellent infrastructure to support the business. Transportation-wise, it has an excellent mass transport railway system, the world's

largest container port, and it has one of the world's most-state-of-the-art airport facilities in Chep Lap Kok on Lantau Island. Geographically, Hong Kong has an excellent position as the gateway into China and is located in close proximity to the Association of South-East Asian Nations (ASEAN) region.

Human Resources. Hong Kong has one of the best workforces in the world because it has a superior educational system. Hong Kong's seven publicly funded tertiary institutions provides training from the undergraduate to the postgraduate level. Biotechnology-based training in strategic fields is available at the various tertiary institutions, while technical colleges/technical institutes/industry training centers conduct higher diploma or higher certificate courses in science, engineering etc. In other words, the technical institutes/colleges, etc., provide technicians for employment in the industry. Hong Kong is an international city with a bilingual educational system. With such a dynamic and energetic business environment, Hong Kong can easily attract renowned researchers from foreign countries and Mainland China.

Financial Opportunities. There are three funding schemes provided by the Hong Kong Government Industry Department to support applied research and development projects. They are the Industrial Support Fund, the Applied R&D Scheme, and Co-operative Applied R&D Scheme. Currently under the Applied R&D Scheme, a sum of HK$200 million is allocated to developmental projects with good market potential. In addition, another sum of HK$50 million is available through the Co-operative Applied R&D Scheme to support similar projects that draw on the work of Mainland researchers.

Government Commitment. The 1997 Government Policy Address, stated that:

- Government will support the stock exchanges' study regarding the establishment of a "venture board" to help small enterprises raise capital.
- Government stands ready to inject up to HK$500 million into the Applied Research Fund, specifically to support the commercialization of research in information technology and other high-technology fields.

- Its goal is to make Hong Kong an innovation center not just for ourselves, but for South China and the region. The center will assemble a high-level committee of academics, industrialists, businessmen and officials to give officials input.

It is believed that the government has shown a significant commitment to Hong Kong's long-term industrial development and is prepared to move on to higher value-added, technology-intensive manufacturing capability.

We have discussed Hong Kong's strength in general technology, infrastructure, human resources, financial opportunities, and government's support of high technology development. There is no doubt that Hong Kong already has the basic requirements to enter the high value-added biotech industry.

But why is Hong Kong still trapped in the early phase of biotechnology development? Hong Kong is somewhere between the first and second phase of development, according to Mr. Lo Yuk Lam, president of Bio-Rad Pacific and chairman of the government Industry Department's Biotechnology Committee.[3] To answer this, we need to ask another question: "Does Hong Kong have an infrastructure fully dedicated to biotech product development?" Up to now, the answer has been, "No."

To bring biotech products to market, we need a "testing and inspection infrastructure" to serve as a platform between industry and academic institutions, building a business and technology environment to attract investors, industrialists and businessmen to Hong Kong to invest into biotech development. To make infrastructure more customer oriented, market driven and efficient, commercial entities with experience setting up this infrastructure should be encouraged.

Product Development

The field of biotechnology has grown into extremely broad, diverse industrial sectors with a large amount of products. Nowadays, biotechnology companies need to invest deeply in R&D to

survive. In this chapter, biotechnology products include pharmaceuticals, Traditional Chinese Medicine (TCM), diagnostic reagents, functional/medical food, medical devices, etc. It is appropriate to define what the development process entails before looking at ways in which it may be made more efficient by using product testing and evaluation outsourcing.

Biotech Product Development

Introduction. Different product development approaches are generally used to produce new chemical entities and generic products. New chemical entities are drug substances with unknown toxicological, clinical, pharmacological, physical, and chemical properties. The following phases of product development proceed sequentially:

1. **Preclinical stage.** Animal pharmacology/toxicology and product chemistry data are obtained to determine the product's degree of safety and efficacy. Data are gathered in accordance with increasingly rigorous procedures, requiring adherence to Good Laboratory Practice (GLP) or, in the case of manufacturing, Good Manufacturing Practice (GMP). An Investigational New Drug (IND) application for human testing is submitted to the Food and Drug Administration (FDA). Since it is likely the product will not get market approval at this stage, no attempt is made to develop a final formulation.

2. **Phase I.** First administration to healthy volunteers (or, in some cases, to patients) to establish tolerability and kinetics.

3. **Phase II.** In the U.S. and Europe Phase II is subdivided into IIA and IIB. IIA: "Proof of principle" studies in patients IIB: Controlled studies in defined patient populations to evaluate the effectiveness of the product.

4. **Phase III.** Large open studies in the general patient population confirm efficacy and expand safety database.

5. **Submission of a new drug application (NDA).** When all clinical trials are completed to the satisfaction of the medical community, and the drug is found to be efficacious by all parameters, an NDA is submitted to the FDA for review and approval.

6. **Phase IV.** Post-marketing studies further define the product's safety of the product under normal use.

Generic Drug Products may be developed after the patent expiration of the brand drug product. A generic drug product contains the same amount of the drug ingredients in the same type of dosage form. From the point of view of testing, generic drug products must be demonstrated to be bioequivalents (have the same rate and extent of drug absorption) of the expired brand drug product. The product may differ from the brand product in the amount and type of excipients and in physical appearance, such as color, size and shape. For the purpose of marketing approval, manufacturers must submit an Abbreviated New Drug Application (ANDA) to the FDA for approval in the U.S. Only bioequivalence studies are required for the ANDA because preclinical safety and efficacy studies have already been performed for the NDA-approved brand product.

Product Development. In order to develop a safe, effective and stable dosage form, different activities and information are required for each drug.

New Chemical Entities

1. **Preformulation** is the characterization of all fundamental physical and chemical properties of the drug molecule and other derived properties of the drug powder and route of administration (e.g. oral, transdermal, parenteral). This information will dictate many of the subsequent events and possible approaches to formulation development. Preformulation activities are usually performed during the preclinical stage. Information required in preformulation is summarized as: Spectroscopy (simple UV assay), Solubility, Melting Points, Assay Development, Stability, Microscopy, Powder Flow, Compression Properties, and Excipient Compatibility.

2. **Formulation Development** is an ongoing activity. Initial drug formulations are developed for early clinical studies. Once the submission of an NDA is considered, an attempt to develop the final dosage form is made.

Product Line Extensions are drug products containing an NDA-approved drug in a different dosage form or in a different dosage strength.

Product Line Extensions	Major Required Information for Regulatory Approval
Solid Oral	- Stability - Bioequivalence - Analytical and manufacturing controls - Clinical trials in the case of modified-release dosage forms
Liquid	- Stability - Safety studies (e.g. local irritation depending on the drug substance) - Bioequivalence - Analytical and manufacturing controls - If the product line extension is not bioequivalent to the originally marketed drug product, clinical studies must be done
Topical	- Stability - Analytical and manufacturing controls - Clinical studies - Safety studies-topical irritation and sensitization
Injectable	- Assurance of sterility and lack of pyrogenicity in manufacturing - Stability, analytical and manufacturing controls for the drug in solution/a large volume parenteral - Bioavailability studies are also required for the drug in a suspension.

Generic Drug Products (e.g. Oral)

1. **Preformulation** of generic drug products usually includes the following actions after completion of the literature review for pharmacokinetic and physiochemical data and patent review:

Evaluation of the brand product	- Formulation characteristics: physical appearance, color, shape, and odor - Chemical characteristics: e.g. potency, dissolution (for solid dosage form), degradation etc. - Physical characteristics: (a) Liquids: color, pH, odor, taste and viscosity (b) Tablets and capsules: disintegration, hardness, thickness (c) Semisolids: skin sensitivity, viscosity, skin feel, and pH
Characterization of the active drug substance	- (a) Reproducibility: at least 3 batches are needed to evaluate reproducibility - (b) Physical characteristics: particle size, density, shape, etc. - (c) Chemical characteristics: evaluation and degradation of impurities and related compounds - (d) Solubility characteristics

2. **Formulation development.** The steps for development should include:

- Evaluation of raw materials and excipients
- Comparisons of the formulation under different physical conditions (e.g. pH, temperature)
- Stability tests on both the brand product and generic product
- Development of a discriminating dissolution method for comparison of the oral generic product with the brand product.

Analytical studies, as well as studies on stability, manufacturing, bioavailability, and bioequivalence will be essential for regulatory approval of generic drug products.

Testing and Inspection Infrastructure

Reasons for setting up the infrastructure

In most major global biotech markets, the concept of "contracting out" or, to use the more sophisticated description, "outsourcing" to outside research organizations to provide preclinical and clinical services, is not a foreign one. These Contract Research Organisations (CROs) have given pharmaceutical and biotechnology companies opportunities to manage their fixed and limited development costs more effectively while targeting their growing biotech product development. Nowadays, there are about 800 CROs worldwide, and half of these are in Europe. The bulk of the growth in the past few years has been recorded in large CROs, which have expanded their range of services to keep in line with the rapid growth of the biotech industry. Specific growth areas include: quality assurance (QA), technical training in GMP, GCP, and the performing of multicenter, international Phase III clinical trials.

At the moment, there is a growing trend among large pharmaceutical and biotechnology companies, to outsource some of their development in the pre-clinical and clinical stages. It seems small emerging and medium-sized biotechnology and pharmaceutical companies have no option but to use CROs to develop their products in order to compete with large companies. Usually these medium-sized companies in Europe and the U.S. depend on assistance from CROs to develop their ideas because they have no or little development expertise to achieve this. In addition to providing GLP status testing services and monitoring clinical trials under the requirements of GCP, CROs are adding value by providing scientific experience, expertise and project management.

Without a doubt, the relationship between biotech companies and CROs is one of the essential factors behind the success and rapid growth of the biotech industry in U.S. and Europe.

Individual market segments, have their own market-driven reasons for necessitating this infrastructure in Hong Kong. In the food industry, all exports must comply with international standards of packaging, quality and safety. The total export in food and food-related products from Hong Kong were estimated to be US$2.7 billion in 1995.[4] For China, one of the most important export is also food products. In order to fulfill the import requirements of Western countries [especially if China intends to enter the World Trade Organization (WTO)], a testing and inspection infrastructure is required to perform comprehensive analysis to comply with regulations such as food labeling and safety testing on preservatives, toxins, bacteria contamination, pesticides, packaging materials, and residual radioactivity, and genetically-modified foods.

Market needs in the pharmaceutical industry

In Hong Kong, there are only small pharmaceutical companies. In terms of manufacturing, there are some 100 holders of pharmaceutical manufacturing licences in Hong Kong, but only 30-40 are active in production. These firms concentrate mostly on over-the-counter (OTC) drugs and, increasingly, generics. Pharmaceutical sales in Hong Kong totaled HK$1.7 billion in 1993 and, for the first half of 1994, about HK$1 billion.[5] Criticism of standards in pharmaceutical manufacture, distribution and sale, due to the widespread ban on the painkiller drug Dipyrone, led to the mandate, in 1994, that GMP requirements be implemented in accordance with international standards. The schedule for GMP implementation has been divided into three stages and will be completed by the year 2000.

In 1994, there were about 1,500 Chinese factories manufacturing Western medicine. These manufacturers produced 24 therapeutic categories of chemical bulks. The industrial turnover was reported to be US$6.5 billion, a 15.6% increase over 1993.[6] The technology used by some pharmaceutical manufacturers is outdated and inefficient. This makes it difficult for China to export its products to countries which require GMP. In importing drugs from Western countries, it is important to perform Chinese clinical trials to study the applicability of the drug(s) in China. Based on the above three points, a testing and inspection infrastructure is required to support Hong Kong and China manufacturers in drug development and quality control, certification of GMP, performance of pre-clinical trials according to GLP requirements, and collaborations with relevant China and local academic centers to perform clinical trials and clinical data management.

Markets needs in diagnostic reagents

In response to the growth of the food and pharmaceutical market, the demand for diagnostic reagents, which are used in food products, human health care, animal health care, and plant diseases. In Hong Kong there are only limited R&D activities in universities, and the sale of diagnostic reagents is only a second-

ary pursuit for pharmaceutical companies. In terms of manufacturing, there are only small factories to manufacture diagnostic kits. In China, the use of diagnostic reagents is limited at present, but the marketing potential is very high because of the large population. In order to open the market for diagnostic reagents, the testing and inspection infrastructure would be required to support manufacturers in the development of diagnostic reagents such as blood screening, analyte and drug monitoring, tumor markers, and the treatment of infectious diseases and certify that the reagents are manufactured under GMP. The infrastructure also would perform specificity, efficacy and stability testing for diagnostic products.

Market needs in TCM. The last five years have seen a tremendous growth in the TCM market. According to the Massachusetts Institute of Technology report **Made by Hong Kong**, worldwide herbal medicine sales were US$12.4 billion in 1994 with 10%-15% annual growth.[7] The dominant market is Asia, and there is increasing acceptance in the U.S. and Europe. However, herbal medicine is sold as food supplements, not as prescription drugs. The report recommends that the development of TCM as pharmaceuticals be given top priority. In Hong Kong, over 95% of TCM medication are imported, mostly from China. Imports from China account for about 80% of proprietary Chinese medicines and 80-90% of raw or processed Chinese medicinal materials. There are about 100 wholesalers of raw or processed Chinese medicinal materials and 200-300 wholesalers of proprietary Chinese medicines. In addition to about 1,600 retail herbal shops, TCM are normally available from pharmacies and drugstores.[8] In March 1997, the "Report of the Preparatory Committee on Hong Kong Chinese Medicine" was issued. The committee recommended ways to train practitioners and control the import and distribution of TCM. The recommendations also include: safety, quality and efficacy evaluations of raw herbal materials and manufactured herbal products; clinical trials of TCM; and new drug development based on TCM.

There were about 900 TCM manufacturers in China in 1994. These manufacturers produced about 5,000 TCM products in 40 different dosage forms. In 1994, China's TCM industry had a turnover of US$2 billion, US$450 million of which was exported.[9] China's TCM experience is rich, and the raw materials and resources needed for TCM manufacturing are readily available; however, the country does not have a comprehensive patent protection policy or adequate good quality control measures.

In order to globalize the TCM market, a testing and inspection center is required. This center would:

- Support manufacturers in achieving consistent quality and certify them in GMP.
- Support Hong Kong and the Chinese government in developing a scientific registration system (e.g. product characterization, product quality and standards, preclinical and clinical demonstrations) which is recognized by the international market.
- Coordinate with universities to provide R&D support to the TCM industry.

Testing & Inspection Infrastructure – Role and Advantages

From the discussion of the market needs in the previous section, a testing and inspection infrastructure is required in Hong Kong. The infrastructure should fulfill the requirements of GLP, Hong Kong Laboratory Accreditation Scheme (HOKLAS), ISO 9000, and GCP, if applicable. Further, it should offer a comprehensive range of services for the development of biotech products such as pharmaceuticals, TCM, medical devices, food, diagnostic reagents, cosmetics, and chemicals. In order to increase the probability of success of this infrastructure, the direct involvement of an enterprise in a similar field is a must.

The role of the infrastructure includes:

- Performing comprehensive analysis of food products for toxicology, nutritional value, additives, packaging materials, and pesticide residue and issue certificate for export;
- Supporting pharmaceutical manufacturers in meeting quality control standards and company specifications of such things as raw material testing & valuation, virus & prion removal, DNA & protein removal, and purity of final product;
- Supporting pharmaceutical manufacturers in the development of new drugs from the beginning or in the preclinical and clinical stages;

- Supporting pharmaceutical manufacturers in marketing products in China by performing Chinese-based clinical studies;
- Coordinating with local universities in preclinical and clinical stages;
- Cooperating with local universities to develop databases to support the drug development industry;
- Assisting the Hong Kong Government in the development of a scientifically and internationally recognized protocol for the registration of TCM;
- Coordinating with world-class CROs and acting as a CRO in drug development to obtain the necessary certification of products for export to the international market and acting as the first CRO to work on TCM;
- Certifying the manufacturing process of drugs and diagnostic reagents under GMP, which is mandatory for entry into the international market;
- Coordinating with world-class CROs to provide training courses in GLP, GMP and GCP and to eventually become a training center for such courses;
- Enhancing the ability of Hong Kong to conduct clinical trials that meet international standards of GCP and making Hong Kong more attractive as a center for developing new drugs;
- Supporting the biotech industry by providing regulatory services, such as the preparation of dossiers for EU and U.S. registration, consultancy and evaluation of dossiers, expert reports, drug master files;
- Providing inspection services to manufacturers and importers. Inspection points might include harvesting, processing and storing of plants, and examination of finished products; and
- Providing health economic services to the industry. The services would include cost-benefit assessments, quality of life measurement and design, and conducting, evaluating and reporting health economic studies.

The advantages of having such infrastructure are:

- **Efficiency:** The infrastructure will have different groups of scientists and facilities for different fields. Developmental costs will be reduced compared to biotech companies that have their own in-house facility.
- **Risk:** The link between this infrastructure and other specialized centers and world-class CROs increases as does the probability of success in the preclinical and clinical stages.
- **Flexibility:** The sudden need to allocate a team of people temporarily from one discipline to a particular developmental stage of a project is a common problem in biotech R&D. A lack of capacity will cause the company to delay the project and increase the cost of development. This infrastructure will create opportunities for biotech companies to partly, of fully, out source their work. In addition, if a company needs to perform tests which are not handled routinely in the company's in-house facility, it will be too expensive for the company to buy the necessary equipment. It will then be rational to use this infrastructure.
- **Speed:** Biotech companies may take advantage of outsourced resources which theoretically allow much more work to be done in parallel during the developmental stage than can ever be contemplated with in-house alternatives. This parallel project strategic planning would push faster product development.
- **Venture Capital:** The cost of bringing a biotech product to market is expensive, and, even where it is financially possible, biotech companies lack experience in successful product development. The infrastructure will assist the company in performing the required testing so it will not need to

invest in expensive testing equipment. As mentioned under "Risk," the probability of successful product development will be increased by support from the infrastructure. Having such backing, biotech companies that are new, or small, or medium-sized will become more attractive both to venture capitalists and to partnership opportunities. In considering a "venture board" of Hong Kong stock market flotation in the future, the attraction to investors is rubber-stamped by the prior approval of venture capital and by technical backing from the infrastructure.

Towards Virtual Corporations Fully Outsourcing to the Testing and Inspection Infrastructure[9,10,11]

As the infrastructure can provide nearly all scientific and regulatory support to Hong Kong biotech companies, small-to-medium-sized companies can conduct R&D in a delocalized sense. This operation style is virtual, since companies themselves perform little or no actual scientific work. The business is mainly focused on project management, in terms of the R&D. To bring their products from discovery to market, companies can use universities for research support and the testing infrastructure for developmental support.

Features of the Virtual Company Concept with Full Outsourcing

A major problem in biotech product development is cost, and this is always a top issue for new biotechnology companies as much as for the larger multinationals. The virtual company would be established with venture capital backing and would run for at least three to five years. It would then seek flotation on the Hong Kong stock market "venture board." To keep expenses as low as possible, there would be no laboratory facilities, no personnel for clinical studies, regulatory affairs, quality assurance, and health economics. The company would maintain only a skeletal staff, such as marketing managers and a product management team for each product to be developed. The communication method among virtual company, testing infrastructure and collaborative academic institutes would be by intranet (an internal communications network), which can provide a secure environment for collaborating groups and can rapidly display clinical trial data. In general, product development using the concept of full outsourcing would be as follows:

Preclinical development

1. Analytical development
   - Analytical method development
   - Product characterization
   - Chemical, pharmaceutical and biological
2. Clinical trial supplies
   - Packaging of clinical/stability supplies

Clinical development

1. Stability testing for clinical supplies
2. Clinical studies
   - Pharmacokinetics
   - Phase I-II-III-IV Research
   - Bioequivalence
3. Biometrics and statistics
   - Study design
   - Data analysis
   - Reports
4. Bioanalytical laboratory
   - Method set-up and validation
   - Analysis of study samples

Product registration and health economics

1. Regulatory affairs
   - Product registration
   - Consultancy on regulatory affairs
   - Expert reports

2. Health economics

- Cost-benefit assessments
- Epidemiological studies

Product pricing and reimbursement - Study, prepare and submit application for product pricing to authorities in the appropriate ministry

Production and quality control

- Chemical, pharmaceutical and biological

The concept of the virtual company with full outsourcing seems to suit the Hong Kong business environment because more than 90% of businesses in Hong Kong are small and medium-sized enterprises. By lowering operation costs for entry into the biotech industry, more industrialists and businessmen will be attracted to invest in this field.

Procedures for setting up the testing and inspection infrastructure (4-Year Plan)

Stage I

Set up a task group* to:

- Collect market information, international regulation on food product, pharmaceutical, TCM, etc.
- Coordinate with world-class CROs to provide training on GMP, GLP and GCP standards to Hong Kong and China biotech companies.
- Act as a coordination center which understands the needs of Hong Kong and China academic institutes, biotech companies and governments.
- Set up a testing and inspection center to provide comprehensive testing, quality control in manufacturing, and biotech product development.

- Arrange public seminars to introduce the testing infrastructure and promote the biotechnology industry.
- Coordinate with world-class CROs for work which cannot be done or cannot be done effectively by the testing infrastructure.

(* The task group should consist of persons who are knowledgeable out local commercial testing and certification and have a good relationship with world-class CROs and Hong Kong and China academic institutes and government agencies.)

Stage II

Set up the testing and inspection infrastructure based on the market.

Decide the scope of services provided by the testing infrastructure. The scope of service will concentrate on providing:

- Assistance to manufacturers for GMP certification;
- Laboratory testing and inspection of food product exports. Testing would be done on: packaging material; nutrition value; microbiological contamination; preservatives; toxins; residual pesticides or herbicides; residual radioactivity; and genetically-modified food products.
- Full-range services to support product development in pharmaceutical, diagnostic reagents and TCM. The services involve: performing safety and quality evaluations on raw TCM materials and on finished products; providing "preclinical, clinical development, product registration & health economics, product pricing & reimbursement and production and quality control" full-range packaged service to pharmaceutical product development; validation of the manufacturing processes (such as virus, prion, DNA, and protein removal); checking for genetic characteristics and stability; protein characterization of products

- Technical information support services to provide updated information on international regulations, technologies development, etc.

- Contract generic drug development services to provide "one-stop" services for pharmaceutical companies, from required laboratory testing to clinical studies on bioequivalence.

- Search for the appropriate location for the main site of the infrastructure. The location of the infrastructure shall be:

  √ At a place where both population and air pollution are low.

  √ In a building which can install facilities for the treatment of incoming air so that the dust level is low enough for trace-level determination.

  √ In a building which can install facilities for the treatment of outgoing air which may have a high concentration of acid vapor, be contaminated with bacteria, etc.

  √ On a floor which is free of vibration and electromagnetic effect to avoid interference with sensitive analytical equipment.

  √ In a building with sufficient space for the installation of a cold room for storage of biological samples or reagents; an incubation room at different temperatures for microbiological or in vitro tests; individual rooms for sample registration, microbiological test sample preparation, inorganic test sample preparation, organic test sample preparation, microbiological analysis, organic or inorganic test instruments, etc.

  √ In a building which has facilities for the storage of dangerous goods, such as gas cylinders, toxic chemicals, bacteria, chemical waste.

- Recruit technical staff trained in analytical, biochemical, instrumental and microbiological testing. They include chemists, biochemists, molecular biologists, TCM specialists, medical doctors, and economists.

- Search for suitable facilities and equipment for the testing infrastructure. The facilities and equipment include but not limited to:

  √ Standard utilities of a laboratory, such as electricity with back-up power supply, 24-hour air conditioning, double-distilled water, on-line tap, deionized and hot water, on-line LP gas, compressed air and vacuum, and a telephone line for data transfer.

  √ Store room with 4°C refrigerator, -20°C, -40°C, and -80°C freezers equipped with back-up carbon dioxide systems.

  √ Constant-temperature rooms for incubation (37, 20, 4 and 20°C) with back-up electricity.

  √ Storage facility for stability testing meeting ICH3 Harmonised Tripartite Guideline recommendations on temperature and humidity control.

  √ Wash and preparative room with disinfects and autoclaves.

  √ Facility for clinical supplies meeting GMP guidelines. The facility should incorporate separate rooms for unit operations and storage, with control and monitoring of temperature, humidity and air pressure differentials.

- √ Facility with main research unit, intensive monitoring unit, clinical biology laboratory and emergency care unit for Phase I Clinical Trials.
- √ Cell culture laboratories for cell bank testing and test article handling.
- √ Molecular biology laboratories with automated DNA sequencing and synthesis in addition to thermal cycling facilities.
- √ Dedicated prion handling and assay laboratory, routinely used to validate removal and inactivation of scrapie from manufacturing processes.
- √ Chemical preparation room with fume hood, microwave digester, rotary evaporator and freeze dryers.
- √ Radioisotope room with scintillation counter and fume hood.
- √ Equipment rooms with various analytical and preparative equipment, such as high-performance liquid chromatography (HPLC) with UV; fluorescence detection with automated solid-phase extraction, with dialysis and column enrichment; capillary zone electrophoresis with UV scanning detector (CZE); gas chromatography (GC) with electron capture and mass spectrometer detector; automated ELISA; UV-VIS spectrometer; atomic absorption spectrometer (AAS); inductively coupled argon plasma spectrometer (ICAP); dissolution; liquid scintillation; and gamma counters.

Stage III

After setting up the laboratory unit, clinical unit and supporting unit of the infrastructure, standard laboratory quality assurance/control procedures and testing procedures will be developed.

At the same time, accreditation from GLP, GCP, HOKLAS, and certification from ISO 9000 will be applied for. During the transition period, the testing or job requests without internal experience will be subcontracted to the world-class CROs. At the same time, local staff will do parallel testing to compare data and gain experience for future jobs.

Stage IV

After getting the recognition of accreditation bodies, the laboratory will perform the job on their own with the support of selective CROs. In addition, a complete marketing team will be set up to promote services to potential clients and the center will seek recognition from international governments, accreditation bodies and international clients.

During the first four years, various services from the proposed infrastructure would become available in phases to support the development of the biotech industry. Eventually, after the completion of Stage IV, the proposed testing and inspection infrastructure should be capable of delivering a full range of services at each stage of product development. Such details are summarized along the chain of product development in **Figure 1**.

Product and Quality Certification

When we have the infrastructure set up as discussed in the previous section, we can use the same infrastructure to provide services on a product-by-product basis and can issue product and quality certification to manufacturers. Herewith is a good example of how to get a product certificate, "CE Marking of Medical Devices & EN 46000 Certification."[13]

Background

Manufacturers of medical devices, pharmaceuticals and healthcare services increasingly require a third-party product and quality system certification to meet regulatory requirements, maximize internal efficiency and provide a defense against litigation. For Europe, this often leads to CE marking.

The EC Directive 93/42/EEC now in force is in has a transition period through June 1998. Its objective is to standardize European regulations for medical devices, and it applies to most

devices sold or used in Europe. Conformity with the requirements is shown for most devices by CE marking the product. Users are already asking for the CE mark, and marking has been mandatory since June 1998. A similar directive covering in vitro diagnostic (IVD) medical devices including reagents, instruments and kits will follow in 1998.

Directive 93/42/EEC classifies devices into four classes of increasing risk (1, 2a, 2b, 3) according to their properties, function and intended purpose. Examples:

Class 1	Swabs, reusable instrumentation (Manufacturers of these products can use the CE mark without the intervention of a notified body as soon as they get a technical file.).
Class 1	Sterile swabs and other sterile devices.
Class 1	Thermometers, sphygmomanometers and other devices with a measuring function.
Class 2a	Catheters, solutions for disinfecting medical devices, syringes, dental products, diagnostic devices.
Class 2b	Prostheses, contraceptive devices, condoms, coronary and respiratory diagnostic devices.
Class 3	Implantable contraceptive devices, devices in contact with the heart or the brain.

Class determines the route to CE marking or conformity assessment procedure. Classification under the IVD Directive will depend on use. Self-testing devices and reagents, used for certain blood analyses will fall into high-risk classes.

EN 46000. New standards were published in 1993 covering quality systems for design and manufacture of all medical devices:

EN 46001:1993: Quality System-Medical Devices-Particular requirements for the application of EN 29001

EN 46002:1993: Quality Systems-Medical Devices-Particular requirements for the application of EN 29002

These incorporate ISO 9001/2 respectively but introduce some additional requirements. In most cases these standards will be used for showing compliance with the quality system requirements of the Directives. Notified bodies must be based in and approved by an EC member state. They also must be defined as competent to carry out the assessment and to issue the quality system certificate, if applicable.

Conformity assessment for 93/42/EEC. In general, all products will require the maintenance of a technical file or design dossier. The manufacturer can self-certify custom-made devices and Class 1 products which are non-sterile and have no measuring function. However, other classes require a notified body to undertake the assessment.

Testing. The technical file includes results on testing and evaluation relevant to medical devices, including:

- Biocompatibility and toxicology studies;
- Microbiological analysis and physico-chemical analysis;
- Clinical trials; and
- Others such as electromagnetic compatibility (EMC) testing, polymer and textile testing etc.

Procedures for acquiring the CE Mark

The procedures can be summarized as follows:

1. Classify the Medical Devices. The product will be classified according to Directive 93/42/EEC.
2. Set up a quality system and a technical file. The infrastructure will form a partnership with a notified body in EC to proceed with further quality assessment, and the infrastructure will provide the testing required to complete the technical file.
3. Obtain certification through a notified body.

4. Get an authorized representative in the EEC.

5. CE-marked the product.

Conclusion

Infrastructure - The proposed testing infrastructure should comprise four major elements:

1. Laboratory Unit

   - Bioanalytical
   - Product Chemistry
   - Biotechnology

2. Clinical Unit

   - Clinical Trials
   - Statistics and Data Management

3. Supporting Unit

   - QA
   - Sales and Marketing
   - Finance and Administration
   - Information System and Telecommunications
   - Regulatory Affairs
   - TCM Consultancy Services
   - Health Economics

4. Animal Testing Unit

   - Outsourcing

The proposed organizational structure is summarized in **Figure 2**.

The infrastructure itself could operate in either a decentralization or centralized manner. For centralization, the whole infrastructure including four units would be built in a single building. For decentralization/virtual set up, the laboratory unit with three subsections could operate at a single site; the clinical unit could operate

in hospitals; and the remaining two units could be grouped together at a single site and act as the main management office.

Comments

Without a doubt, Hong Kong can play an important role in the manufacture of biotech products. This has been identified by the Massachusetts Institute of Technology research team in the report **Made by Hong Kong**.[14] Hong Kong should also play a role as an international biotech center not just for ourselves, but for China, especially Southern China. Biotech is a high-value added business from which we will acquire our benefit eventually.

How to accelerate the development of the high-value added biotech industry is an urgent agenda for the Hong Kong Government, local industrialists and businessmen. In this chapter, I have discussed why we need a testing and inspection infrastructure to support biotech product development in Hong Kong, the role of infrastructure, and the procedures necessary for setting up such a testing center. I have also tried to imagine that there will be many small and medium-sized companies serving as virtual corporations which fully out source scientific work to the proposed infrastructure for product development. The virtual companies would benefit from having lower set-up costs and higher probability of success in product development. As such, the virtual company will become more attractive both to venture capitalists and partnership opportunities. If the establishment of a "venture board" on the Hong Kong stock market were successful, this could offer venture capitalists an exit strategy for their investments, thus raising confidence in committing money to biotech development in Hong Kong.

Whatever form the biotechnology industry should take, it should include a general infrastructure with human resources, transportation, information technology, etc., and a specialized infrastructure tailor-made for this particular industry. Without a doubt, Hong Kong already has a general infrastructure; what we lack is a specialized infrastructure. I conclude that a testing and inspection specialized infrastructure is a necessary bridge between industry and academic institutions to accelerate the development of the high value-added biotech industry.

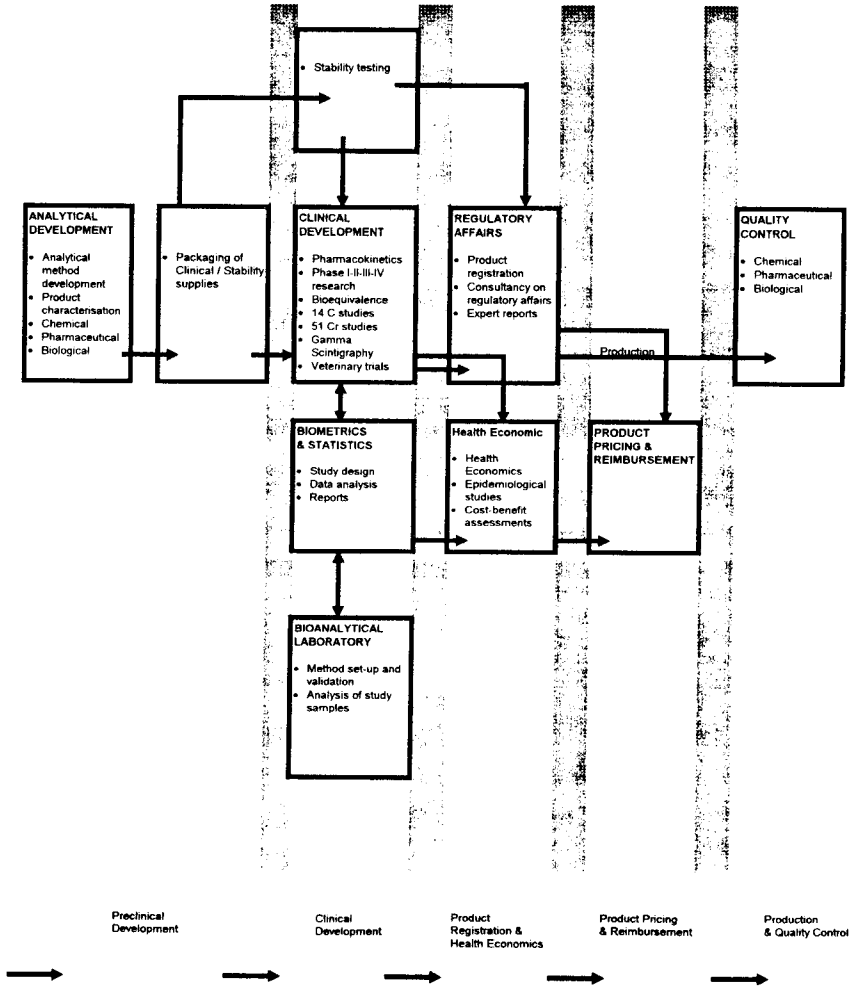


Figure 1. Biotech Product Development

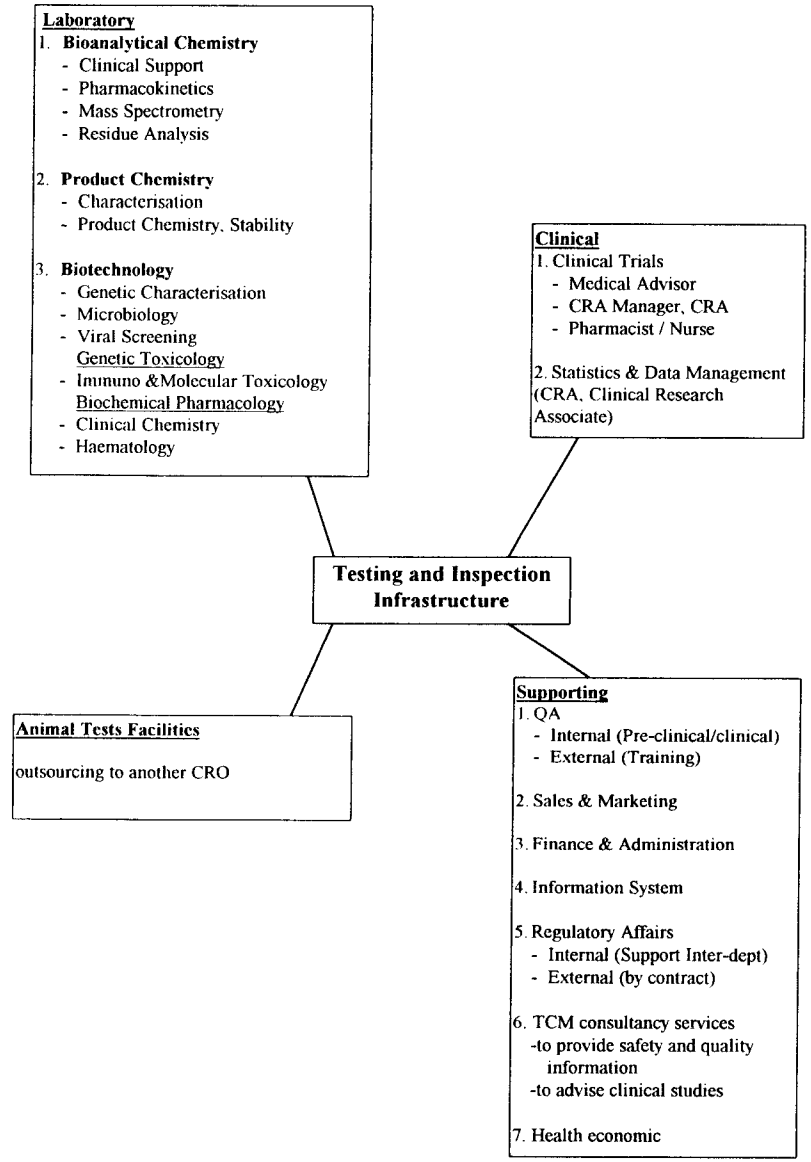


Figure 2. Testing and Inspection Infrastructure: Organizational Structure

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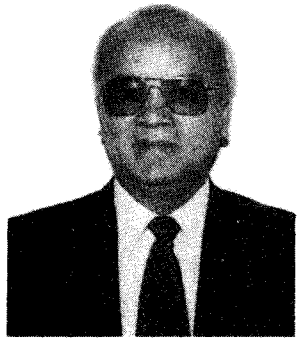
The Role of Universities

Chapter 14

Training of Biotechnology Personnel

By

~ Samuel S.M. Sun, Ph.D. ~
Chairman, Department of Biology
The Chinese University of Hong Kong



***Samuel S.M. Sun, Ph.D.**, is chairman of the Department of Biology at The Chinese University of Hong Kong. Sun received a B.Sc. in botany/zoology at The Chinese University of Hong Kong.; a B.Sc.Sp. in plant biochemistry at The University of Hong Kong; a M.Sc. in plant biochemistry at The University of Hong Kong; and a Ph.D. in botany/horticulture at the University of Wisconsin in Madison.*

Introduction

The establishment of the double-helix structure of DNA in 1953 triggered rapid development in DNA-related technologies. Major advances during the following 30 years included: the discovery of the first restriction enzyme and DNA transformation of E. coli (1970); molecular cloning in plasmids and gene transfer into cells (1972); Southern analysis and DNA sequencing (1975); the generation of transgenic mice from microinjected embryos (1980); and the transfer of a bean gene into sunflower cells and tobacco plants (1983). These technical advancements generated great enthusiasm and expectations for biotechnology's potential to improve healthcare, agriculture, environment, and other industries, which, in turn, induced the birth of the modern biotechnology industry and its rapid growth. In 1996-1997, the United States biotechnology sectors alone employed some 312,500 workers. Biologists with molecular biology and biotechnology expertise are the core component of this workforce and their innovation and technical capability are critical to the success of this new industry. Because of good job prospects as well as the involvement of frontier science in biotechnology, study programs in biotechnology proliferated in universities worldwide in the 1980s, attracting many students trained to fill the manpower void.

This chapter deals with the training of biotechnology personnel for the Hong Kong biotechnology industry, a sector of high-tech industries that are currently being emphasized and supported. The goal and requirements for developing and establishing programs to train highly qualified biotechnology personnel are discussed.

Program Goal

The overall goal of biotechnology training programs, in my opinion, is to prepare competent biotechnology personnel with the following qualities:

1) A strong background in biotechnology and related fields;
2) Competent and up-to-date technical skills;
3) Innovation and problem-solving capabilities;
4) Appreciation of applied research and the entrepreneurial spirit; and
5) Knowledge of intellectual property, regulatory and other biotechnology issues.

Desirable Qualities and Training Philosophy

A Strong Background in Biotechnology and Related Fields

The training program should prepare students not only with a strong specialization in biotechnology and closely related fields, including molecular biology, genetics and cell biology, but also with broad fundamentals in subfields, including biochemistry, physiology, microbiology, animal and plant biology, organic and analytical chemistry, to provide a holistic knowledge foundation. This specific yet broad base knowledge should promote problem identification, realistic experimental design, planning, problem solving, and innovation. It should also provide career adaptability and versatility, which assists trainees seeking and pursuing other science careers if needed or so desired in the future.

Competent and Up-to-date Technical Skills

Biotechnology research requires intensive experimental work and diverse molecular techniques. In addition, new molecular instruments and techniques are being rapidly and continuously developed and made available. Thus it is not only critical to inform students about up-to-date molecular methodology and technology, but, more importantly, to provide them with opportunities to gain hands-on experience and to develop the capability to adopt new technologies. This can be done through laboratory courses, individual experimental projects, journal club-type discussions, and internships with biotechnology firms. As molecular biology research and procedures often deal with minute amounts of experimental materials and involve multiple steps, it is essential to train students to be precise, careful, patient, and persistent.

Innovation and Problem-Solving Capabilities

Biotechnology is an applied science. It aims at development and production of new, improved, safer, and less expensive products and processes. The ability to develop innovative strategies and workable plans for solving problems and to create new products is the key to success in biotechnology endeavors. Students who have a strong and broad scientific background would have the knowledge base to connect, venture, create, and be resourceful yet realistic. In training, recent advances and examples of biotechnology successes and failures should be analyzed and discussed so that novel ideas can be appreciated and lessons learned. Students should be given opportunities to create and imagine. It

is especially beneficial for M.Phil. and Ph.D. students to have room for independent thinking and exploration.

Appreciation of Applied Research and Entrepreneurial Spirit

Biotechnology may involve elements of basic science research, and biotechnological approaches can be used to address fundamental scientific questions. The ultimate goal of biotechnology, however, is to utilize the principles and technologies developed from modern biological sciences to produce products with application value. While some biotechnology trainees may become academic, government or private-institute researchers and conduct research with basic interests, more will enter biotech firms, corporations and research centers to undertake applied research. Biotechnology research projects are product-oriented and often prescribed and shorter termed. In addition, due to its commercial nature, biotechnology research often seeks patent protection, which may lead to delays in publication or no publication at all if the company so decides. On the other hand, scientists working in the biotechnology industry do not need to teach and may not be required to write grant proposals, yet they receive, in general, higher salaries. Biotechnology students thus must understand the applied nature of biotechnology research and the pros and cons that may be associated with industrial jobs. Ultimately it is important to develop an appreciation of the value and contributions that biotechnology could bring to society.

As biotechnology research involves current molecular technologies capable of generating genetically modified organisms and great commercial potential, biotechnology is a wide-open and fertile frontier for science and commercial exploitation and development. Students with an entrepreneurial spirit will prosper in such environment. The entrepreneurial spirit could be instilled in students through case studies of successful biotechnology efforts as well as failures, internship programs with biotechnology firms, invited seminars from biotechnology industry, and other interactions.

Knowledge of Intellectual Property, Regulatory and Other Biotechnology-Related Issues

Successful biotechnology research and development will result in proprietary technologies and products and will generate patents for protection. Students need to be informed of the im-

portance of and the issues related to intellectual property. Trainees also should be sensitized to local, national, and international biosafety and regulatory guidelines, as biotechnology research involves recombinant DNA technology and genetically modified organisms. Likewise, students should be aware of bioethical issues that may arise in biotechnology research and development.

Training Programs

With the desirable qualities and training philosophy outlined above, training programs for different levels of students, i.e. bachelor of science (B.Sc.), master of philosophy (M.Phil.), and doctor of philosophy (Ph.D.), could be developed to meet the target expectations.

B.Sc. Degree

At the B.Sc. level, for a three-year program on a semester system, it is important for students to build a solid foundation of knowledge in the beginning years with courses in microbiology, animal and plant biology, genetics, cell biology, organic chemistry, physiology, biochemistry, and associated laboratories. With this background, students can then move into the areas of molecular biology and genetic engineering and their associated laboratories. In their senior year, students would concentrate on biotechnology courses, including animal biotechnology and plant biotechnology, with microbial biotechnology and environmental biotechnology as elective options. Patenting, regulatory, bioethical, and related issues could be covered in the biotechnology courses or in a specific course or workshop designed for this purpose. A methodology course (such as methods in biotechnology) covering basic and current biotechnology methodology and techniques, with an emphasis on hands-on experimentation for students to gain technical skills, is essential. To further strengthen students' research and communication skills, each senior student could undertake a year long experimental project in a selected laboratory under the supervision of a teaching staff member and give a symposium-type presentation of the results at the end of the training. For students to gain industrial experience and prepare for the job market, summer internship programs could be set up for placing students in the laboratories or offices of biotechnology firms. Seminars with invited speakers from industry, universities, government agencies, and private institutes, making presentations on biotechnology or related topics would create excellent opportunities to expose students to a broad range of information and ideas.

M.Phil. and Ph.D. Degrees

For M.Phil. and Ph.D. students, the training should be more research oriented. However, adequate course work should be required: 1) to make up for possible background deficiency during B.Sc. study; 2) to broaden scientific base information through subfield studies; and 3) to gain in-depth and current information in the student's specialized area of research. These courses could be graduate courses and/or upper-level undergraduate courses, especially those biotechnology program courses described above. For the thesis research, it would be highly desirable to have a rather defined biotechnology project which could be completed in two years (M.Phil.) or three years (Ph.D.), and through which the student could practice a variety of methods and techniques in testing their hypotheses. However, especially for Ph.D. students, the research should be novel, as there is no shortage of creative thesis research projects in biotechnology. Seminar programs, journal clubs, regular lab meetings, scientific meetings, and teaching assistance would enrich students' knowledge and experience. However, among all these activities, it is important to give students the opportunity to do independent thinking and to be creative and self motivated.

Concluding Remarks

Training biotechnology personnel, to a great extent, is similar to training personnel for other scientific disciplines. However, the product-oriented, high-technology, rapid-advancing, and competitive nature of biotechnology does present some challenges for developing training programs. The desirable qualities and training philosophy I have outlined reflect my solution to this challenge. A final point will be that the training should take into consideration the current status, future prospects, and the niche and limitations of Hong Kong and the region's biotechnology industry so that the best-qualified and most appropriate personnel can be timely trained.

Financing Biotechnology in Hong Kong

Chapter 15

Biotechnology in Hong Kong: Investors' Sentiments

By

~ Walter K.K. Ho, Ph.D. ~
Chairman, Department of Biochemistry
The Chinese University of Hong Kong



***Walter k.K. Ho, Ph.D.**, is chairman of the Department of Biochemistry at The Chinese University of Hong Kong. He received his A.B. in biochemistry and economics and his Ph.D. in biophysics from the University of California, Berkeley. Ho also is an honorary professor at Zhejiang Academy of Agricultural Sciences in Hangzhou, China and at the Neuroscience Research Center, Guanghzou Medical College in China. He is chairman of the Biotechnology Planning Committee and Biotechnology Lab at The Chinese University of Hong Kong and a member of the Biotechnology Committee of the Industry and Technology Development Council of the Hong Kong Government Industry Department.*

Hong Kong is an exciting city. The most exciting part of it is the feeling of money in the air. Business is a way of life in Hong Kong, and people love to do business and make money.

Since the early '50s, Hong Kong's economy has changed face many times. With these changes, different business opportunities have evolved and made Hong Kong into an economic powerhouse in Asia. In the early '50s, Hong Kong was a transit port linking the East with the West. Import and export was the mainstream business, and the first crop of Chinese businessmen made their money trading with China and Southeast Asia. As more and more refugees from China migrated to Hong Kong, textile and light industry began to flourish. This pushed Hong Kong to the next level of prosperity. The '70s was the golden age of Hong Kong's manufacturing industry, as the export of electronics, plastic toys and clothing grew by leaps and bounds. The early '70s was also an important period because it marks Hong Kong's first exposure to the boom and bust of its own stock market. The Hang Seng Index dropped from a high of 1,700 to 150 in just six months. In spite of all the misgivings, Hong Kong learned how to make use of the stock exchange to raise capital and expand its businesses.

Manufacturing has always been the backbone of Hong Kong's economy since the post-War World II period. By the early '80s, internal demand for better housing ignited a boom in the local real estate market. The price of housing went from HK$300 to HK$400 per square foot to over HK$1,000. A small riot was set off when people queued up to buy flats in a new development in Shatin. Investment in real estate was the "in thing" to do. It was around this time that some of the major textile manufacturers gave up their businesses and became developers. In hindsight, this was a good decision, as those who continued to pursue textile manufacturing saw a rapid downturn of their business in the late '80s and '90s.

Good things never seem to last. By 1983, Hong Kong's stock and real estate market suffered a second crash. The news that China was going to take Hong Kong back by 1997 was a nightmare come true for all Hong Kong residents. Overnight, all the confidence and enthusiasm about the future of Hong Kong disappeared. The optimism was replaced by plans to close shop and migrate to a safer place. China running Hong Kong was unimaginable to most Hong Kong residents, as the two societies were light years apart. So, from mid-'80s to early '90s, life stood still for Hong Kong. Of course, there were some ups and downs dur-

ing this period, such as the worldwide stock market crash in 1987 and the Tiananmen Square incident in 1989. Within this period, everybody thought about moving assets and businesses overseas.

While most were thinking about leaving Hong Kong, a handful of local industrialists and businessmen saw the opportunity to expand their manufacturing base in China where there was cheaper land and labor costs. Very soon, the entire Pearl River Delta was working for Hong Kong. This winning combination made Hong Kong manufacturers competitive again.

With China's economic reform and steady open door policy, Hong Kong's negative attitude toward 1997 began to change. Hong Kong sees its new role as the bridge between China and the rest of the world. The banking and finance sectors expanded rapidly as more foreign money flowed into Hong Kong. Infrastructure projects, such as the building of the new airport, also contributed to the boom of the '90s. All of a sudden, Hong Kong became the most attractive place in the world to invest.

In contrast to previous economic expansion, the boom of the '90s was basically restricted to the finance and service sectors. Manufacturing could no longer survive the high cost of labor and land in Hong Kong. Factories were either relocated north of the border or closed for good. Industrialists were more interested in real estate and stock speculation than running their own businesses. With this change in investment climate and the countdown to 1997, it was not difficult to understand why everybody in Hong Kong was more interested in making a fast buck than taking the time and risk to build a business. In contrast to the '70s, real estate speculation in the '90s had very little impact on the price of industrial units (flats where Hong Kong factories are mostly located), as nobody saw any potential in this sector.

The opening of China has provided many investment opportunities for Hong Kong businessmen. It has also provided an escape route for Hong Kong manufacturers who want to compete against other Southeast Asian countries, such as Thailand and Indonesia. Toys, clothing, shoes, and consumer electronics can be manufactured in China for a fraction of the cost in Hong Kong. With this convenient arrangement, there is very little need to change Hong Kong's traditional manufacturing strategy. Like Hong Kong, major cities in China were perceived by Hong Kong companies to be investment paradises for real estate. Coupled

with the unrelenting enthusiasm and positive thinking of Mainland partners, Hong Kong companies poured huge sums of money into China to build homes and offices. With the slowdown of the Chinese economy in 1994, the oversupply of real estate in China has tied up a great deal of Hong Kong investment money. This is particularly unfortunate, as some of this money might have been earmarked for the development of new business and the expansion of manufacturing facilities.

When China first announced in 1983 that it would take back Hong Kong, no one ever expected the level of prosperity Hong Kong attained just before the 1997 handover. Hong Kong enjoyed a low unemployment rate, a boom in real estate and stock markets, a stable dollar, high personal income and high confidence and pride associated with being part of China again. In spite of these optimistic figures, Hong Kong's business strength and its traditional approach to running a business have eroded quietly. In the '70s, Hong Kong people expected to work hard in order to get ahead. They ran and developed a business and made sure it was okay by managing it properly. In the '90s, these attitudes no longer exist. People expect to do the least amount of work for the greatest return. They want quick money and are opportunists. Hong Kong has somehow been transformed into a frontier town of China, where everybody wants to come and make a fast buck. Speculation is the name of the game. Real estate prices in the fashionable Repulse Bay area have almost doubled in less than one year. People queued up in long lines for applications to subscribe to red chip stocks. Young and old hoarded coins bearing Queen Elizabeth's head, in hopes of reaping a hefty profit by selling them as souvenirs. All of a sudden, the whole population was engulfed in a wave of speculation; everybody dreamed of getting rich fast.

Hong Kong has been hailed as the paradise of business and investment since the early '60s. It is difficult to find a businessman who will not agree that Hong Kong is the best place to do business. The famous economist Milton Friedman loves Hong Kong because it is one of the few societies in the world which truly practices his theory of a free economy. Hong Kong has always taken pride on its freedom to invest. It has never been the government's wish nor desire to dictate measures to interfere with market forces. With this fervent pursuit of a laissez faire policy, Hong Kong businessmen are trained to rely on their own instincts and judgements to make investment decisions.

The first rule of thumb for starting a business in Hong Kong is, "Do not go into a business that you are not familiar with," a philosophy borrowed from an old Chinese saying. What this means is that businessmen are very conservative in Hong Kong. They would rather do nothing than venture into something which they are not sure of. This investment attitude has restricted the flow of capital to a handful of areas Hong Kong is traditionally comfortable in. Typically, these include real estate, consumer-oriented light industry, telecommunication services, the restaurant and fast food industry, hotel management, banking, financial brokerages, and retailing. Technology development has never been a favorite topic in Hong Kong. Most businessmen feel it is too risky, takes too long a time to develop and requires a large sum of money. Worst of all, none of them feel comfortable with it because they cannot perceive a return on their investment within several years. Take Hong Kong's favorite investment of real estate, for instance. A developer can count on getting his money back with a profit margin of 50-200% in three to five years. How can technology development compete with such a handsome and quick return! An investment manager of a famous brokerage house once told me that he would rather invest in a toilet that offers a choice of flushing volume than in high technology. He rationalized that he could envision a market for such a toilet but not for a biotechnology product. This pragmatic attitude is one of the biggest stumbling blocks in promoting high technology in Hong Kong.

Another problem in technology development is the lack of know-how and successful examples. Although Hong Kong has three universities which have been rated among the top 10 in Asia (**Asia Week Magazine**, May 23, 1997), their research activities have not attracted much interest from local businessmen. The barrier between the academic and business communities is mainly due to the attitude of the two sectors toward each other. On one hand, industrialists do not want universities to do their R&D because they think university professors are too slow and tend to be more interested in the pursuit of knowledge than in solving problems. On the other hand, university professors think industrial projects pay too little and cannot help them publish. Only in recent years, with more funding from the Industry Department, have universities begun to collaborate with industry. In contrast to this apathy, professors of civil engineering and architecture have always been close to the local building industry. Perhaps the traditional manufacturing industry in Hong Kong does not require much technology input, as it is still oriented toward a "me-too" commodity market.

Academicians have made a lot of noise about the potential of biotechnology leading Hong Kong into the 21st Century. To businessmen, electronics and information technology are closer to home. At least they can feel and use them in their daily activities. Talk to anybody in Hong Kong about the mobile phone, and they understand what information technology is about. Talk to them about biotechnology, however, and chances are good that nobody on the street can give you one decent example.

Why are people in Hong Kong, more specifically investors, so ignorant and indifferent to biotechnology?

- Biotechnology products are not consumer oriented and, as a result, people cannot see their market potential.
- There is no biotechnology industry in Hong Kong and no successful example, therefore no confidence.
- People perceive biotechnology as a highly technical subject and do not feel comfortable investing in it.
- Biotechnology research in Hong Kong is mostly upstream, and investors are reluctant to invest in immature technology.
- The effort needed to market a biotechnology product, such as pharmaceuticals or diagnostic tests, is uncertain because they may require substantial testing to satisfy licensing requirements.
- From past experiences, biotechnology is a highly competitive business and biotechnology companies going bankrupt in the U.S. are still fresh in investors' minds.
- Hong Kong investors have always been pampered with fast, high-rate investment returns from real estate and stocks. Biotechnology is unlikely to compete with these traditional channels of making money in Hong Kong.
- Wages for biomedical personnel are close to those in the U.S. and higher than that in U. K.. This high cost of labor coupled with the lack of industrial ex-

perience forces investors to face more risks starting a biotechnology company.

- Hong Kong has only a very limited market for biotechnology products, and a good sales network must be established. This is not economical, particularly for a start-up company.

- Raising money for any type of industrial project is not an easy task in Hong Kong and, for biotechnology, it would be nearly impossible, since bankers would demand tangible assets, such as real estate for collateral.

Given the insurmountable odds against starting a biotechnology venture in Hong Kong, the question remains, "What can we do?" Of course, the easiest way out is not to invest in biotechnology, a decision already reached by most investors in Hong Kong or Asia. If we really believe that biotechnology can bring Hong Kong into the high-tech era of the next century, what can we do to improve its attraction to investors? To start out, we should take measures to address each and every one of the issues mentioned above. Biotechnology is a relatively new technology. It was born only in the early '80s and, at the moment, it is only a teenager, at best. In Asia, with the exception of Japan, it is not even an industry yet. Like a growing child, we must give it nourishment and time to grow. What this means is that we should put resources into building a strong infrastructure. The infrastructure of the U.S. biotechnology industry was well established way before even the word "biotechnology" was used frequently. The availability of R&D money, the establishment of relevant government agencies (e.g. FDA, USDA), the existence of a food and pharmaceutical industry, the commitment of universities to quality biomedical research are all part of such an infrastructure. It is unreasonable and perhaps wasteful to expect Hong Kong to be able build such an infrastructure within the span of a few years. Nevertheless, with Hong Kong's return to China, it is possible to make use of the resources available in China to achieve these goals.

Because of Hong Kong's traditional investment philosophy, we will need to foster a new breed of entrepreneur willing to push for a biotechnology industry. Hong Kong investors have been pampered too much by easy money from real estate and financial dealings, and they are unlikely to have either the patience or foresight to pursue technology-oriented projects. The

new biotechnology entrepreneurs should have a strong China background and a deep perspective and firm commitment to science and technology. This kind of enthusiasm can be easily sensed in Shenzhen, where a budding biotechnology industry is already taking shape. Since 1985, over 50 biotechnology companies have been formed in Shenzhen, with activities ranging from reagent manufacturing to plant culture, diagnostics and pharmaceuticals.

One important source of biotechnology entrepreneurs when the industry was first started in the U.S. was the pool of university professors. Hong Kong has seven universities and two medical schools, and there are many professors with good qualifications. Hong Kong has been talking about biotechnology for the last 15 years and, yet, not even one local professor has quit his job to start a business in biotechnology. Why? This may be due partly to the lack of incentives and partly to high opportunity cost. Universities in Hong Kong are committed to undergraduate teaching. A professor's primary duty is to teach. Research, at best, is only second to teaching, a fact that none of the universities would willingly admit. Compared with universities in America, the amount of time a professor in Hong Kong can spare on research is significantly less. Coupled with the lack of team support, e.g. postdocs and experienced technicians, it is extremely difficult to focus on long-term R&D. Moreover, as substantiation and promotion depend on academic publication, it is unwise to spend time on product development.

By international standards, professors are paid well in Hong Kong. Quitting a professorship in Hong Kong to go into business would mean the loss of a secure, high-paying job worth about HK$1.2 million per year. Professors in China, who get paid HK$2,000 per month have every incentive to go into business. If one of them is successful in a biotech venture, he would earn 10 to 100 times more. In contrast, a Hong Kong professor would have a hard time convincing himself to quit his teaching job if the business venture could not yield a return of more than HK$2 million per year. Coupled with the uncertainty and risk inherently associated with developing a biotechnology product, a professor would have to be very brave to go into business by himself. With the introduction of Hong Kong's Industrial Support Fund in recent years, it becomes a bit more attractive for Hong Kong professors to get involved in industrial R&D. Unfortunately, this arrangement can increase the level of R&D, but it cannot enhance the entrepreneurship needed to build a biotechnology industry.

In addition to entrepreneurship, management and the concept of quality are also essential ingredients for a successful biotechnology industry. Hong Kong has plenty of expertise in management and quality control. Unfortunately, they are mostly limited to the electronic and service sectors. Expertise in biotechnology has remained mostly at the research level in the past 10 years. Students trained in our universities lack the concept of quality and the ability to find solutions for problems. Together with the lack of opportunity for training in an industrial setting, it is not likely that Hong Kong has the right human resources to staff a biotech industry. Hong Kong is not alone in this situation. Although China has a large bio-industry (which is involved in such traditional things as making antibiotics, vitamins and Chinese herbal formulations but nothing high tech). Its management skills and technical competence are still far from satisfactory compared with that of the West. Hong Kong is in a Catch-22 situation. On one hand, it must build the human resources required for a biotechnology industry but, on the other, it has no industry to train the right people. How can we break this dog-chasing-his-tail situation? One solution is to attract foreign companies to Hong Kong, another is to set up joint ventures so that foreign partners can provide training. Unfortunately, the high cost of doing business in Hong Kong prohibits such a deal unless some incentives, such as land subsidies, can be part of the agreement. For the long term, we must have a policy for training the right kind of manpower for a biotechnology industry. Research is only one of the four wheels on the biotechnology wagon. The others are: entrepreneurship, human resources and management skills. Unless we get all these together, investors will be reluctant to jump on this biotechnology bandwagon.

ADDENDUM

Since the writing of this article in November 1997, Asia and Hong Kong have experienced the worst financial crisis in recent years. Some major economies in the region, such as Korea, Thailand and Indonesia, have completely collapsed, and it will take years for them to recover. This economic turmoil in Asia has been attributed to financial mismanagement and blind expansion of highly speculative investments. The situation is similar to the U.S. savings and loan crisis in the late '80s. In Hong Kong, we have weathered this crisis a bit better than our neighbors. Nonetheless, we still suffered a 50% loss in our stock market and a 30% loss in our real estate value. Worst of all, the tourism industry has experienced a downturn of more than 50% in visitors from Southeast Asia, Japan and Taiwan. Adding these together, our finance and service industries, which seemed so invincible only a few months ago are now dragging our economy to a showdown.

One good thing that the recent financial crisis precipitated is the realization by government as well as investors that Hong Kong's economy is too dependent on paper investments, such as stocks and real estate. I hope this change in attitude will drive Hong Kong to pay more attention to investing in technology-based industry, including biotechnology. Since the handover, the new SAR Government has pledged to stabilize real estate prices by supplying more land for development. This move is correct, as most inflationary pressure in Hong Kong comes from high rent and high land prices. I am certain that people in Hong Kong can survive on a lower salary if they do not have to pay these horrendous prices for their homes.

Adjustment to Hong Kong's high land price policy will not be an easy task. Everybody, from real estate developers to flat owners, has a vested interest in it. The recent drop in real estate prices has already raised outcries from the business community, pressing the government to slow down in the supply of land for building flats. It is now up to the government to steer Hong Kong from its previous high land price policy to a more stable land policy so that resources can be better used for other types of investments. If this is successful, Hong Kong's economy should experience a period of more healthy growth in the next century.

Chapter 16

Venture Capital for Biotechnology in Hong Kong

By

~ Thomas Tsun Yung Cheung ~
Founder
Innomed Group Limited, Hong Kong

~ Abigail Yu-Fang Jung ~
Assistant to the Director
Innomed Group Limited, Hong Kong

Thomas Tsun Yung Cheung *is the founder of Innomed Group Limited in Hong Kong. After graduating from the University of Wisconsin at Madison with a B.S. in mathematics, computer science and statistics and from Cornell University with a Master of Engineering degree in operations research and industrial engineering, Cheung joined Arthur Andersen & Co. in Hong Kong. An active biotechnology player in Hong Kong and China, Innomed engages in projects such as molecular diagnostics, DNA fingerprinting, cord blood banking, stem cell research and applications of cell therapy technology. Cheung believes that in order to maintain its competitive edge, it is essential that Hong Kong develop its own high-tech industries with high value-added products and services. He envisages biotechnology as the most challenging and promising industry for the region in the immediate future.*

Abigail Yu-Fang Jung *is the Assistant to Director of Innomed Group Limited. She graduated from the University of California at Berkeley with a degree in Molecular and Cell Biology, with an emphasis in Neurobiology, and a minor in East Asian (Chinese) Studies. Jung was with Andersen Consulting LLP in San Francisco prior to joining Innomed Group Limited in Hong Kong. She hopes to improve healthcare in Asia by contributing to the development of biotechnology in Asia.*

Introduction to Venture Capital

Venture capital is risk equity capital invested in high-growth and/or innovative enterprises. Or, in simpler terms, venture capital is money invested in small, emerging companies by firms interested in supporting their growth in return for a share of the company. Venture capital is available to companies in all industries and all stages of development.

The four main development stages of companies in need of venture capital funding are seed, startup, expansion and mezzanine, or buyout. Companies in the seed phase are in the process of developing their product or service. They consist of little more than ideas and require capital research and development. Startup companies have their ideas conceptualized yet they need capital to test and develop their concepts. This is the stage at which most new ventures fail because it inherently contains the most risk and requires the most funding. Traditionally, it is at this point that the venture capitalists step in; however, most modern-day venture capitalists shy away from this stage due to its highly risky nature. This is particularly true for biotechnology investments. Ventures in the next stage, the expansion stage, usually require several rounds of financing. These companies have proven track records of commercializing their products and need capital to expand their operations in production, marketing or other related areas. The final stage is the mezzanine stage in which private companies are on the verge of going public, or listing on a public stock exchange. These companies are often ready for their initial public offerings (IPO) in one or two years and hope to reduce their liability with venture capital funds. At the same time, these companies can benefit from the expert guidance of venture capital firms during the IPO process.

While venture capital is available to companies in all industries and development stages, most venture capital firms focus on specific industries and/or stages of development. Neither tangible assets nor historical financial statements are the main concern of traditional venture capital investors, with the exception of those involved in the expansion or mezzanine stages in which case historical financial data will play a large role in investment decisions. Instead, the focus of most venture capitalists is on the management, future potential and intangible assets of the potential investment.

Traditional debt financing is seldom available to entrepreneurial enterprises because they generally lack the collateral, track record and earnings required to procure loans. Other types of fundraising, such as listing on a stock exchange, are not available to small entrepreneurial enterprises due to their inability to meet the restrictive listing requirements. Most entrepreneurs seek initial seed capital from family members, friends or wealthy individual investors who are willing to take the risk associated with startup ventures. This informal investment community finances the vast majority of new enterprises and plays an invaluable role in the entrepreneurial process. Venture capital firms, on the other hand, are funded by a network of institutional investors including: pension funds, insurance companies, foundations and endowments, professional money managers, wealthy individuals, foreign investors and other venture capitalists. Generally speaking, venture capital firms are the link between investors looking for high returns and entrepreneurs in need of capital.

Essentially professional managers of risk, venture capital professionals assess thousands of business plans a year and invest in only a small number of the most promising ventures. This comes to an average of about three to four a year. Once the firm has decided to invest in a particular venture, it will often take an active role as a strategic manager of the company. The venture capital firm will often hold a seat on the company's board of directors. Venture capitalists provide both the essential risk equity capital as well as the management expertise necessary to fuel the rapid growth of entrepreneurial ventures.

The advantages of capital from venture capitalists lie not only in the money, but also in the value-added services venture capitalists can provide. These services are invaluable and essential to the success of the ventures. Such value-added services include wide industry knowledge, management expertise from previous ventures, financial and strategic planning, recruitment of key personnel, access to technology and international markets, negotiation and execution of mergers and acquisitions and realization of public listings.

While not all venture capitalists operate in the same way, there are a number of characteristics common to most firms.

- General characteristics of venture capital firms:
- Finance new and rapidly growing companies;

- Have some type of equity investment in the companies;
- Target a wide range of industries and development stages;
- Add value to the companies by active participation;
- Have a medium- to long-term perspective, usually a three-to-five-year commitment;
- Expected returns based on long-term capital gains;
- No collateral or other security involved; and
- Decision process not necessarily influenced by past performance record.

Several basic criteria are required of entrepreneurial companies by most venture investors, as mentioned earlier. These include primarily quality management, large market and high growth potential, a proprietary product or service, and an assured way of exiting from the investment.

Quality management is probably the single-most important requirement that any growth enterprise needs to meet. The ultimate success of a venture is determined by the quality of the entrepreneurial management team. The reason venture capitalists focus so much on the management team is that the companies they finance are based on abstract ideas and plans rather than proven accomplishments. Venture capitalists will look for signs that the management team will be able to successfully deal with the inevitable hardships and adapt to the ever-changing marketplace. They prefer management teams with substantial experience in the industry in which the company expects to compete. Intimate knowledge of the relevant industry will give the company a distinct advantage, as management will be able to compete more effectively. The track records of management team members are also extremely critical. For example, members who have successfully developed a former company are more likely to find investors the second time around. Not only would they be well acquainted with the venture capital community, they would have past successes to validate their appeals. Because many entrepreneurs have experienced failure at some point in their entrepreneurial efforts, an important mitigating factor is the circum-

stances surrounding past failures and how management dealt with past challenges. Venture capitalists also look for teams that have worked well together on previous projects. Knowing the strengths, weaknesses and different operating styles of fellow team members allows for a more efficient and effective operation.

High growth potential is another extremely important characteristic of young enterprises that need financing. Ideally, these emerging growth ventures are able to address large markets and, if possible, become major players in the industry. One old rule of thumb suggests that a venture candidate should be able to achieve revenues of US$50 to US$100 million within five years of the first financing, assuming other rounds are provided as needed. Due to such high growth expectations, many venture capital firms invest in industries where such growth is more readily possible, such as in the information technology and biotechnology industries.

Venture capitalists also prefer to invest in industries on the rising part of the growth curve rather than at the peak. Instead of trying to enter a saturated market with improved products or services, they would rather back companies in the forefront of a new industry. Many successful venture-backed companies feature novel or proprietary products or services. Successful venture-stage companies must often rely on a strategy that gives it the lead in its new or emerging market. Successful venture capitalists invest in ideas that can create new industries or new ways of life rather than just refined or updated versions of existing entities.

The ease with which a venture capital firm can exit from its investment is a critical component of the business proposal. Venture capital firms usually sell back their shares to the original owners, to a third party or to the public through an IPO on a stock exchange. Oftentimes venture capital firms will choose not to fund certain businesses due to the lack of satisfactory exit channels.

Nature of Venture Capital in Asia

While business and financing operate on the same principle around the world, each region will inevitably have its own differentiating characteristics due to culture, history and tradition. The venture capital industry is no exception.

The main difference in venture capital between the East and the West is the nature of the investors themselves. While most

venture capitalists around the world scrutinize their prospective investments carefully, Asian venture capitalists tend to take caution a step further. They are known to be extremely risk-averse, requiring proof or guarantee of success before committing any of their capital. Once a type of venture is known to be successful, however, they are very quick to get into the action and fund other companies in the same industry. Another important feature is a common short-term perspective with respect to investing. Most investors are more interested in generating quick returns than in supporting long-term investments. Continuing on this theme, private investors are often more interested in personal wealth rather than the growth and development of a company or industry. They would prefer to invest in low-risk investments with less potential for return than high-risk investments with much greater potential.

Sources of venture capital in Asia are also slightly different from those in the West. Typical Asian sources include high-net-worth families, insurance companies, red-chip companies (China companies with head offices in Hong Kong), direct investment divisions of investment banks, direct investment divisions of commercial banks, independent venture capital firms, and subsidiaries of U.S. venture capital firms.

According to the **Asian Venture Capital Journal** (1997 edition), Asian venture capital and private equity continue to increase. Currently, total funds under management with a direct interest in Hong Kong and China, are well over US$10 billion. An effect of the Asian currency crisis on the investment industry is the increased availability of capital as cautious investors withdraw their money from the unreliable stock and property markets. Currently, there are 27 major venture capital funds that invest in Asia. Of these, 15 funds invest directly in Hong Kong and China. Only seven of these funds are listed and they are trading at a significant discount to their net asset value per share.

While Asian venture capital firms invest in the full gamut of developmental stages and industries, the amount committed to each one differs by year. While expansion and mezzanine stages still see most of the financing, it is important to note that the seed and start-up financing stages are beginning to receive more funding. Prior to the economic crisis of 1997, infrastructure projects such as construction, transportation and communication received most of the capital invested in Hong Kong.

The following list summarizes key investment factors considered by major Asian venture capital firms:

1) Past historical accounting record;
2) Business development plans;
3) Market analysis and financial forecasting earnings forecast;
4) Product/service evaluation and likelihood of success;
5) Background of management team;
6) Up-and-coming or developing market niche;
7) Terms of contract—fair terms and price;
8) Likelihood of profit realization; and
9) Method of exit

Not only do they differ principles from most other venture capitalists, Asian venture capitalists also have a slightly different interpretation of equity investment. While American venture capitalists often limit their involvement with their ventures to supplying capital and retaining a seat on the board of directors, Asian venture capitalists play a more active role in the day-to-day management of their ventures. They will often provide the company with experienced management and resources to oversee the daily operations of running the company, significantly adding value to their investments.

Not only are Asian venture capitalists different, Asian entrepreneurs are also different from their Western counterparts. One main difference is their view of venture capital funding. Asian entrepreneurs prefer to raise capital from family, friends, personal savings, and bank loans. They often prefer debt financing to direct investments. They would rather obtain financing from commercial banks, even at high interest rates, than dilute their earnings by sharing ownership of their enterprises. This is one of the reasons the venture capital industry is still relatively unknown and underdeveloped despite its thirty-year history in Hong Kong.

Access to Public Funding: Listing on a Public Stock Exchange

One major source of capital for U.S. biotechnology companies that is unavailable to most Hong Kong companies is a listing on a public stock exchange. The Nasdaq Stock Market, set up in the '70s, is the world's largest electronic screen-based market. It has two tiers: the Nasdaq National Market, for Nasdaq's larger companies, and the Nasdaq SmallCap Market, for emerging growth companies. Nasdaq's goals were to bring "level the playing field for the individual investors" and "be the stock market where growth companies come to raise capital" (Nasdaq Website, 1998).

Nasdaq helped create the biotech industry in the U.S. almost 20 years ago when American biotech firm Genentech raised $35 million in an initial public offering. Nasdaq president Alfred Berkeley compared the biotechnology industry to the early cable TV industry, another sector that started with big plans but few tangible assets. "Back then there wasn't enough VC [venture capital] money in the world to finance biotech. Nasdaq made the decision to allow its companies to raise financing before they had earnings, figuring that there's no reason that they couldn't raise money publicly if they fully disclosed what their intents were." (Nasdaq Website, 1998) The exchange's early support is evident in its current roster of companies: nearly 85% of all publicly held biotech companies trade on Nasdaq.

Nasdaq is also responsible for the enormously successful high-tech industry in the United States. Due to the extremely high-risk nature of high-tech companies, most were not able to obtain funding from traditional banks. Instead, high-tech entrepreneurs turned to venture capitalists interested in developing high-risk, yet high-potential companies. Without the existence of Nasdaq as an acceptable exit channel, many venture capitalists would not have invested in high-tech companies. Many large U.S. companies, such as software giant Microsoft, choose to remain on Nasdaq, despite being able to meet the more stringent listing requirements of the more prestigious New York Stock Exchange. Thus, Nasdaq became the world's second-largest equity market in the world in less than 25 years. It currently lists more than 5,000 companies and has a market capitalization of US$1.4 trillion.

Significance of a "Nasdaq" in Hong Kong

A key component of a strong, stable economy is a fair and open securities market. It provides the capital necessary to cultivate new ideas, giving companies the chance to flourish and in turn fosters vital growth through the creation of jobs and opportunities. The presence of a free market encourages citizens to invest in private enterprise and share in the economic potential of their country. Since most small companies cannot meet the listing requirements of the major stock exchanges, many countries have established secondary markets specifically targeting growth companies. In the region, countries with secondary markets include Japan, Singapore, Taiwan, Thailand and Malaysia.

The establishment of an alternate market to Hong Kong's Main Stock Exchange, or Second Board, in which the listing requirements are more feasible for small growth companies, is currently under debate. Its main objective would be to provide capital for emerging companies to facilitate their business development and/or expansion. The establishment of a second stock market, similar in principle to Nasdaq, is critical to the development of the biotechnology industry in Hong Kong. The primary reason is that without an acceptable outlet releasing them from their high-risk investments, many Asian venture capital firms are reluctant to fund emerging growth companies from an unfamiliar developing industry. And without the capital and guidance provided by the venture capital firms, small Asian biotechnology companies have little chance of long-term survival and growth.

Currently, the Main Board's listing requirements exceed the capabilities of most emerging companies. Only well-established "blue chip" companies are able to meet the high entry requirements of the Main Board. A Second Board with lower and simpler listing requirements would provide growing companies with the opportunity to raise much needed capital for expansion and development. This would allow biotechnology companies in Hong Kong to grow and increase their services, contributing to the development of a thriving biotechnology industry in Hong Kong. In return, a successful biotechnology industry would benefit Hong Kong in the form of employment opportunities, economic development and international prestige.

The Exchange Commission of Hong Kong is currently considering creating a Second Board as a separate market from the

Main Board. This Second Board would have a growth theme targeting emerging companies in all industries and sectors which are in need of additional capital to finance development or expansion.

In order to emphasize differences between the two markets, the Second Board would have different listing requirements and would maintain its own governance, structure and management. Precautionary measures would be taken to inform investors of the high risks associated with growth companies, such as potential volatility, low liquidity and a greater chance of failure. In addition, the Second Board would be promoted as a market for small and growing companies, specifically high-tech and Mainland companies. The fate of the Second Board, which rests in the hands of the Securities and Futures Commission, the Stock Exchange of Hong Kong and many other Hong Kong Special Administrative Region's agencies, should be determined by the end of 1998.

Although the Second Board idea was proposed more than 10 years ago, it was not met with much enthusiasm and was consequently put on the shelf. Recently, however, the idea of a Second Board has resurfaced and has generated a significantly warmer response. Despite the argument that Hong Kong needs a Second Board in order to encourage economic growth in the high-tech and biotechnology industries, many concerns have been voiced regarding the proposal. Some of these issues are listed below.

1) A high-risk market would be abused by Hong Kong companies;

2) Improper regulation of the market would affect Hong Kong's reputation as an international finance center;

3) Inadequate information on the small companies would be unfair and detrimental to investors;

4) The economic turmoil in the region makes the present a bad time to embark on a new venture of such magnitude;

5) There may be a shortage of qualified companies to list on the Second Board;

6) The development of a Second Board would be better served after the economies of Hong Kong and China are more in sync; and

7) The cost of forming a Second Board may not be justified if not enough companies choose to list there.

To counter some of these objections, many protective measures have been built into the Second Board proposal. In order to notify investors of the potential risk involved in the performance of small, emerging companies, the Second Board would constantly warn investors of the greater risks involved. The target investor group would be sophisticated investors more likely to conduct a thorough and objective appraisal of the business aspects and the risks involved prior to investing in Second Board companies. There would be a proposed minimum investment of HK$250,000 to ensure that only experienced investors invest. To protect minority shareholders, shareholders would be able to request liquidation of a company under special mitigating circumstances. Firms sponsoring the potentially listed companies would be subject to tougher pre-qualification requirements than those of the Main Board will. Only professional firms with high integrity and professional standards would be allowed to sponsor companies for listing on the Second Board.

The Second Board will also require listed companies to frequently disclose detailed company information to investors so that investors are kept abreast of company development. In addition to the annual and interim reports required by the Main Board, companies listed on the Second Board would be required to provide quarterly financial statements and a detailed comparison of the actual and projected company progress. Companies listed on the Second Board will also be required to strengthen corporate governance.

In order to regulate the Second Board effectively, a separate division of the Main Board of the Hong Kong Stock Exchange would monitor Second Board companies and notify the market when a Second Board company fails to meet disclosure of corporate governance obligations. In particular, a separate and dedicated unit would be set up by the Exchange to monitor compliance of listing obligations of Second Board companies and to take appropriate action in the event that a breach of listing obligation is identified. Educational and promotional programs would also be in place to inform investors of good and bad corporate practices and emphasize the importance of risk awareness and assessment.

The proposed entry requirements and conditions of the Second Board are:

1) A two-year track record demonstrating "active business pursuits" under the same management and ownership and describing the company's progress and achievements during that period;

2) A guarantee, immediately after listing, that the public shareholders will hold more than HK$30 million of the company's assets and at least 35% of the issued share capital;

3) A retainment of at least 35% of the issued share capital for a minimum of two years following listing by the management and a minimum of one year by the financial shareholders;

4) No minimum or maximum capitalization required, however, a proposed minimum free float requirement fee implies a minimum market capitalization at time of listing of HK$46.1 million;

5) Only new shares will be issued to the public at the time of listing; and

6) No more than half of any initial offering may take the form of a placing.

The Second Board proposal also contains special provisions or alternate listing requirements for technology-based companies to encourage the development of a high-tech industry in Hong Kong. As Nasdaq funded the growth of the high-tech and biotechnology industries in the U.S., the Second Board may be a critical factor in the birth of the same industries in Hong Kong. The existence of these industries is crucial to Hong Kong's economic growth as it develops in areas other than financial services and real estate.

Current Situation in Light of Asian Economic Crisis

The Asian currency devaluation crisis is changing the traditional Asian business structure of the past 15 years. Taken from the macro perspective, this shaking of the Asian economies is simply a part of a larger pattern. While it might be years before

the effects are fully realized, and many more before they are offset, it is important to understand the cyclical nature of these global trends. Asia's economy will eventually right itself. It is simply a matter of time.

In the meantime, Asian business dynamics are changing drastically, especially in finance. Controlling stakes of good assets, traditionally held by local investors, are being sold to foreign investors for the first time. Companies caught with too much foreign debt felt the squeeze the most. The liquidity crunch on local companies and the personal portfolios of their CEOs and other major shareholders has many companies in desperate need of cash. Local companies that never would have allowed foreign investors to hold equity shares have been forced to capitulate due to their overwhelming debts. Even major companies and institutions in South Korea, Thailand and Indonesia who would never have allowed for foreign investment prior to the crisis have been forced into doing so.

The venture capital industry is also getting into the action. With the availability of many fundamentally sound companies desperate for investors to bail them out, venture capitalists do not need to invest in the volatile Asian markets. In addition, venture capitalists are now able to obtain significantly better terms and equity stakes than before the economic crunch. High performing companies that once would have been able to dictate the price and provisions of any contract are now lessening their demands considerably. Buying up distressed assets has become very popular in the venture capital community, even with firms not previously specializing in buyouts. Unknown startups, competing with well-known "blue chip" companies, are finding it even more difficult than before to raise funding.

There is one lesson to be learned from the recent devastation to the region's economies. The need for Hong Kong to expand into "value-added" industries became apparent, as Hong Kong's economic foundation of stocks and real estate proved unsound.

Barriers from the Venture Capitalist's Perspective

The barriers to biotechnology development in Hong Kong cannot be ignored. There are a number of serious obstacles that impede the process. The main one is that biotechnology is a difficult industry in which to invest. Not only does it require large

sums of money and a long-term perspective, the potential for return is uncertain. Convincing Asian investors of the benefits of biotechnology can also be difficult due to the unfamiliar concepts involved. Unlike Western investors who have seen the benefits of the biotechnology industry, including its contributions to the medical and agricultural community as well as the high return to investors, Asian investors have no such success stories to convince them.

The lack of a biotechnology infrastructure already in place serves as a significant deterrent to building a biotechnology industry in Hong Kong. Research institutions and accumulation of talent and skilled labor takes many years to develop. Government funds are critical at this stage because of the proportionate amount of capital required to set up an infrastructure of this magnitude. Convincing university students to pursue studies in the sciences when few employment opportunities exist upon graduation is another difficult problem. Despite the current financial and real estate troubles, many university students still choose careers in those fields because the potential for high return is well known.

Another factor hindering biotechnology development is the size of the potential market for biotechnology products and services. The demand for advanced healthcare in Asia is not nearly as great as it is in the United States. Although private healthcare is on the rise in Asia, the potential market of those who not only want, but also can afford biotechnological services and products in China is undetermined. Biotechnology, used for medical purposes, is still a new concept to most of Asia, and local people may not understand the need for it. China, though a huge emerging market, has not reached the point in its economic development where it can afford expensive, upstream biotech products.

Viewpoints from a Local Biotech Entrepreneur

Ironically, despite the many serious problems brought on by the present economic turmoil in Asia, it may eventually prove to be beneficial to the development of a biotechnology industry in Hong Kong. Despite all the obstacles to biotech development in Hong Kong at the present time, there remains one main irrefutable point: Biotechnology will eventually develop in Asia. This will occur with or without Hong Kong's participation. It is up to Hong Kong to decide whether or not it wants to be part of the

coming biotechnology and healthcare revolution in Asia. While there are many considerable challenges facing local biotechnology entrepreneurs, they must persevere despite the present difficulties.

If viewed from a short-term perspective, the fledgling biotechnology industry in Hong Kong has little chance of receiving venture capital funding. At the present time, it cannot hope to compete with multinational well-established firms for venture capital. But if the situation is viewed with the idea that the biotechnology industry will eventually succeed in Asia, it suddenly becomes a matter of timing and getting into the rat race early on. Long-term investors, who have withdrawn funds from the unstable real estate or the stock markets and are now searching for more lucrative investment opportunities, should look toward biotechnology as a potential option. Because biotechnology venture capital is scarce even at the best of times, biotechnology companies are forced to offer significantly better terms and conditions to their venture capital partners. And with the troubled blue chip companies competing with them for venture capital funding, small biotech companies often have no choice but to offer significantly better terms than other less risky companies. As a result, there is no better time than the present to invest in biotechnology growth in Hong Kong.

While upstream biotechnology oftentimes involves extremely high risk research and development efforts requiring huge amounts of funding and spanning many years, this is not the kind of biotechnology suitable for Hong Kong. As stated in the previous chapter, biotechnology in Hong Kong will develop in conjunction with PR China. At present, Hong Kong and PR China are not yet able to compete with other nations in high-end research and development. Although proprietary research and development is important to Hong Kong and China's future, the present needs of Asian nations differ from those of Western nations, thereby dictating the types of technology and healthcare that should be introduced. Because Asia's Third World countries have different healthcare concerns than industrialized nations such as the United States, Hong Kong's biotech industry should be geared toward meeting the needs of the region. As a result, Hong Kong and PR China's biotechnology industries should be involved in providing lower end biotech products and healthcare services. These industries do not possess the same risk and capital requirements that high-end research does. These products and services, successful in other countries, would target a larger market and would be able to generate quicker return on investments.

Hong Kong's ability to support a biotechnology industry relies heavily on its infrastructure. Without the economic policies and financial infrastructure conducive to small business development, Hong Kong cannot hope to remain competitive in the high-tech and biotech industries. The government first needs to implement a mechanism, such as a small business loan program, by which startups are able to obtain funding for growth and development. Then the government needs to establish a Second Board so that these startups are able to acquire the financing they need for expansion. Without a Second Board or alternative exit avenue by which venture capital firms can "cash out" of their investments, many venture capital firms will not invest in small biotechnology companies. Without venture capital, biotechnology companies will not be able to survive in Hong Kong. UNESCO's most recent World Science Report, sums up the current biotechnology situation perfectly, concluding that while there exist technologies ready for exploitation, "it is the financing and will to put these technologies in place that are needed."

Regulatory & Intellectual Property Issues

Chapter 17

Achieving World-Class Pharmaceuticals: Accelerating Biopharmaceutical Development in Hong Kong Through Quality and Regulatory Enhancement

By

~ Edward Lau, Ph.D. ~
Founder and President
E.L. Associates, Inc., Wilmington, Delaware
&
Director of Education, Science & Technology
United States-China Intellectual Property Institute
Flushing, New York



***Edward P. Lau, Ph.D.**, is founder and president of E.L. Associates, Inc., Wilmington, Delaware, a pharmaceutical consultation group specializing in serving the health care industry in the U.S. and Asia-Pacific regions with product registration, quality assurance and quality control, GMP auditing/certification, formulation and analytical method development for prescription, generic and herbal drugs as well as pharmaceutical technology transfer, partnering and joint venture. Lau is also director of education, science & technology for the United States-China Intellectual Property Institute, a non-profit company in Flushing, New York, dedicated to encouraging understanding and the free exchange of technology between the two countries. Lau received his B.Sc. from the University of Manitoba, Winnipeg, Canada; his M.S. in pharmaceutical chemistry at Butler University, Indianapolis, Indiana; and his Ph.D. in physical pharmacy from the University of Wisconsin in Madison. Lau has more than 30 years' experience in the U.S. pharmaceutical industry in the areas of analytical method development, pharmaceutical research and development, quality assurance and control as well as regulatory and compliance operation including product registration (IND, NDA, ANDA, and FAP). Lau has worked with four major pharmaceutical corporations: Hoffmann La Roche in Nutley, New Jersey; G.D. Searle in Chicago; Pennwalt Pharmaceuticals in Rochester, New York; and DuPont Biomedicals and DuPont Merck Pharmaceuticals in Wilmington, Delaware, in directing analytical and pharmacy R&D, product registration and regulatory compliance, QA/QC toward the introduction of pharmaceutical products to the market.*

Introduction

Moving the Hong Kong biopharmaceutical industry to a world-class level requires strong regulatory involvement with product registration, manufacturing audits, and compliance inspections. In addition, greater investments must be made in research and development, quality assurance, and quality control. This chapter explores how the U.S., Europe and Japan currently handle these issues. Emphasis is placed on U.S. experience and practices since their industry and regulatory agencies are considered to be among the most advanced and rigorous in the world. Also recent changes in U.S. policy have created opportunities that can greatly benefit Hong Kong industry. Finally, the discussion reviews involvement of government along with academic and the private sector to support world class status.

As in the recent publication of Made By Hong Kong, the biopharmaceutical products referred to in this chapter include: Biotechnology Products, Generic Pharmaceuticals, and Traditional Chinese Medicine (TCM) Products identified as higher priority in pharmaceutical development in Hong Kong. The comprehensive and extensive presentation and discussion of this chapter are intended to provide benchmark planning resources and models for future pharmaceutical development in Hong Kong. Current status of quality compliance for the U.S. and other international markets are delineated and compared.

Challenges of Pharmaceutical Manufacturing in the Worldwide Market

Developing and marketing of human pharmaceutical products is a unique challenge. The requirements of product safety and efficacy are of primary concern since new drug products are expected to promote well being, relieve sickness, and prolong life.

In many parts of the world today, marketing and manufacturing of pharmaceutical products occur under strictly enforced government regulations, much to the benefit of the pharmaceutical industry. For example, in the U.S., the FDA's strong regulatory requirements for the pharmaceutical industry provide a stellar image for the industry and unshaken consumer faith in the products. Also, small pharmaceutical manufacturers can confidently develop products according to published guidelines and regulatory practices, such as Good Manufacturing Practice (GMP), rather than following manufacturers' regulatory interpretations, which may be incorrect.

While innovative, time consuming, and expensive research and development are key factors in the discovery of a successful product, strict quality control is crucial to its product integrity. To achieve quality excellence, every effort must be made to assure that quality is built into the product during the development and manufacturing processes in addition to the conventional quality control testing of a finished product. Although the investment of developing a new pharmaceutical product with quality is high, the returns of such investment is generally well rewarded.

Changes in economic conditions in North America and Europe have led to major pharmaceutical manufacturing companies frequently out-sourcing operations for cost effectiveness. This change in manufacturing philosophy has provided greater opportunities for smaller, more highly efficient and cost effective contract laboratories to provide technical services, packaging, quality management and production specialists. As Hong Kong has the proven ability to manage small organizations with flexibility for change and augmented with well trained work force and understanding of the worldwide business practices, Hong Kong will benefit from this change of strategy from the U.S. and Europe and should embrace this opportunity with resources for the new challenge.

In the past, Hong Kong's industrial success was based on innovation, flexibility, reduced labor costs, manufacturing quality, fast investment return, and operation freedom with minimal government involvement. However, the primary areas of production were plastic flowers, shoes, apparel, toys, and electronics. None of these areas, with the exception of the recent involvement in electronics, were either "high tech" or scientifically resourceful, and none will support the future success in biopharmaceutical development. The challenge to Hong Kong, as it moves toward world class pharmaceutical manufacturing, is to cope with government regulations, to have patience with long term investment commitments and slow capital returns, and to demand both high quality and ethics.

U.S. Pharmaceutical Industry

To build a new biopharmaceutical industry in Hong Kong for local and worldwide markets, a valuable lesson may be to study and model drug industry after the U.S. industry's infrastructure,

operational policies and quality management procedures, considered the most successful in the field.

The mission statements of many U.S. pharmaceutical businesses organizations state that their profits and continued growth must be built on quality, innovation in healthcare products and services. The mission of the business is well defined. Such statements confirm that the foundations of the U.S. pharmaceutical business are built, for the most part, on R&D and quality.

Typical Organizational Structure

The organizational structure of U.S. pharmaceutical companies differ from each other based on their historical development, cultural environment and operational efficiency. Nevertheless, the basic organization may be described as follows:

Office of the CEO -
- Administration
- Finance
- Marketing and Sales
- Human Resources
- International
- Research and Development
- Production
- QA/QC

As shown in the above organizational structure, QA/QC reports directly to the CEO, illustrating the significance of quality management and business goals

Types of Business

The U.S. pharmaceutical manufacturers may be classified in the following categories: ethical or branded, generic, biotechnology products, and over the counter (OTC) products. These categories are described below.

- **Ethical or Branded Prescription Products**

  Most pharmaceutical businesses in the U.S. belong in the ethical or branded prescription category. These companies are based in research and development to produce innovative products for human prescription drugs and animal health products, as well as the manufacturing of generic drugs,

diagnostic agents, OTC products, health care products, medical devices and vitamins.

The prerequisite for market introduction in this group is the lengthy and expensive approval of the New Drug Application (NDA). Manufacturing of prescription products is regulated by cGMP. Most of the larger firms in this group have manufacturing sites throughout the world, particularly in U.S., Puerto Rico, Europe, Australia and Japan.

Examples of this group include: Merck; American Home Products; Johnson & Johnson; Warner Lambert, Novartis; Smith Kline Beecheem: Glaxo-Wellcome; Rhone-Poulenc Rorer; Hochst-Roussel-Marion and Pharmacia-Upjohn.

- **Generic Or Multisource Products**

The second manufacturing group produces generic or multisource products. "The Waxman Hatch Act" of 1984 permits the manufacturing and marketing of pharmaceutical products by firms other than the original innovator after receiving Abbreviate New Drug Application (ANDA) approval. Since the chemical generic name of the original product is used rather the brand name, the product is generally referred to as "Generic." When more than one firm obtains approval for marketing the same product, it is known as a "Multisource Product." A generic product must have the same active ingredients and route of administration as the innovative product. Although no clinical trials are required, bioequivalency of the generic to the product must be exhibited and documented in the ANDA.

The introduction of the generic product permits greater competition among drug products within the market resulting in lower costs but minimal impact on quality.

The prerequisite for the product market introduction is the approval of the ANDA. Generic products may be manufactured by either a generic or a

branded prescription product house. Manufacturing must comply with cGMP. Due to low costs, many healthcare providers, including state purchasing agencies and insurance companies, prefer the use of generic drugs for patient prescriptions. In many states, a prescription for a branded name product must be specified by the physician; otherwise, the pharmacist may have the right to replace it with a lower cost generic product.

Some of these firms producing current generic products include: Geneva, Bolar, Ivax, Copley, Warner Chilcott, Pharmacia-Upjohn, Endo and Watson.

- **Biotechnology Products**

Biotechnology products are pharmaceutical products prepared by industrial processes using biological systems. For some industries, the processes involve the use of genetically engineered organisms. The preparation of the products generally involves: Recombinant DNA, Monoclonal Antibody/Hybridoma, Continuous Cell Lines, and Cellular Therapy Technology. Examples of these biotechnology medicines include drugs that must be free from the possibility of virus contamination such as those used to treat individuals suffering from hemophilia. Also, currently available are cancer drugs "programmed" to treat tumor cells; and substances that enhance the body's ability to heal (or protect itself against) life threatening diseases such as AIDS.

The prerequisites for marketing of a biotechnology drug include approval of the Product Licensing Application (PLA) and compliance with cGMP manufacturing guidelines. Both innovative biotechnology firms and large pharmaceutical manufacturers are involved in the business of introducing new products in this category.

Examples of these biotechnology derived products firms are: Merck, Bristol Myers Squibb, Abbott, Lilly, Pfizer, Schering-Plough, Hoffmann La Roche, Cetus, Amgen, Genetech, Biogen, Chiron, Centocor.

- **Over-the-counter (OTC) Products**

  The over-the-counter (OTC) or non-prescription products for self-treatment are medications available without a physician's prescription. The consumer buys theses remedies directly from a retailer. These products are intended to treat symptoms of minor discomfort, illness, or injury, and include drugs such as:

  √ Analgesic tablets, for headaches;

  √ First aid preparations, for a cut or abrasion

  √ Cough suppressants, for a nagging cough

  √ Antifungal agents, for athlete's foot

  √ Antiperspirants, for underarm wetness

  Some OTC manufacturers are McNeil of J&J, Whitehall of American Home Products, Warner Lambert, Bayer, Vicks.

- **Animal Health Products**

  Animal health or veterinary drug products are medicines intended for animals other than man, including drugs used in animal feeds. in some cases, animal drugs may be the same as the human drugs approved by NDA, but approval of the New Animal Drug Application (NADA) is required before marketing can start. For "animal for food" (e.g., chicken, cow and pig), additional requirements (i.e., environmental impact studies, human toxicology reports and drug residue levels in meat for food consumptions) are needed. Until recently, some approved human drugs with the agreement by the FDA may be used for animal health usage without additional registration.

- **Other Products**

  Many other products related to the pharmaceutical business are not discussed here; these products include:

√ Diagnostic Products

√ Radiopharmaceuticals

√ Vitamins and Nutritional Products

√ Medical Devices

Similar situations regarding types of business for the pharmaceutical products may existed in Europe and Japan.

Quality – Road to Success

Success of the pharmaceutical industry in the U.S. and many other parts of the world is directly related to innovative research and development (R&D) activities and the superiority of quality assurance and control (QA/QC) process. The quality of a product is not achieved by merely testing the finished products but is a continuous process beginning with discovery research through product development, manufacturing, product registrations (IND/NDA/ANDA) and market introduction with postmarketing support. Although the government regulatory agency (FDA) imposes quality systems, i.e. GLP and GMP to the U.S. industry, quality control systems in many companies are frequently more extensive and sophisticated than those demanded by regulations. The compliance of these regulatory practices is viewed as minimum requirement for R&D, manufacturing and QA/QC.

Although some may view quality control in a negative light, significant profits may be lost due to problems in quality control such as product recall, regulatory constraints including product suspension, competition, or litigation disputes. If physicians and patients perceive poor product quality, profit will be lost. All of this could be avoided by the diligent use of sound quality control practices. Products must be safe, effective and delivered in a conventional or novel mechanism to meet the demands of government regulations and ensure consumer, physicians, and health care provider confidence.

Quality Concept and Quality Control Process

As quality is the key concern in the pharmaceutical manufacturing, a general review of the quality concept and the process of quality control is essential.

According to Webster's Dictionary, "Quality" is defined as a "peculiar and essential character," a "degree of excellence," and a "distinguishing attribute." Industry leaders have expanded on these basic meanings to develop strategies for quality assurance and performance in quality management operations.

Joseph M. Juran, the guru of the American quality engineering, identifies in his book **Juran on Quality by Design** that quality as " the prerequisite of business success." For pharmaceuticals, it is more than a prerequisite: quality is a mandatory commitment. Juran cites the loss of market shares, product failure and waste as results of poor quality planning. Product quality, according to Juran, requires that the product conforms to: specifications, standards and procedures. Product quality should include the following components:

Features	Performance
Competitiveness	"User Friendly"
Product Safety	Reliability
Availability	Durability
Esthetic Appeals	Process Capability
Process Yields	Cost of Poor Quality

The QA/QC quality management concept according to Juran is defined in his book **Quality Control Handbook** as follows:

Quality Assurance (QA) – is defined as the activity of providing, to all concerned, the evidence needed to establish confidence that the quality function is being adequately performed. Quality function is the entire collection of activities through which we achieve fitness for use, no matter where these activities are performed.

Quality Control (QC) – is further defined as the regulatory process through which we measure actual quality performance, compare it with standards, and act on the difference.

The process of quality management in the pharmaceutical industry has evolved independently. Today it can be described as similar to the "Juran Triology Concept" in three elements: quality planning, quality control and quality improvement.

Quality Planning

In a typical U.S. pharmaceutical company, Quality Planning for a specific product is the responsibility of both the Product Selection Committee and a Project Team. Their quality planning activities are similar to those described by J.M. Juran.

In the Product Selection Committee, members consist of personnel representing a cross section of management, including medical, R&D, QA/QC, regulatory, production, sales, marketing, finance, legal, safety and human resources. Their mission is to evaluate and accept or reject proposals on the development of a product for regulatory registrations (IND, NDA) and subsequent market introduction. Proposals are based on the recommendation from the R&D on their discovery lead. The selection process focuses considerations on the efficacy and safety of the drug; the identity of the patients and their needs; the market size; the company's business goals; the competition in the drug business; the availability of the financial resources and the technical capability. Since it is a critical decision-making step, high level management is generally involved.

Another task force of Quality Planning is a Project Team. Members from different operational groups are generally mid-level managers in the technical disciplines with managerial control of resources. Groups represented on this team are Medical, R&D, Production, QA/QC, Regulatory Affairs and Project Management. The team's primary mission traces the entire path of development from product design to market introduction of an interested product designated by the Product Selection Committee. The challenges for this team are project planning, resolution of resource conflict, and adherence to the predetermined time line of project goals.

Quality Control

The Quality Control process includes:

- Evaluating actual quality performance
- Comparing actual performance to quality goals
- Acting on the difference

For the last two decades in the pharmaceutical industry, the use of terms "QA/QC" and the names of the respective departments in quality management have been evolving. Some firms consider QC as a subsection of the QA Department, primarily for laboratory testing. Others treat QA as a subsection of the QC Department, chiefly responsible for inspection and audit func-

tions. Regardless of the confusion in names or even the uniformity of the organizational structure through industry, these departments are responsible for the activities that ensure product quality.

Fundamental to U.S. pharmaceutical quality is the belief that quality is built into the products and is not tested out of the products. Therefore, many activities focus on the following:

- Incoming material;
- Process validation;
- Equipment calibration;
- In-process control;
- Product failure investigation and correction;
- Environmental control;
- Definition and adherence to standard operating procedures.

The compliance with government requirements (such as cGMP and GLP) is essential, reinforcing a superior quality control system.

Quality Improvement

Quality Improvement: raises quality performance to unprecedented levels. The process includes the following steps:

- Establish the infrastructure needed to secure annual quality improvement.
- Identify the specific needs for improvement and form project team.
- Establish project team with clear responsibility for bringing the quality improvement project to successful conclusion for each project.
- Provide the resources, motivation and training needed by the teams to diagnose the causes and simulate establishment remedies.
- Establish controls to maintain the gains.

Once a pharmaceutical product is released in the U.S., factors related to product failure have been anticipated and corrected so that opportunities for direct product improvement are few. In this regulated industry, most product quality changes require the pre-approval of the government regulatory agency, FDA. Since

the pre-approval process can be very time consuming, a great deal of time is focused on "getting it right the first time." Quality Programs such as "no margin for error," "zero defects," and "total quality management" motivate high quality design and manufacturing, resulting excellent products and leave little room for improvement. Quality circles and product improvement teams exist for improvements related to economics and services provided such as higher production yields, better packaging, faster delivery to distributor and improved educational programs for consumers and health care providers.

Indirect quality improvement of products is another perspective active in the industry. It does not involve in the product itself, but provides opportunity for another new product based on the experience of an existing product. Therefore, identification of the consumer's need for the line extension and implementation of the development into a new product is a significant activity. Line extension of a product is the development of related products extending from the original product. The line extension product could be dosage forms with different strengths or different forms such as control released tablets, injectable, topical cream and ointment or novel drug delivery systems including transdermal delivery patches. Generally, the concept of the extension product is based on the infrastructure of the product improvement program.

Quality Excellence of Pharmaceuticals

As discussed in the previous section, success of the pharmaceutical business is closely related to quality, both in products and services. Although the industry is regulated by the Food and Drug Administration (FDA), the pharmaceutical industry has placed itself frequently in quality environments and requirements which are above the expectations of the government agency. Many companies occasionally partner with the FDA or USP through their trade organizations to establish standards and processes to shape quality advances. For examples, the development of the Good Laboratory Practice initiated by the industry, expanded by the Pharmaceutical Manufacturing Association (PMA) and finally sent to FDA for processing to become official regulation.

Quality Standards – Specifications

In the U.S. pharmaceutical industry, establishing specification is the first step after exploratory research to bring a product

to market. Specifications are the quality definition of an article (product or the related materials for production) by which acceptance eventually market distribution are based. The specifications of pharmaceutical products, both drug substances and dosage forms, are defined by:

IDENTITY, PURITY, STRENGTH, AND QUALITY

After IND and NDA, compliance with the specifications becomes mandatory, due to industry commitment to FDA and quality. Changes of specifications generally require regulatory approval. License by the ethecal manufacturer for exclusive marketing of a pharmaceutical product is effective for a specified time after NDA approval (generally 17 years). At the end of this period and upon approval of Abbreviated NDA (ANDA), the manufacturing and marketing of the equivalent product may proceed by a generic firm. This generic product must meet the compendial standards published by the U.S. Pharmacopeia (USP) in the respective monograph.

Compendial Quality Standards

The official quality standards of drug substances, dosage forms, testing methods and the related practices may be found in the U.S. Pharmacopeia and National Formulary (USP/NF). This U.S. compendial organization, U.S. Pharmacopeia Convention (USPC), is a non-government agency, the only compendia in the world which is independent from the government and has the authority to set official quality standards.

At appropriate time or near the expiration of the innovative product exclusivity, the USP publishes a monograph of a drug article, either for drug substances or dosage forms. These USP monographs have the same criteria to define the quality of the innovative products. In fact, the similar criteria for quality are used by all compendia of the world.

Most U.S. Pharmaceutical manufacturers prefer USP grade materials to prepare their products. The USP grade materials are drugs or excipients which are tested according to current USP monographs before the release of each production lot. When applicable, drug substances, excipients and dosage forms in the generic, over-the-counter products as well as the components of the new drug product must meet the compendial standards enforced by the FDA. The test methods and other standards in the USP also meet legal drug product requirements.

Cost of Quality

The cost of product quality may be estimated, calculated and quantified. However, this cost is difficult to separate from the cost of production as many quality operations are mandatory and required business expense. While the cost of building product satisfaction may be estimated, the cost may not be an effective way to illustrate the "pay-off" in the investment of quality building.

Quality deficiency in pharmaceutical products performance often results from product mix-up, contamination, instability, poor content uniformity and dissolution, dissolution in solid dosage forms, or label error. Such failures may result in temporary product market suspension, product recall, or product withdrawal. The financial impact of such occurrences can result in litigation and losses of revenue, customer confidence, and competitive edge.

In addition to the product quality performance, the quality of product registration generated from R&D and manufacturing is pertinent to business profits. Delay of FDA approval because of unsatisfactory documentation or supporting experiments can greatly affect the market introduction dated; therefore, market shares may be lost to a competitor.

Government Involvement in Regulatory Practice

Development of pharmaceutical products for human use is a unique experience to introduce a new product into the market place. Since the expectation of a new drug product is closely related to human life - particularly in promoting well being, relieving sickness and prolonging life, the requirement of a product's safety and efficacy is an important concerns. In many parts of the world, the market and manufacturing are controlled by the government regulatory agency because of the influence on life. Pre-established requirements have to be met before a drug product is introduced to the market.

The regulatory process to achieve the above concerns consists of two major operations:

Product Registrations such as IND, NDA, ANDA, Animal NDA, FAP (Food Additive Petition), and 510 (k), (Medical Devices) are the quality commitment of the manufacturers for the production, testing and storage of the marketed products.

Compliance Practices such as cGMP and GLP are practices to monitor and measure the development and manufacturing.

Drug Manufacturing and Quality-Regulated Business

The characteristic of a U.S. pharmaceutical product is generally related to its excellent quality and efficacy. The manufacturing triumph of these products is based not only on the performance of a drug company, but also on the regulatory agency that oversees its operation. To build a solid product, the regulatory agency establishes and imposes guidelines on product registration and rigorous quality requirements.

The genuine commitments of the drug firm for manufacturing, product support and quality control are other, essential parts of the success.

For the last few decades, pharmaceutical development in the Western world has been well established and is predominantly a government regulated business. Laws and regulations in development, registration, manufacturing and quality control of a drug products have been established for the industry. Therefore, a small pharmaceutical manufacturer can develop products according to published guidelines and following other known regulatory practices, such as Product Registration Processes: IND, NDA or ANDA and Quality Compliance Programs: GMP, GLP and GCP.

History of U.S. Regulatory Development

Regulatory organization, authorized to perform similar regulatory activities as the current FDA, was established during the Civil War. Concerned about potential deleterious health effects, the Bureau of Chemistry of the U.S. Department of Agriculture was later authorized to investigate food adulteration as early as 1879. After the turn of the century, drug laws began greater development. U.S. drug laws may be best illustrated as follows:

1906 **Pure Food and Drugs Act**

- Required drugs to meet official standards of strength and quality

1938 **Federal Food, Drug and Cosmetic Act**

- Required new drug manufacturers to prove safety through an NDA submission
- Allowed drug marketing to begin 60 days after NDA submission, if FDA posed no objection

1951 **Durham-Humphery Amendment**

- Dictated which drugs needed prescription drug labels

1962 **Kefauver-Harris Amendments**

- Required proof of effectiveness before marketing
- Required manufacturers to comply with GMP
- Made FDA approval of NDA the prerequisite for marketing

1966 **Drug Efficacy Study Implementation (DESI)**

- Contracted with government agencies to evaluate the effectiveness of 4000 drugs which have been evaluated for safety

1972 **Drug Listing Act**

- Required manufacturers to maintain and report to FDA, current inventory of drug produced

1976 **Medical Devices Amendments**

- Addressed issues such as investigation use, cGMP and other restrictions
- Required same efficacy and safety standards as drug for life-sustaining and life-supporting devices
- Redefined distinction between drugs and devices

1979 **Good Laboratory Practice**

- Compliance of GLP became effective on June 20, 1979. Proposed first draft on November 16, 1976

1983 **Orphan Drug Act**

- Provided companies with tax breaks and a limited exclusive license for drugs designed to treat "orphan" diseases or conditions

1984 **Drug Price Competition and Patent Term Restoration Act**

- Expanded ANDA process to allow generic manufacturer to market identical versions of off-patient drugs without costly nonclinical and clinical testing
- Allowed research-based industry to receive patent extension to recover patent lives lost during FDA review

1986 **Drug Exports Amendment Act**

- Allowed U.S. drug maker to export certain human and animal drugs, biologicals and biological intermediates, not yet approved by the FDA

1987 **Prescription Market Act**

- Prohibited practices that might result in the sale of drugs that are adulterated, misbranded, counterfeit, expired or subpotent

1988 **Generic Animal Drug and Patent Term Restoration Act**

- Allowed the generic versions of veterinary products (approved after 1962) to be manufactured and sold

1990 **Nutritional Labeling and Education Act**

- Required all package foods to bear Nutritional Labeling and health clams

1992 **Generic Drug Enforcement Act**

- Imposed debarment and other penalties for illegal acts involving ANDA

1994 **Dietary Supplement Health and Education Act**

- Established specific labeling requirements, provided a regulatory framework, and authorized FDA to promulgate GMP regulations for "dietary supplements" and "dietary ingredients" and classified them as food

1996 **cGMP Revision**

- The latest cGMP revision published in the Federal Register on May 3, 1996

Regulatory Agency in the U.S. – Food and Drug Administration (FDA)

Organization of FDA

The Food and Drug Administration (FDA) is a subdivision of the Health and Human Services (HHS), headed by the secretary of the HHS who is appointed by the President of the U.S.. The commissioner of the FDA reports to the secretary and prepares proposed regulations for his/her approval. These regulations are published in the Federal Register and can become the force of law. The office of operation (one of the nine offices of the FDA) is comprised of eight centers as listed below. The director of each center reports to the commissioner:

- Center of Drug Evaluation and Research
- Center for Biological Evaluation and Research
- Center for Devices and Radiological Health
- Center for Food Safety and Applied Nutrition

- National Center for Toxicological Research
- Center for Veterinary Research
- Office of Orphan Products Development
- Office of Regulatory Affairs

Functions and Authority

The principal function of the FDA is to protect consumers by enforcing the law passed by Congress. These laws were intended to assure the safety of foods, drugs, biologics and medical devices sold in the U.S.. Specifically, enforcement of the regulations associates with the following areas of activity:

- Quality of the product including the manufacturer's control of consistency of separate batch or lots of product, the identity, purity and stability.
- Promoting and advertising the product, largely determined by the product's labeling.
- Storing and manufacturing facilities of the product.
- Submitting data to ensures accurate claims which reflect the documented product information.

Official Guidelines

From time to time, the FDA publishes guidelines in the Federal Register or in the agency's publications to aid the industry compliance with the regulatory expectations. These guidelines establish principles or practice of applicability and state procedures of standards which are not legal requirements but acceptable to FDA if a subject matter falls within the law administered by the commissioner.

Some of these U.S. regulatory guidelines include:

- Manufacturing and Control Guidelines of IND's and NDA's
- Guideline on the Preparation of Investigational New Drug Products
- Guidance for Industry – Content and Format of IND's for Phase 1 Studies of Drugs, including Well-Characterized, Therapeutic and Biotechnology Derived Products

- Guideline on Formatting, Assembling and Submitting New Drug and Antibiotic Application

Regulatory Authority in Europe and Japan

Regulatory Agencies in the European Union

In the European Union, the legislative and executive power rests mainly with the European Commission which is assisted by 24 Directorate Generals (DG) headed with a commissioner in each sector. Specifically, the head of unit of the Directorate III/E3 (reporting to the Commissioner of the Directorate III) is responsible for regulatory requirements and laws regarding pharmaceutical products.

The establishment and updating of pharmaceutical registration requirements is the responsibility of the Standing Committee on Medicinal Products for Human Use. The committee consists of representatives of member states' representatives and a European Commission representative as chairman. The authorizing and supervising of medicinal products throughout the European Union is the responsibility of a central agency, the European Agency for the Evaluation of Medicinal Products (EMEA). The agency works closely with the European Commission and, most importantly, with the Directorate General III, the Committee for Proprietary Medicinal Products (CPMP) and the member states of the European Union. The primary task of the agency is to provide guidance on tests and clinical trails to demonstrate the quality, safety and efficacy of medicinal products to the member states of the European Union.

The member states are responsible for many tasks and duties which form the basis for the functions of the single European licensing system. Among a variety of tasks, the adoption of the laws of the European Union into national law is a critical responsibility. Also, member states are responsible for inspections of pharmaceutical manufacturers' facilities and updating of EMEA's experts list which ensures the integrity, availability and expertise.

Regulatory Agencies in Japan

In Japan, the Ministry of Health and Welfare (MHW) is the government agency ultimately responsible for the approval of New Drug Application (NDA). The MHW consists of nine separate bureaus. Businesses relative to pharmaceutical products are

handled mostly by the Pharmaceutical Affairs Bureau (PAB) which is similar to the FDA in the U.S..

The NDA is processed by the Investigation Division, one of eight division of the PAB, which evaluates and approves New Chemical Entities (NCE). In their involvement with NDA, the investigation Division of the PAB has only "administrative guidance" in nature. The in-depth NDA review in Japan is performed by the Central Pharmaceutical Affairs Council (CPAC), an advisory organization to the MHW to investigate and review important pharmaceutical issues. The CPAC consists of outside experts, mostly faculty members at major universities or research institutes in fields such as pharmaceutics, pharmacology, toxicology and clinical sciences.

The Inspection and Guidance Division of the Pharmaceutical Affairs Bureau has the responsibility for the controls of quality and manufacturing of pharmaceutical products such as overseeing the Good Manufacturing Practice (GMP) and other regulatory compliance.

Product Registration

Product Registration Process – U.S.

To obtain U.S. permission for starting a new product clinical study or for marketing a new drug, an application must be submitted to the FDA. Upon approval, or meeting the requirement, the clinical study or market introduction may be proceed. Regulatory registrations may be classified according to the stage of development and the nature of the products:

Investigational New Drug (IND)

IND is a proposal to the FDA to obtain permission for clinical trial of a new drug. This applications is for exemption from the prohibitive status of an unapproval drug from being shipped in the interstate commerce, the first step toward the marketing approval. The submission include Animal Toxicology and Pharmacology Studies; Chemistry, Manufacturing, and Control (CMC) information; Clinical Protocol and Investigator Qualifications.

The FDA neither approves or disapproves IND. After a 30-day review period, clinical studies may be initiated unless receiving notification from the FDA on "clinical hold."

New Drug Application (NDA)

NDA is basically the manufacturer's request to the FDA for marketing a new drug product in the U.S.. As a contract between the FDA and the manufacturer, it relates the firm's commitment in the manufacturing, quality standards and drug development activities. Some information included in the NDA may have been submitted earlier in the IND but with additional and revised information in the NDA submission. Data and information includes: Chemistry, Manufacturing and Control (CMC), Non-Clinical Pharmacology and Toxicology, Human Pharmacokinetics and Bioavailability section, Microbiology (for anti-infective drugs only), Clinical and Statistical sections, Case report forms and tabulations, Samples and Labeling.

The review process is time consuming and complex and requires extensive interaction between the sponsors and the agency. Generally, the time for approval of a NDA is approximately eight to 12 years.

Biological License Application (BLA)

For biological licensing, two different processes may bring the biotechnology derived product into the market upon FDA approval.

For certain well characterized biotechnology and synthetic biology products a single application – Biological License Application (BLA), is required to gain approval for market distribution. Four categories are defined for this process:

- Therapeutic DNA plasmid product
- Therapeutic synthetic peptide products of 40 or fewer amino acids
- Monoclonal antibody products for in vivo use
- Therapeutic recombinant DNA derived products

For all other biological products, sponsors must submit two applications – an Establishment License Application (ELA) and Product License Application (PLA). Both submission processes (BLA or ELA/PLA) may include nonclinical and clinical data, chemical and biological information, product manufacturing process and facility. Ultimately, the single application BLA system may be the future marketing approval model for submission of all biotechnology derived products.

The FDA prefers to meet with the sponsor before the submission for establishing dialog and contacts, discussing application and the review process. Generally, the time required for the review is much the same as the NDA.

Abbreviated New Drug Application (ANDA)

For marketing a generic drug product, ANDA is required. ANDA is the application for duplicating a drug product that NDA has previously approved. The submission requires CMC data but without data from expensive clinical trials. Demonstrated evidence of the human bioavailability is required. In some cases, this requirement may be waived and substituted with a dissolution study.

The time required for the ANDA is much shorter than the NDA, in about a year or less.

Drug Master File (DMF)

A Drug Master File (DMF) is a document containing confidential information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs. In the U.S., the submission of the DMF is solely at the discretion of the holder. It is not required by law or FDA regulation. A DMF is normally submitted by someone other than a drug product applicant to provide detailed information concerning toxicology, chemistry, manufacturing and control aspects. The information contained in the DMF may be used to support an Investigational New Drug Application (IND), a New Drug Application (NDA), an Abbreviated New Drug Application (ANDA), another DMF, an Export Application or amendments and supplement to any of these.

A DMF is not a substitute for any of the above applications. It is not approved or disapproved by the regulatory agency. Technical contents of a DMF are reviewed only in connection with the review of an IND, NDA, ANDA, or an Export Application.

In cases where ownership of the NDA and ownership of the DMF are different, cross-reference to the DMF may be made by several manufacturers. For example, the DMF of an excipient is submitted by an excipient manufacturer, and a NDA of a dosage containing the said excipient is filed by manufacturer A and also manufacturer B. Both NDA's may make reference to the same DMF without further describing the excipient used in their products.

DMF may be further separated into five different types based on the natures submitted, as follows:

Type I	Manufacturing sites, facilities, operating procedures and personnel.
Type II	Drug substance, drug substance interme diate and materials used in their prepara tion or drug product.
Type III	Packaging Materials.
Type IX	Excipients, colorant, flavor, essence, or materials used in their preparation.
Type X	FDA-accepted reference information.

For a bulk pharmaceutical chemical (BPC) intended to be sold in the U.S. market for generic manufacturing (USP grade materials), a filing of DMF of Type I and Type II with the FDA are desirable.

Other Registrations

510 K - For the marketing of medical devices including instruments, apparatus, implements, machines, contrivance, implant or in-vitro diagnostic agents, 510(k) is the registration process.

Food Additive Petition (FAP) - For agents used in the food enhancement such as artificial sweeteners and food substitutes, Food Additive Petition (FAP) is the registration process required for marketing.

Product Registrations in Europe and Japan

Product Registration in Europe

In Europe, a Marketing Authorization Application (MAA) must be filed by the manufacturer with the competent authorities of the member states (the mutual recognized procedure) or with the EMEA (the centralized procedure) to obtain a market authorization.

For drugs derived by means of recombinant DNA technology, controlled expression of gene coding for biological active protein in prokaryotes and eukaroytes (including transformed

mamalian cells) and hybridoma and monoclonal antibody methods, the use of the centralized procedure is mandatory. For some innovative products, either of the two procedures may be used.

The outline of the dossier (the registration) is the same for drug and biological medicinal products with specific additions and changes for certain types of products. Unlike the FDA product registration process, The European Union dossier does not distinguish between the NDA, PLA and ELA.

In the application dossier, the expert report prepared by a qualified person in the individual area of expertise plays a critical role in the licensing of medicinal products. The expert report covering safety, efficacy and quality may be classified into three parts:

Part 1 - Chemical, Pharmaceutical and Biological Documentation: cover the manufacturing, quality aspects, control tests, and stability.

Part 2 - Pharmaco-toxicological Data: discuss the preclinical animal data.

Part 3 - Clinical Report: summarize the comprehen sive clinical data and clinical experience.

In addition, a single document of the Summary of Product Characteristic (SPC) containing essential information on the properties and the characteristics of the product must be included as part of the dossier.

Product Registration in Japan

In Japan, the marketing approval of a drug product is the responsibility of the Ministry of Health and Welfare (MHW) upon the satisfactory review of the Ingredients, Quantities, Manufacturing Methods, Directions, Dose, Indications, Efficacies, Standards and Test Methods in the application.

Manufacturing or Import Licenses — A license must be obtained for anyone intended to manufacture (or import) drugs for each manufacturing plant (or business office).

Drug Manufacturing Approval — Other than those drugs which are listed in the Japanese Pharmacopoeia but exempted from the approval process, an approval for manufacturing (importing) must be obtained for each drug.

In other words, drugs which are exempted from the approval process, such as some JP drugs, require only licensing for the manufacturing plant or office. However, most drugs required approval for manufacturing as well as plant licensing.

The New Drug Applications (NDA) in Japan may be classified into eight categories:

1. Drugs with new chemical entities
2. Combination drugs with new chemical entities
3. Drugs with new routes of administration
4. Drugs with new indications
5. Drugs with new formulations, such as controlled release products
6. Drugs with new dosages
7. Drugs with new strength/ formulas or combination drugs with similar composition
8. Others (Generics)

In the approval process, the NDA of a Biotechnology derived product in Japan is treated in the same way as synthetic drugs. The NDA is processed by the Investigation Division of the Pharmaceutical Affairs Bureau (PAB) of the Ministry of Health and Welfares (MHW). The review and evaluation of the NDA are essentially conducted by the Central Pharmaceutical Affairs Council (CPAC), the third party advisory for the minister. The official approval is issued by the Ministry. Recently, the MHW announced the reform of the current drug approval system. The review function and responsibility will be transferring to a newly founded organization, the Drug Investigation Center in the National Institute of Hygienic Science. The reorganization will also shift the responsibility for the NDA review in Japan from the CPAC which consists of outside experts to an internal review system by full-time staff, similar to that of the U.S.

For registration of non-prescription drugs, MHW outlined the following principles for considering the approval of non-prescription drugs:

1. Ingredients and composition shall be within a range which assure safety and efficacy of the product.

2. Indication shall be for preventing or treating minor ailments or maintaining and improving health.

3. Direction for administration, dosage and dosage forms shall be described in such manner as to be easily understandable to the lay person.

Approval standards for manufacturing have been established for cold medicines, antipyretics, analgesics, antitussives and expectorants, gastrointestinal drugs, cathratics and antimotionsickness agents. The approval of these nonprescription products are now the responsibility of the prefectual government in Japan.

Drug Development Processes and Product Registration

The activities of QA/QC are extensively involved with every function of the pharmaceutical business including Research and Development (R&D). Understanding the entire development and manufacturing cycle, from candidate identification to the market introduction is necessary to describe the functions and the responsibility of QA/QC for the purpose of product registration and subsequent manufacturing compliance.

Development and Manufacturing Cycle:

Discovery Research –› Candidate Identification –› Preclinical R&D –› IND –› Clinical Trial-Phase I –› Clinical Trial-Phase 2 –› Clinical Trial-Phase 3 –› NDA –› Preapproval Inspection–› NDA approval for marketing–› Market Distribution –› Post marketing surveillance and support

Drug development requires a series of highly complex and technologically oriented processes. The processes may be divided into many components or phases to explain the total efforts. The preferred approaches are described as follows:

Stage 0 - Discovery Research Activities:

- Chemical Synthesis or isolation - Based on previous knowledge, or hypotheses, a new chemical entity is isolated, purified or synthesized.

- A series of chemical analogs is also synthesized primarily for patent protection from the lead compound.

- Pharmacological Testing - These chemicals are then tested for pharmacological activities such as screening for lead.

- Candidate Identification - The successful candidate is characterized and proposed to the Product Selection Committee for acceptance as development product for IND registration.

- Product name Assignment - A research code number or a product name is assigned to the compound of interest and used throughout the product life.

QA/QC Involvement: Advisory capacity only.

Stage 1 - Preclinical Development Activities:

- Safety Assessment - Toxicology Studies in animals. (GLP)

- Drug Metabolism in Animal. (GLP)

- Chemical Scale-Up. (GMP)

- Preformulation and Formulation Development. (GMP)

- Clinical Supply Preparations. (GCP,GMP)

- Analytical Method Development. (GLP,GMP)

- Specifications setting for drug substances and dosage forms (tentative.) (GMP)

- Stability testing with stability indicating method. (GMP)

- Preparation and submission of IND. (FDA Guide)

QA/QC involvement: assure GLP, GMP compliance in the development groups: Pharmacy Development, Analytical Development, Chemical Development, Toxicology and Metabolism/Pharmacokinetics.

Stage 2 - Clinical Studies and Product Development Activities:

- Phase 1, Clinical Trial: Evaluate drug safety and dispositions (metabolism and pharmacokinetics) in healthy volunteers. (GCP)
- Phase 2, Clinical Trial: Demonstrate efficacy and safety in patients. (GCP)
- Phase 3, Clinical Trial: Confirm long-term safety and efficacy in patients. (GCP)
- Conclude animal studies in safety assessment and metabolism. (GLP)
- Complete chemical synthetic process for production. (GMP)
- Finalize finished product including dosage image (with marketing), dosage strengths (with medical) formulation, package, label and insert. (GMP, GCP)
- Expand stability studies and assign expiration date. (GMP)
- Firm up specifications for drug substances, dosage. forms, in-process control and analytical methods (GMP)
- Prepare environmental assessment data. (per FDA guidance)
- Complete validation studies needed for NDA: (GMP)

  √ Process validation in bulk drug substance.
  √ Process validation in dosage forms (some may complete after pre-approval inspection).

  √ Analytical method validation.
  √ Cleaning validation, Computer validation.

- Establish system and prepare documentation and procedure related QA/QC operation, such as Standard Operation Procedure (SOP), training programs and records, QA auditing, out of specifications investigation and recall procedure.
- Submit Drug Master File (DMF) per guidelines.

QA/QC involvement: assure compliance in GMP, GCP and GLP by working Group in R&D, Manufacturing and QA.

Stage 3 - Manufacturing Activities:

- Review "Technology Transfer" from R&D.
- Provide process validation including Installation Qualification(IQ), Operation Qualification (OQ), and Performance Qualification (PQ).
- Develop manufacturing procedure and in process control per "Technology Transfer" for large scale production.
- Manufacture production lot for compliance and market introduction.
- Plan, coordinate and implement multi-sites and/ or global manufacturing.
- Establish Post NDA approval operation for QA/ QC regarding inspection, sampling, testing and release.

QA /QC involvement: assure GMP compliance and document accuracy and completeness.

Stage 4 - Product Registration Activities

- Coordinate FDA meeting and query response, revise report for submission by the Regulatory Affairs group.

- Prepare and submit product registration documents: NDA or ANDA.

- Prepare and coordinate FDA Pre-approval Inspection.

QA/QC involvement: assure compliance of GMP and document quality and accuracy.

Stage 5 - Regulatory Compliance Activities

- Assure continued regulatory and post-marketing compliance in all operation groups.

- Phase 4, Clinical Trial

- Develop mechanism and system for "Change Control."

- Alert operations in new regulations, proactive for the upcoming compliance.

QA/QC involvement: FDA regulation compliance.

Regulatory Compliance

Types of Pharmaceutical Products Meeting cGMP Compliance

Some pharmaceutical business involves manufacturing of the finished product or marketing one or more components of the final products. Some manufacturers specialize in one of the components, e.g. bulk drug chemicals, pharmaceutical excipients or package components. The others may include more than one. A majority of the manufacturers focus their production in bulk drug chemicals and dosage forms, including novel drug delivery systems, discussed below:

Bulk Pharmaceutical Chemicals

Bulk Pharmaceutical Chemicals (BPC) are the active chemical substances responsible for the therapeutic effect of the drug. Generally, they are synthesized by a chemical process or isolated from the plants or animal origins. These chemicals may be developed initially from the discovery research of the innovators and scale-up for development and manufacturing, or they may be

listed in the compendia such as U.S. Pharmacopeia. Purity of the chemical is the key factor to be considered. The control of purity is the exclusion of impurities and contaminants; therefore, the purification process as well as the analytical method play important roles.

As the physico-pharmaceutical properties of a drug substance, e.g. particle size, crystallinity of the solid (polymorphism and hydrate), frequently affect its bioavailability. They have received increasing attention as a quality criteria. Furthermore, the control of optical purity is being considered, since the recognition of the biological and therapeutic significance's of a specific optical isomer. Advances of separation techniques make resolution of isomers feasible. Thus, chiral purity, when applicable, will be another quality desired by the industry.

Although the cGMP was originally intended for the finished products, similar compliance to cGMP for the manufacturing of BPC is regarded by the FDA as mandatory. The innovative products must be accepted in the IND registration prior to clinical trials.

Dosage Forms

Pharmaceutical dosage forms are a delivery system compound with the active drug substance and a number of ingredients to facilitate ease of administration and manufacturing. Generally, the dosage forms are in the forms of solid, liquid, injectable solution, nasal spray, cream and ointment. They are collectively know as conventional dosage forms.

Recent technological advances, new routes product administrations and better ways to achieved patient compliance have been developed and accepted by the market. These products are known as novel drug delivery systems which include controlled or sustained drug delivery, transdermal patches, nasal delivery and target site specific delivery in biotechnology products. In many cases, the idea of these products developed for market is the result of the practice in quality improvement. cGMP requirement must be followed for the manufacturing of dosage forms.

Quality Systems for Pharmaceutical Industry

The processes, organization, procedures, and resources used to control variables in production are known as quality systems. These systems which may be used in the pharmaceutical manufacturing include:

Current Good Manufacturing Practice (cGMP)

In the U.S., cGMP is a FDA mandatory quality program to ensure that pharmaceutical products are consistently produced and controlled according to the quality standards appropriate to their intended use. The compliance for the manufacturing and quality may be summarized as follows:

- Responsibility and authority of the quality control unit for establishing standards, writing procedures, performing testing and approving (or rejecting) product release.
- Training for qualified personnel, maintenance of adequate facilities and appropriate equipment.
- Quality control of components, containers and closures of drug products with written procedures.
- Packaging and labeling control including tamper-resistance packaging for OTC products, inspections and expiration dates.
- Production, process control and reprocessing: deviation recorded and justified.
- Storage and distribution of drug products.
- Laboratory control including specifications, standards, sampling, plan and testing.
- Testing of drug products conforming to specifications of identify, strength, quality and purity to be released for distribution.
- Stability testing of drug products.
- Calibration of instruments, apparatus and recording devices.
- Validation for manufacturing process, analytical method, equipment cleaning, microbiological control, electronic data reduction and computer processing.
- Program, method and procedure documented in written forms.

- Retention of reserved sample for drug substances and drug product.
- Retention of records and reports related to production, control or distribution. Document retained as readily available for regulatory inspection and annual evaluation.
- Return and salvage of drug products.

Although no new cGMP requirement has been added, new in-depth guidelines for several areas have been published, particularly in conjunction with the International Conference on Harmonization (ICH).

These areas are:

- Validation of analytical methods
- Stability testing for new dosage forms
- Photostability testing of new drug substances
- Impurities in drug substances and dosage forms
- Environmental assessment

The cGMP in the U.S. was originally developed for the dosage form or finished product and is also used for the bulk drug substances in the absence of the published guidelines. However, specific GMP's have been published, proposed or being reviewed. These GMP's include:

- cGMP for Medical Devices
- cGMP for Foods in General
- cGMP in Manufacturing. Packing, or Holding Dietary Supplements
- cGMP in Large Volume Parenteral for Human Use
- cGMP for Dietary Supplements

Similarly in the European Union and Japan, the drug firm must hold a valid authorization to manufacture its product. The requirement is based upon the implementation and continued assurance of GMP by the manufacturer. The compliance of the practice in Europe is the responsibility of the appropriate regulator of the member states. In Japan, the GMP compliance is the responsibility of the Inspection and Guidance Division of the Pharmaceutical Affairs Bureau.

Good Laboratory Practice (GLP)

In contrast to cGMP, which regulates manufacturing and its related quality control activities, GLP covers research activities. The most significant difference is in the requirements of archiving for test samples and data. All raw data, documentation, SOP's, protocols, final reports and specimens (with some exceptions) must be retained. The archiving facilities must be constructed to allow orderly storage and expedient retrieval of items mentioned above.

GLP regulates all non-clinical studies and was originally intended for toxicity testing only. The requirements of analytical measurements and methods in support of toxicological studies are included in the GLP. The QA/QC may serve as the quality assurance unit (QAU), responsible for monitoring each study to assure that management facilities, equipment, personnel, methods, practice, controls, SOP's, final reports and arches conform to the regulation.

Similar practices are required in Europe and Japan.

International Organization for Standardization (ISO 9000)

The ISO 9000 series is a set of quality standards and procedures for certifying that organizations meet a consistent, acceptable quality. The ISO 9000 process requires that organizations reduce each of the operations of their core processes to a set of standard operating procedures (SOP's). These are the standards by which a company then operates and against which it is measured. The performance relative to these standards is analyzed and the deviation from the SOP-established threshold is identified. The correction is made by using Total Quality Management (TQM) processes.

The ISO 9000 series is a set of five international standards that define a system for quality management and assurance. The standards cover product design and development, production, inspection, testing, installation, and services. The five quality-system standards have different purposes:

ISO 9000 - explains key quality concepts and provides guidelines for selecting and using ISO 9000 to 9004.

ISO 9001 - includes the broad spectrum of design, development, production, installation and services capability.

ISO 9002 - covers production and installation including basic elements (e.g. management responsibility, control system review and training) and QC elements contained in ISO 9003.

ISO 9003 - focuses on quality control of finished products including detection and control of defective products.

ISO 9004 - guides manufacturers in development of quality management systems and deals with such issues as product liability and safety.

While the cGMP is a FDA mandatory quality management system in the U.S., the ISO 9000 is voluntary for quality registration. However, a rigorous process for the ISO 9000 registration is required. ISO 9000 is not well accepted by the U.S. pharmaceutical industry for therapeutic products because of the mandatory regulatory practice. The cGMP designed specifically for the pharmaceutical industry, is superior to the ISO standards with the exceptions of purchasing, not considered in the GMP and training which is less stringent than ISO 9001. Nevertheless, many companies with ties to Europe are feeling increased pressure to tell their customers that they are certified or seeking certification because the acceptability of ISO 9000 is synonymous to standards in Europe.

Total Quality Management (TQM)

The total quality management (TQM) is a recent managerial reengineering concept which is a philosophical or cultural approach in quality improvement and is more than just a process. TQM applies quality management to all business divisions, Administration, Finance, Marketing, R&D and Manufacturing, resulting in enhanced customer satisfaction, better products and services, improved productivity, and increased profits.

The concept of TQM may be viewed from the Malcomb Baldrige Award criteria:

Leadership
Information and Analysis
Strategic Quality Planning
Quality Assurance of Products and Services
Quality Results
Utilization of Human Resources and Customer Satisfaction

TQM differs from the traditional QA/QC process driven by GMP regulations emphasizing control, testing and compliance, and is measured by recalls, complaints and rejections. The involvement of the TQM process essentially includes people and continuous improvement orientation. The concepts such as empowerment, customers, partnership, trust and teamwork are important. Training and continuous training, performance, positive feedback, and recognition are the heart of the culture.

International Conference on Harmonization

Until recently, different countries have had different requirements for the development of a drug product. For example, products developed in the U.S. must follow the FDA guidelines which may be different from United Kingdom's or Germany. Consequently, the U.S. developed product may not be marketed in Europe until additional costly experiments of the European regulatory agency are completed. Until now, developing one product for the worldwide market has not been economically feasible.

To avoid duplication efforts of product registration and manufacturing in world trade, the FDA has been working in a forum, the International Conference on Harmonization (ICH) with their counterparts and the private industry from the U.S., the European Union and Japan to harmonize regulatory criteria and procedures. The participants consist of three government agencies and four private trade organizations The government agencies are the U.S. Food and Drug Administration (FDA), the commission of the European Communities (EC), and the Japanese Ministry of Health and Welfare (JMHW). The private organizations are represented by International Federation of Pharmaceutical Industry organization (IFPMA), U.S. Pharmaceutical Research and Manufacturers Associations (PhRMA), European Federation of Pharmaceutical Industry Associates (EFPIA) and Japan Pharmaceutical Manufacturers (JPMA).

The objectives of the International Conference on Harmonization are to (1) provide a forum between regulatory authorities and drug industry on requirement for product registration in the U.S., European Union and Japan; (2) identify and modify R&D procedures to utilize human, animal and material resources economically without compromising safety: and (3) recommend practical ways to interpret and apply technical guidelines for registration. The areas of interests for harmonization include stability

testing, quality specification (including impurities), validation, chemistry, manufacturing and control (CMC) sections for product registration, contents of pharmacopeia, toxicity testing, clinical testing of biotechnology derived products.

Hong Kong – A Place to Build Pharmaceuticals for the World Market

Hong Kong is in the superior position to provide resources to create worldwide pharmaceutical manufacturing business. The successful industrial experience in electronic, toy, textile and high fashion appeals has proved Hong Kong to be an ideal place for labor intensive and highly skilled industry.

The advantages of Hong Kong as an ideal place to manufacture and supply products to the world are:

- Efficient banking organization.
- Solid judicial and legal system.
- Fluent use of English language.
- Strong education and training of the scientific personnel.
- Well developed hotel, housing and transportation facilities.
- Experienced business establishment with the Western world, China Japan and the other Pacific Rim regions.

The barriers for the pharmaceutical industrial development in Hong Kong are:

- High land and labor cost.
- Limited availability of raw materials.
- Lack of scientific stimulation especially in the research and development.
- Shortage of manpower trained for the pharmaceutical science, technology and quality control areas.
- Lack of sophisticated and stringent government regulatory demands to warrant quality acceptance.

As indicated previously, advancement for harmonizing regulations from U.S., Europe and Japan into one similar standard is taking placed. Efforts to unify the development requirements

national Conference on Harmonization (ICH). It is now realistic to develop products for the world market with clear guidance and without duplicated efforts in the registration process. The success of ICH initiatives creates opportunities for small manufacturers such as Hong Kong manufacturers to participate the world market pharmaceutical business.

Current Status of R&D and Manufacturing in Hong Kong

According to 1995 government statistics, the drug industry is the largest sector of the chemical Industry in Hong Kong in terms of number of companies (38.3%) and employment (35.9%).

The pharmaceutical industry in Hong Kong is relative small by world standards. In the past, most of the prescription products in Hong Kong were imported from Europe, U.S., Japan and Philippines. Only recently, generic products are made locally. The pharmaceutical industry is mainly in two manufacturing areas: OTC Health Care Products (toiletries) and Traditional Chinese Medicinal products. The manufacturers for the OTC products are generally small with limited production lines, and the Traditional Chinese Medicinal manufacturers are largely family owned. The formulations and processes of their products are commonly kept in secret and passed from generation to generation. The operation are also in small scale with antiquated facilities. For both manufacturers, the technology and facility are somewhat simplistic, thus the majority of the products are oral liquids and solid dosage forms such as tablets, capsules and elixirs. Few bulk drug chemicals are manufactured in the region as that manufacturing requires sophisticated technology and facilities. As the Hong Kong GMP are to be enforced fully by the year 2000, these facilities will be upgraded to comply with the regulatory requirements. The great challenge mean that some do not survive as a pharmaceutical manufacturer.

For the generic manufacturers, most of them are new. Therefore, their facilities are generally planned with the GMP compliance in mind. The generic products are for the local market or for developing countries. It may be extended to U.S. or European market if opportunity arose. Like most of the newly built Hong Kong factories, the generic manufacturing facilities are located in the Pearl River region of China (since land and lobar are expensive locally). Businesses are headquartered in Hong Kong.

Although some research on recombinant NDA is underway in the universities, discovery and manufacturing of biotechnology derived products do not existed in Hong Kong currently. Significant efforts to promote biopharmaceutical industry have been advanced. For example, The Hong Kong Jockey Club Charities Trust has allocated one-time funding to establish two separate institutes: The Hong Kong Institute of Biotechnology (HKIB), an independent institute adjacent to the campus of The Chinese University of Hong Kong and the Biotechnology Research Institutes (BRI), a center operating inside The Hong Kong University of Science and Technology. Since most of the grant for both organizations has been used for building construction and equipment purchasing, little funding remains for research and development.

One of the missions of the HKIB is to attract biotechnology business into Hong Kong, thus the unoccupied manufacturing facilities of HKIB are offered for lease to small starting-up biotechnology firms. Some contracting projects including the DNA sequence of the malaria vaccines and antigents are being carried out with the U.S. National Institutes of Health (NIH) with support funding from the World Health Organization (WHO). In addition, a GMP Supporting Service Unit was established with additional government grant monies to assist the local pharmaceutical industry with GMP implementation. Recently, this unit has expanded into the Hong Kong Pharmaceutical Technology Center with the long term goal of developing and upgrading the pharmaceutical technologies in Hong Kong.

On the other hand, The BRI is focusing its research on protein folding and stability, development of neuroprotein as therapeutic drugs and diagnostic agents, and plant biotechnology for the local crop plants. A Traditional Chinese Medicine Center also has been established within The Hong Kong University of Science and Technology with government funding for Drug Development, Safety, Standardization and Reformulation of the herbal drug products.

Product Registration in Hong Kong

Under the Pharmacy and Poison Regulations, pharmaceutical products must be registered with the Pharmacy and Poison Board (processed through Department of Health) before entering the Hong Kong market for distribution. The registration require-

ments for safety, efficacy and quality must be met according to guidelines. The sponsor for filing is the manufacturer if products are manufactured in Hong Kong. For products manufactured outside Hong Kong, the importer or the local branch, subsidiary, representative, agent or distributor of the manufacturer are responsible for the filing of application.

According to present regulations, some pharmaceutical products are exempt from registration. These products include: (a) preparation made solely of Chinese herbal medicines, (b) substance imported by pharmaceutical manufacturers solely for the purpose of manufacturing their own pharmaceutical products, (c) products manufactured in Hong Kong to be exported by the manufacturer. To establish credible image, of the Hong Kong pharmaceutical products by the stringent regulatory requirements, must be reflected by the regulatory demands. The responsibility and involvement of the regulatory agency of the above mentioned products should be re-examined. Considering the goal of a consistent and excellent standard for all products manufactured in Hong Kong, these exemptions are not acceptable.

To provide an uniform standards for all pharmaceutical products made in Hong Kong, a registration process must be established and implemented for Traditional Chinese Medicine (TCM) which may have different requirements but should have the same principles as other drugs. Drug substances imported for manufacturing of a finished product should not be exempted from the registration process and should be included as part of the product registration of the finished dosage forms. Hopefully, all products for exportation will be the major focus of the pharmaceutical industry and should have the government involvement to ensure quality and International compliance. Exemption from the registration will circumvent the regulatory assistance and intervention. Furthermore, without the registration process, affirmation of quality commitment of the pharmaceutical firms, enforcement of GMP compliance by the regulatory agencies would not be possible.

Regulatory Compliance – Good Manufacturing Practice (GMP) in Hong Kong

The driving force of the establishment of GMP in Hong Kong is the desire to move the Hong Kong pharmaceutical products into International commerce to satisfy the World Health Organization (WHO) Certification Scheme. A GMP guideline modeled after the WHO and the neighboring countries was published in 1994.

The implementation of the GMP program for the large scale operations to produce drugs in finished dosage forms, (including large-scale process in hospital and the preparation of Clinical Supplies) was announced by the Pharmacy and Poison Board in 1995. The board has established a three phase program with date of completion to be followed as detailed in the subsequent paragraph. The full GMP implementation is targeted for completion by the year 2000.

Phase 1 - completion of the following by 12/31/96

- Training in appreciation of Principles of Quality Assurance
- Validation process and procedure
- Documentation of Complaint Procedure
- Drug Recall Procedure
- Qualification of Contract facilities (Production and Analytical)
- Implementation of Self Inspection and Quality Audit

Phase 2 - completion of the following by 12/31/98

- Training in appreciation of Principles and Practice in Quality Control
- Establish requirements for personnel training and hygiene
- GMP Compliance for handling starting materials, packaging items, and finished products
- Implementation of Documentation System and Practice

- GMP Compliance of Active Pharmaceutical Ingredients

Phase 3 - Completion of the following by 12/31/2000

- Meet GMP requirements in Facility and Equipment
- Training in understanding the Principles and Practice in production
- GMP Compliance in manufacturing of Sterile Products

The Need for GMP Certification and Third-Party Audit in Hong Kong

In the U.S., GMP is monitored by the FDA with similar regulatory agencies in the European Union or in Japan. Deviations from the GMP are generally cited by the regulatory body upon unsatisfactory inspection and a non-compliance letter is issued, indicating the deviations from the regulations. Correction of such deviations must be completed within a pre-determined time. Citations of non-compliance are generally known to the public. Therefore, GMP compliance for a manufacturer should be well established. On the other hand, in a developing country, the status of GMP compliance is not as clear. The regulatory agency may not be ready or available for inspection. Thus, some firms consider themselves as GMP manufacturers, based on their own audits of the evaluation of facilities, process and personnel and their interpretation of regulations rather than the observation and scrutiny by government agents or independent, reputable, private inspectors.

To bridge the gap of regulatory practice in the Asia-Pacific region, an independent, credible and authoritative support organization may be needed to perform accreditation, similar to the FDA compliance inspection. A business opportunity is therefore possible for an experienced regulatory consulting group to formulate a program resembling that of the FDA and commercially available to the manufacturers to certify their GMP Compliance.

This certification program must be developed and managed by persons with superior academic backgrounds, highly trained

in QA/QC disciplines with years of experience within the pharmaceutical industry and within a country where GMP has been practiced widely and critically for an extensive period of time with continuous updating. Program Inspectors for certification must be specially trained for the intended purpose. Academically, they must have strong pharmaceutical backgrounds. The facilities and equipment used for the services must be state-of-the-art.

Since government regulations and other legal commitment are critical aspects of the pharmaceutical business, legal professionals (practicing lawyers specializing in pharmaceutical law with scientific background in pharmaceuticals) and regulatory affairs specialists or former employees of the FDA who are familiar with the current regulations and skills to interact with government agency are also key members of the team of the service provider.

GMP Certification

With a team approach as discussed above, the GMP certification program offers the developed procedures for certification to the Hong Kong manufacturers based on activities such as the following:

1. Assess and audit existing facilities, resources and current practices of a pharmaceutical firm.
2. Evaluate current practice of a manufacturing site vs. regulatory requirements and identify deviations from regulations.
3. Issue report with proposed corrective actions.
4. Draft plan to assist clients to correct deviations found. Assisted activities include identifying resources, prioritizing and planning with consultations as well as provide training, if needed.
5. Reevaluate and re-access manufacturing practices vs. committed corrective actions in previous GMP deviations.
6. Accredit with ratings relative to the degree of compliance excellence and endorse GMP certification.

Alternatively, the service provider may give courses to drug firms to assure GMP compliance. Workshops may train in-house specialists with a self-auditing process to evaluate compliance. In addition, the service provider may provide consultations for the inspection process and may provide resources to correct deviations.

The certification program is a third party independent evaluation of the GMP compliance, and the process is a review by professionals specializing in the task intended. Since the entire process from assessment through deviation, corrective action, rating and to the certification is performed by the service provider. No in-house resources are affected; therefore, no production activities are hindered. Credibility of the certification is high because an independent firm specializing in the process intended performs the evaluation.

Opportunities such as the workshop for self-auditing can be extremely cost effective. For example, the training course may be used by manufacturers to carry out their own inspections. Thus, the cost of the development of a training workshop is shared by all users, and the cost of expenses for a single firm is minimal. On the other hand, the depth of auditing and inspection is limited by the training and experience of the in-house inspector. In some cases, the auditor may inadvertently overlook deviations which are critical; therefore, the conclusion of the GMP compliance may not be valid. The limited resources consumed by the auditing activities, especially for a small firms, may affect business progress. Most of all, the credibility of being investigated by an independent consultant as in the certification program, is absent from the self-auditing training course.

New Opportunity for Biopharmaceutical Business Development in Hong Kong

Overview

In a GMP Workshop for Pharmaceutical Manufacturing by Hong Kong Institute of Biotechnology (HKIB) in 1996, the author, Edward Lau of E. L. Associates, Inc., a pharmaceutical consultant in the U.S., used his experience and observation to suggest the following pharmaceutical business areas to be developed in Hong Kong for the world market. Some similar development areas with suggested priority were also indicated in the book **Made by Hong Kong** written by the MIT group based on their research and interviews.

- Traditional Chinese Medicine (TCM) and Herbal Drug (Priority 1*)
- Generic Products (Priority 2*)
- Biotechnology Development and Manufacturing (Priority 3*)
- Bulk Pharmaceutical Chemical Manufacturing
- Over-the-counter (OTC) and Healthcare Products
- Contract Laboratories and Manufacturing Centers

* *areas indicated with priority designated by the MIT Study*

Discussion and Recommendation for Future Growth Development

Detailed discussion and recommendations for the development of Hong Kong's future pharmaceutical industry are presented as follows:

Traditional Chinese Medicine (TCM) and Herbal Medicine

The utilization of herbal medicine in maintaining health and treating diseases has been increasingly recognized in the U.S. Health care concepts have shifted from conventional western medicine alone to other approaches in searching for "alternative medicines." Furthermore, the search for lower cost medical care, the increase of population from foreign lands familiar with herbal medicine, the acceptance of multicultures – all contribute to the popularity of herbal medicines in the U.S. market.

RECOMMENDATION FOR FUTURE GROWTH:

The MIT group in their book **Made by Hong Kong** recommends the development of the herbal drug or TCM to be the first priority for the future Hong Kong pharmaceutical industrial development. I agree with this recommendation as the market, the expertise and recent research advance are favorable in the development of TCM as a potentially successful venture in Hong Kong.

Since this area is the top priority for the future growth of Hong Kong pharmaceutical development, extensive discussion and suggestions for the planning and implementation will be discussed separately in details.

Generic Products

The U.S. generic business is projected to increase three times to $12 million by 2000. Furthermore, the conventional human

products, animal health products, transdermal patches, other delivery systems as well as home diagnostic testing (glucose, pregnancy, cholesterol, osteoporosis) will be entering the generic market.

Although ANDA registration is required for marketing approval in the U.S., manufacturing and testing of the product may be done in a foreign country with exporting into the U.S., upon satisfactory FDA foreign inspection and the commitment to the ANDA. In addition, the local generic market including China and other parts of the South East Asia may prove to be a profitable venture to be involved as the acceptance of the low cost qaulity generic products manufactured in Hong Kong may rival with those of the major generic houses in the U.S. and Europe.

RECOMMENDATION FOR FUTURE GROWTH:

A business niche in the generic manufacturing in Hong Kong should be sought. Because of the low competition in the worldwide generic market, animal healthproducts and diagnostic agents should give a higher priority as business development items. Single unit package products for the hospitals, transdermal systems, metered dose inhalers, sustained release dosage forms may also be good profit making products in the generic business.

Biotechnology Product Development and Manufacturing

Biotechnology products are pharmaceutical products prepared by the collection of industrial processes that involve the use of biological systems. For some of the industries, these processes involve the use of genetically engineered organisms. The preparation of the products generally involve Recombinant DNA, Monoclonal Antibody/Hybridoma, Continuos Cell Lines and Cellular Therapy Technology. These medicines are for hemophilia, free from the possibility of virus contamination; drugs for cancer that are "programmed" to zero in on tumor cells; and substances that can enhance the body's ability to heal or protect itself against life threatening diseases such as AIDS.

The prerequisite for marketing of this biotechnology drug is the approval of the Product Licensing Application (PLA), and the manufacturing follows cGMP. In addition to innovative biotechnology firms, large pharmaceutical manufacturers are involved in the business. Since Hong Kong is developing its resources for such industrial ventures with facilities and support e.g. the Hong Kong Institute of Biotechnology and Biotechnology Research Center, expansion of this business opportunity for the world market competition is appropriate.

RECOMMENDATION FOR FUTURE GROWTH:

Although biotechnology products may not occupy the highest priority in the development of biopharmaceutical industry in Hong Kong (as pointed out by the survey report of the MIT group,) the products have specific interest for Hong Kong and Asia development. Particularly, the biotechnology products related to the TCM: the growth of ingredients of herbal plants such as Ginseng and the herbal plant in a controlled environment to produce herbs with consistent quality will be an area of importance for biotechnology development.

Bulk Pharmaceutical Chemical Manufacturing

Currently, the biggest U.S. imports in the pharmaceutical business are the Bulk Pharmaceutical Chemicals (BPCs), active drug chemicals. Most of the exporters are in India, China, and Italy. The primary products are the USP items used by the generic or OTC trades. Other chemicals exported may include intermediates for the synthesis of a new drug substance (chemicals in the IND, NDA).

The challenges of building a pharmaceutical business outside the U.S. for the purpose of exporting BPCs are complex and costly. The problem of quality with foreign manufacturers leads the FDA to focus more attention and scrutiny on this issue. Meeting cGMP such as facility and process validation, purity profiles and the passing of FDA foreign plant inspections are some of the challenges.

However, the rewards in the business are great with a bright outlook for the future, because of several factors:

- Large number of the generic firms using compendial BPC, thus a large share of market existed.
- Selection of BPC supplier by the generic manufactureres are based on competitive price, Creating an opportunity for the new comer with low price.
- Just-in-time inventory practice allows the fast delivery vendor to earn the contract.
- The added values in product quality (e.g. particle size, chiral purity, crystal modifications) gives another incentive for competition.

- The increase acceptance of the FDA on foreign quality materials creates opportunity for overseas suppliers.

For the firms interested in exporting bulk pharmaceutical chemicals to the U.S., request to the FDA for foreign plant inspection should be made. Prior to the inspection, the current practices of a particular site may be evaluated against the "FDA Inspection Guides" and the "Guide to the Inspection of Foreign Manufacturing Plant" to identify their inadequacies or incompliance and to establish plans to meet the requirements. In addition, the applicant exporting drug products to the U.S. may prepare and submit Drug Master Files (DMF) to the FDA for reference.

Although the FDA does not have authority to impose regulatory compliance in a foreign country, the foreign plant which does not pass the FDA inspection may not be able to export their products to the U.S.. U.S. Customs will not allow drug products into the country without consulting with the FDA on the results of the foreign inspection.

To plan a Hong Kong manufacturing facility which meets the FDA requirements, the need for future expansion should be identified and planned, e.g. a GMP facilities to comply with the International Committee on Harmonization (ICH) requirements. Also, validations including facilities, processing, analytical methods, computer and cleaning should be considered. In the beginning, building all the required sections may not be necessary; however, it is usually more economical to build all appropriate facilities into the initial phase. The following quality considerations should be included with the business planning:

- Emphasize Quality Assurance and Quality Control
- Establish modern analytical laboratory with state-of-the-art technology to test materials for quality excellence beyond compendial testing
- Select target compounds based on the market shares
- Assure the drug substances produced meet the specifications of ICH or meet universally all the specifications in USP, EP and JP for the worldwide market or meet client's stringent criteria, if requested

- Consider value added quality product, e.g. particle size, polymorphism, organic volatile impurities, chiral purity, and superior chemical purity exceeding compendial standards

RECOMMENDATION FOR FUTURE GROWTH:

As 70% of bulk pharmaceutical chemicals of the U.S. generic drugs is purchased from the foreign manufacturers, a share of this business for the Hong Kong manufacturers is considerable. In addition, the supply of generic drug substances to European and China markets and to the emerging generic manufacturers locally, the business in BPC should be an attractive venture for the Hong Kong industry. Although Hong Kong does not have existing BPC facilities, building a new state-of-the-art manufacturing plant to comply with the cGMP will be a plus. Starting new business with new facilities providing high quality products will be easier than converting existing facilities to comply with the regulation.

OTC and Healthcare Products

Patent medicine as known in Hong Kong has been a mature pharmaceutical business for many years. However, updating the manufacturing and QA/QC practices required by GMP will open a new market in the U.S. Although marketing with advertising is essential but costly for the success of the OTC products, partnering with large U.S. firm may reduce such expense. Taking advantage of higher labor motivation and lower labor cost in the Pacific-rim areas, production including packaging may be performed locally and exported to the U.S. or sold in Asian markets.

RECOMMENDATION FOR FUTURE GROWTH:

The U.S. market of imported OTC products may not be a viable business for Hong Kong manufacturers. The OTC producers in the U.S. are numerous and are generally large conglomerates with strong marketing forces and high output technology. However, as Western medicine becomes increasingly accepted by consumers in Asia, the OTC products in Hong Kong may find profitable shares of the market locally and in China and other Pacific Rim countries. Cosmetic and health care products (toiletries) may also be considered for development along the OTC products.

Contract Laboratories

Until recently, like most of the U.S. industries, all manufacturing facilities and their related resources in pharmaceutical plants

were "in-house" operations. The advantages were the close control of the operations with effective interaction between management levels with clear accountability. Disadvantage has been the loss of flexibility due to rigidity of the organization structure and management-labor relationship. In most cases, shifting resources from one group to the other becomes extremely impractical, if not impossible.

For a fully operational business, the "in-house" operation is an acceptable practice. However, when the business is slow, and the manufacturing is not running of full capacity, it becomes an expensive operation. During recent years, because of strong foreign competition, some of the manufacturers in the U.S. have been forced to "downsize." An alternative way to continue operation is to shift to third party manufacturing either within the U.S. or abroad. Subsequently, the third party operation or outsourcing has become an important part of the American business.

In meeting the new demands of outsourcing, many contract laboratories and manufacturers have been established in recent years. This new development in the contract services including manufacturing, research and development, quality assurance and control has been accepted by the industry as a cost-effective alternative. Small in size, compared with the large pharmaceutical firms, the contract operation is generally dynamic and efficient. The quality of its operation has been regarded as critical to the success of the contracting business. Furthermore, the U.S. pharmaceutical industry has long experience in setting up their production in Puerto Rico. Working with an off shore contractor will not be a problem for them.

RECOMMENDATION FOR FUTURE GROWTH:

Most of these projects are granted to U.S. contract laboratories and manufacturers at this time. However, Hong Kong should be equally qualified as an outsourcing resource for pharmaceutical and biotechnology with the high level of English communication, higher level education and training, low labor cost/ motivation ratio, flexibility in handling small orders, sophisticated electronic data transfer, quality banking, transportation and hotel facilities.

Expanding existed scientific research laboratories with ICH cGMP, GLP, and ISO 9000 coupling with state-of the-art facilities, equipment and trained scientists will create extensive business opportunities.

Development of Traditional Chinese Medicine (TCM) in Hong Kong

Introduction

The 1994 Dietary Supplement Health and Education Act (DSHEA) allows the botanical materials to be marketed as dietary supplements. Their compliance requirements are usually less rigorous and differ from over-the-counter and prescription products in labeling, scientific support required, and manufacturing procedures. Conversely, a botanical product, currently marketed as a food, could be regulated as a drug if the manufacturer seeks a claim that the product can diagnose, prevent, treat or mitigate illness. Since the increase of treatment with botanical drugs and the FDA vigilance for restricted use due to safety, obtaining registrations, IND and NDA are desirable for a firm intending to market herbal drug products in the U.S.

To capture the U.S. market shares of herbal materials as dietetic supplements without NDA, improving quality to establish QA/QC processes must be undertaken to ensure long term market superiority. The potential of the market growth is great. At the present time, users of botanical drugs are less than 10% of the U.S. population. With the assurance of quality products in efficacy and safety, physicians and the remaining 90% of the population may consider use of the botanical drugs

Currently, the manufacturers in Hong Kong are primary in the business of production of finished dosage forms or formulated compounds such as tablet, capsules, liquid or ointment. Most of these manufacturers have been in business for many generations. However, the facilitates, process and formulation are not as sophisticated as the Western medicine. Antiquated facilities, traditional formulae and process have been passed down for generations without improvement (keeping the original formulation and compounding process is continuously believed to be a secret which must not be altered). Recently, because of the initiation of the GMP, many firms have changed their culture and improved their facilities. Nevertheless, the traditional honored formulation and compounding process have not been touched. A scientific formulation development including processes and control resulting in stable, bioavailiable, quality and elegant products will be a new challenge for the industry. Packaging and labelling will also be key issues to be addressed. To this end, a coordinated central development program should be planned and implemented to

create research centers in the universities, vocational colleges, pharmaceutical institutes and private contract laboratories to test of pharmaceutical products, develop new formulation and processes to ensure quality, bioavailability and stability for the existing TCM products.

The Challenges for Future Growth

Roles for Private Sector

To move the TCM into the world market with a strong quality image, some roles that the private sector (including vocational school and universities) may seek are listed below:

Modernization of Development and Manufacturing for TCM Products

Most of the recent efforts in establishing Hong Kong pharmaceuticals for world class markets are heavily focused in QA/QC aspects and to some extent in product safety as evident from the TCM related projects under the Industrial Support Fund (1994-1997). Ten out of twelve projects are concentrated in the above mentioned areas. While it is important to be concerned about product quality, it is even more crucial to seek sound scientific approaches in the formulation and manufacturing of a product.

It is not logical or even profitable to have good testing procedures for products without quality. In the Western drug products, the development and manufacturing of dosage forms occupy tremendous shares of resources during the development such as in NDA stage. The quality is built into the products and maintained by in process control and product release testing.

Presently, most of the TCM products in Hong Kong are manufactured by the time honored formulations of ancient processes. These products do not have the scientific advantages to have optimal performance such as production efficiency, bioavailability and stability. Furthermore, the old procedures will not be adapted to the process validation procedures as required by the GMP. Definitely, the old process does not allow products to have built in quality.

Since most of the TCM products are in the solid dosage forms, reformulation of these dosages should have the highest priority in the modernization activities. Converting the old formulation with

scientific approach into state-of-the-art tablets and capsules (immediate release and controlled release) must be initiated immediately.

The advantages of modernization may include:

- Production efficiency, market expansion and cost effectiveness
- Quality enhancing for consistent product performance and dosage uniformity
- Improved aesthetic and pharmaceutical elegance
- Facilitating of processes and cleaning validations.
- Patent protection
- Line extension

Other dosage forms which may be considered for modernization are:

- Reconstituted Powders
- Oral Liquids
- Parenterals
- Transdermal and Transmucosal Delivery Systems
- Freeze Dried Products for Medical Food or Dietary Supplements
- External Application - Dermatology Products

Herbal Extract Concentrates

Extraction of a herb or combination of herbs may be produced as a raw material for manufacturing. This practice of using extracts is a preferred technique for manufacturing herbal products in Europe. Using extracts instead of ground dry herbal material for compounding in dosage forms has many advantages and should be promoted. As a viable business venture for the local and overseas markets, extracts should be available as an active drug substance.

The advantages of using extracts in the manufacturing of dosage forms are obvious:

- Ease of handling , packaging , storing and sterilizing

- Convenience for assay, measure and transfer.
- Protection from degradation by light, oxidation and storage in low temperature for enhanced stability.
- Suitability for processes such as mixing, granulation, compressing and drying.
- Subject to purification, reprocessing and enhancement in bioavailability in some cases.

Centralized Service Laboratory

Most of the pharmaceutical firms are relatively small. It may not be feasible financially for an individual company to invest in operating an up-to-date facility and equipment with trained personnel. However, a cost effective laboratory may be set up by sharing expense with several companies for common interest functions such as product development, product testing for QC, method validation, stability testing and problem solving. This laboratory is managed by representatives of the participating companies with authority in objectives and priority setting and resource allocation.

Currently, similar practice exists in terms of analytical development by the Chinese Medicinal Material Research Center, The Chinese University of Hong Kong. However, their objectives are more in basic research and are not dictated by the industry needs. Routine quality control methods are not in their consideration. Furthermore, their services are not available for the QC products release for manufacturers.

Research and Development

Enhancement of R&D program in the universities and private institutions will be helpful for future growth. Many research programs are supported by government grants to universities. However, most of them are related to the quality control aspects of herbal medicinals with the objective to modernize the TCM industry. A balanced program in the development of dosage formulation and pharmaceutical technology should be developed.

Private research programs specifically for a profit organization with strong motivation as an investment for the profit growth of a company, common in the U.S. and Europe should be encouraged. The scope of R&D should be expanded. Issues which have been neglected related to pharmacological, toxicological, pharmacokinectics and clinical studies of a drug should be addressed.

Most important, areas which lead to the discovery of a new drug hold the key to changing the future of a company: (1) Medicinal Chemistry in identification, isolation, purification and synthesis and (2) Pharmaceutics in formulation development, product stabilization, drug interaction, novel drug delivery systems and automation in manufacturing should be supported.

TCM Education and Contiguous Education Program

In addition to formal education programs in universities and vocational schools for TCM, continuous education programs for TCM such as the regulatory and QC management, analytical techniques, dosage forms development, manufacturing technology should be developed and offer to the industry in upgrading their knowledge and improving their practice.

Roles for the Government

Government regulatory authorities play an important role in establishing the best quality image through stringent regulatory requirements for Hong Kong pharmaceutical products including herbal or Traditional Chinese Medicine products

Certification for the Crude Drug Materials

Establish a certification program by the regulatory authority for certification of crude botanical drug materials or herbal-slice products. This program is similar to the FDA's antibiotic certification in the U.S.. Every lot of the drug material must be submitted to the agency for testing according to the published monograph. Upon satisfactorily meeting the specifications in the compendial monograph, the lot in question is then released with certification of analysis issued by the government laboratory for market distribution.

The intent of this task is to provide credible independent assurance that the raw drug materials are efficacious with quality and safety. In addition to the conventional testing for identity, impurity, quality and strength, bioavailability and bioburden testing may be included in the monograph. For the drug materials to have toxicity, additional acute toxicity testing may be included to ensure each lot of the drug entering the market as safe and of good quality.

GMP for Herbal Drugs

Establish a Good Manufacturing Practice (GMP) for Herbal Drug Products. Due to the significant differences in nature between herbal medicinal products and western pharmaceuticals, the application of the GMP for herbal medicinals may not be cost effective or practical. In the U.S., the cGMP is intended for the finished dosage forms. However, other compliance practices are either in use or being considered. Such compliance practices are medical devices, drug substances, parenteral products. Presently, a proposal of the cGMP in manufacturing, packing, or holding dietary supplements including herbal drugs has been forwarded by the FDA in the U.S.. The proposal is modeled after the GMP of food rather than drugs. As the current GMP for Hong Kong industry intend to be totally implemented by 2000, it may not be advantages as for the herbal industry and may not be applicable in this field for the production and control. A new GMP applicable to the herbal industry should be proposed in Hong Kong by the trade organization, developed with the government regulatory agency for implementation.

Mandate Product Registration of TCM

At the present time, the herbal or TCM products is exempted from registration under the current Pharmacy and Poisons regulations. Mandatory registration will ensure all pharmaceutical products manufactured in Hong Kong bear the same quality image. The registration process may be in the form of a drug master file (DMF) format including Type I: Manufacturing Site, Facilities, Operating Procedures and Personnel, and Type II: Drug Substance, Intermediates, Material Used in Preparation or Drug Products. Application must be filed with the regulatory agency for appropriate review. Product may be sold after approval from the agency.

GMP Auditing and Inspection

Consider outside resources. Regulatory authority may establish the regulatory system, such as GMP, but such authority also verifies that the requirements are well understood and followed. The process of inspection by the regulatory agency in conjunction with training and education programs in-house or by private quality control experts should ensure compliance with the regulation. A third party independent auditing program such as "GMP Certification" performed by a credible and experienced quality expert may be an alternative to the traditional inspection by the

government agency. This alternative may assist the regulatory agency to improve the compliance efficiency with utilization of outside resources, especially when the experience is new for the regulatory agency with limited resources. However, this approach must gain full support and cooperation from the government, and they should have good and frequent interaction with the auditing consultant to be sure the system adheres to regulations

Publishing Official Monograph for Hong Kong Herbal Drug Products

Prepare a monograph exclusively for Hong Kong products (similar to the German Monograph E). Because of the uniqueness and quality demands of the local products, a monograph exclusively for the Hong Kong products should consist of specifications (including acute toxicity if indicated) and testing methods, stability, storage and packaging. This monograph should be harmonized with other compendia such as U.S. Pharmacopeia, Chinese Pharmacopeia, European Pharmacopoeia, Pharmacopoeia of Japan, if possible. Such a monograph will provide a published quality criteria of the Hong Kong products that may prove to be superior in the world market of herbal medicine. Linking to the monograph publishing activities, establishment and distribution of reference standards must be considered.

Appendix: Development of Monograph for Herbal Drugs

As previously indicated, a herbal drug monograph specifically prepared for the Hong Kong industry in botanical drugs or TCM is required for the testing of botanical drug materials and dosage forms to meet the superior quality and safety of the products manufactured in the region. The TCM manufacturing in Hong Kong may be classified into three types of product forms:

- Botanical Drug Materials or Herbal-Sliced Products
- Concentrated Herbal Extracts
- Dosage Forms or Formulated Compounds

Quality assurance/quality control procedures for the hecterogenuious botanical drug materials, concentrated extracts and dosage forms can be developed based on conventional pharmaceutical practice. The botanical drug materials display unique

properties, forms and homogeneity criteria as conventional bulk drug substances and pharmaceutical dosage forms. Because of their uniqueness, some aspects of quality standards development should be considered for the botanical drugs:

(1) Efficacy and Therapeutic Use

In contrast to conventional pharmaceuticals with well defined therapeutic use, herbal materials have little scientific documentation for their pharmacological activities. Traditionally, these materials have been used as remedies treating certain illnesses as well promoting health and well-being.

Although testing for end-point effects of a drug is difficult, verification of the general beliefs of the therapeutic use for each material is important. Therefore, a program similar to those sponsored by the government regulatory agency and carried out by the research centers of universities or private contractors should be adopted to accomplish this purpose.

This program should have two phases:

> **Phase 1.** In-vitro Screening Testing: for the immediate need. These studies should be completed by the year 2000 or shortly after. In-vitro screening such as a receptor blocking assay should be considered.
>
> **Phase 2.** Pharmacological or Clinical Studies. The conclusive therapeutic indication with conventional clinical studies may be studied.

Thus, a criteria for the "Traditional Belief in Therapeutic Use" should be added in the government published herbal drug monograph of the botanical drugs if scientific data have not been obtained. Criteria may be subsequently revised accordingly to "Therapeutic Indication Based on the In-Vitro Studies or Clinical Studies" as soon as data becomes available.

(2) Safety and Toxicity

The safety of most of the botanical drug materials is not well established when compared to conventional pharmaceuticals. Components responsive to the toxicological effects are not identified in most cases. Until toxic components have been positively identified, the component detected in the toxic lot (distinguished by chromatographic techniques between toxic and non-toxic materials of the same species) has to be assumed toxic.

Safety of a botanical drug may be considered according to past accumulated experience since the use of some herbal materials has continued over extensive periods of time. However, the compendia must developed and studies performed to verify the general beliefs. A safety assessment testing should be established promptly. Testing such as In-vitro toxicological testing may consider appropriate.

For monographs of a material known to have toxicity variation related to specie difference, influence by time of harvest along with soil and climate conditions, an in-vitro toxicological testing should be included. Acute toxicity must be identified and tested as included in the monograph for a material found to be toxic.

Sterilization and fumigation of the herbal materials may be used to safeguard the microbiological contamination. Chemical residue and its decomposition trace, frequently undesirable or even toxic, must be controlled. Bioburdent limits similar to conventional pharmaceuticals should be established.

(3) Specifications

Most of the botanical drugs are in the dehydrated form, usually dried under the sun in open fields. Contamination with foreign material such as insects or bacteria is a frequent finding. Therefore, quality control procedures including visual or microscopic observation with acceptance standards and limits should be established. Separation of contaminants must be attempted to comply with the compendial limits.

Quality controls for concentrated extracts and dosage forms may be similar to the conventional pharmaceuticals with specifications to assure identity, quality, purity, strength and bioavailability when applicable.

(4) Stability

Priority studies do not have to give stability for the dried materials for immediate attention. The materials are believed to be preservable for a longer storage period. However, package requirements and storage conditions must be established for the dried botanical materials to protect their integrity. This requirement should be general and practical for acceptance. Past experi-

ence, along with stability kinetics, should be the base to determined expiration dates.

For the concentrated extracts and dosage forms, stability testing programs for the conventional pharmaceuticals may be applicable.

(5) Analytical Testing

Cost effective analytical procedures must be considered in consideration of Harmonization with other compendia. Other parts of the world may not find expensive equipment and complicated analytical methods practical for the quality control testing.

A two-tier analytical procedure can be established:

- Compendial Method - may be developed using relative inexpensive technique, e.g. TLC, UV or Colorimetric Identification.

- Reference Method - may be established using best technique available. e.g. LC MS/MS, NMR or Capillary Electrophoresis. Investigational studies for these two methods are compared and published in the compendia to establish the equivalency and limitation of the compendial method.

The compendial method is for the quality control purpose because of its long time proved experience and cost effectiveness. The reference method is intended for technical investigation, problem solving, trace impurity detection, stability evaluation, structure elucidation and to provide insight for technological issues.

(6) Reference Standards

In addition to the Reference Standards for the botanical drug materials, a single component Analytical Extract Standard should also be prepared to facilitate analytical testing. This extract similar to the Reference Standards, may be certified with a defined expiration date. Both of the standards should be distributed by the compendial agency.

With considerable efforts plus basic knowledge and experience in conventional pharmaceuticals along with full understanding of the unique properties and characteristics of the herbal materials, these challenges for the botanical drug standard setting and analytical method development may be met.

Education and Professional Training

This section discusses educational needs and requirements of the Pharmaceutical Industry, including formal graduate and undergraduate education, licensing and special training. A variety of continuous learning is reviewed to highlight available program options.

In the U.S., undergraduate pharmaceutical education requires five years for a BS in Pharmacy. Alternatively, a Doctor of Pharmacy with six years training may be offered in some states. A degree (that may become the only official program in the U.S. for the future) is an extension of the BS degree with special topics of study. The candidates of either degree will become licensing pharmacists after 1000 to 1500 hours of practice in drug stores or hospitals and passing a state broad examination. Graduate training is offered for the MS and Ph.D. with extensive research projects specialized in Pharmaceutics, Pharmaceutical Chemistry, Pharmacokinetics, Pharmaceutical Analysis or Economic and Marketing. Most of the graduate degree studies are for the Ph.D. program with about four years study after the undergraduate degree. Recently, master degree programs specialized in Quality Control and Regulatory Affairs have been offered because of the high demand for advance training in these fields.

The School of Pharmacy at The Chinese University of Hong Kong is the only school offering formal pharmaceutical training in the territory. Relatively new, the program is primarily for the training of prescription pharmacists. The Hong Kong Technical College (Chai Wan), a vocational school has program in training supporting pharmacy personnel. Schools may enhance their current program to include technical courses in R&D, pharmaceutical manufacturing, and QC management for the training of personnel tailored to the industrial needs.

The effectiveness of the work force begins with the hiring of well trained and qualified personnel. The maintenance of those qualifications within the current rapidly changing workplace requires close attention to updating education. Continuous education is a crucial aspect of good business sense for a company if employees are to be involved in the quality and proficiency of their work. Training can also determine state-of-the-art status of facilities and techniques with adherence to requirements of the cGMP, personnel qualifications section.

Professional short course training is frequently offered by private business or consultation firms, professional organization or government regulatory agencies. Some of the courses are:

- cGMP, GLP and GCP
- Preparation of IND, NDA and ANDA.
- QA/QC Systems and Regulatory Affairs
- Clinical Study, Bioavailability and Pharmacokinetics.
- Dosage Form Development and Clinical Supplies Preparation
- Internation Conference on Harmonization (ICH) Issues
- Process and Cleaning Validation
- Analytical and Stability Method Development and Validation
- Quality Audit and Inspection
- Information Management, Documentation and SOP

In China, the State Pharmaceutical Administration of China (SPAC) has an elaborate program in continuous education training. In addition to operating a training center at Beijing for the practical education courses for the industry, training workshops in visiting the U.S. for pharmaceutical regulators and executives are held with lectures and filed trips. Workshops held for the last two years at the University of Delaware, U.S.A., were Intellectual Properties and Patent Protection, Continuous Educations, QA/QC and GMP.

In Hong Kong, because of the GMP commitment, much efforts has been placed in understanding of principles and training. Particularly, the Hong Kong Institute of Biotechnology is active in offering workshops and seminars on the issue. Hong Kong Technical College (Chai Wan) also participates in holding training GMP seminars for the local industry. Continuous education for pharmaceutical manufacturing in Hong Kong appears to be well underway. Some coordinate efforts may be planned for the future to regulate the quality of the courses offered and to avoid duplication and expense.

Hiring the best employee available, facilitating ongoing education in their fields, establishing Standard Operating Procedures

and documenting the training objectives and the process – these are included in the formula for industry education.

Future Pharmaceutical Development and Practice in Hong Kong

Modeling Industrial Practice with U.S., Europe and Japan

The leaders of the pharmaceutical industry based on their regulatory requirements, manufacturing technology, quality management, and marketing and distribution practise are mostly in U.S., Europe and Japan.

The Hong Kong industry will have an advantage if it learns from other countries' successes and mistakes applying them into building the new business. The local trade organizations, such as Hong Kong Pharmaceutical Manufacturing Association may organize seminars or workshops inviting the experts or the executives in the higher management from the leading companies to lecture on topics in administration, strategic planning, training and education, manufacturing technology, regulatory compliance and quality managements learning process. Field trips to visit these leading companies to gain knowledge of the actual operations to build virtual network and to maintain good relationships with the trade organizations and individual firms in the U.S., Europe and Japan may prove to be a valuable tool to build and upgrade the industry.

Harmonizing Regulations and Sharing Resources with China

As Hong Kong and China are sharing future political and economical progress, it will be practical for Hong Kong to harmonize regulations in product registration and regulatory compliance with China. It certainly will be profitable for Hong Kong if this harmonization may be extended to the ICH levels.

Apparently, because of the high cost of land and labor in Hong Kong, the manufacturing of drug products will be done in the mainland, while the administration, business development, R&D and QC management will be handled in Hong Kong. Therefore,

harmonization of regulatory requirements may avoid costly compliance of two sets of different regulations for the same product.

Improve Communication on Regulatory Requirements to Promote Quality Excellence

In the process of establishing regulatory laws and guidelines, manufacturers should have an opportunity to review and voice their opinions and objections prior to finalization. In this way, unrealistic demands on regulatory compliance may be avoided. Currently, the laws, guideline and target dates of implementation (e.g. GMP by 2000) established by the government are not consulted and evaluated with the industry to find out if the objective can be met.

Recognizing in the industry, the success of a pharmaceutical industry is related to the stringent and sophisticated government regulatory requirements. The performance of the regulatory bodies are the reflection of the quality of the product. The process of product registration in submission, review and approval and the task in auditing of GMP compliance are the major activities of the regulatory agency.

At the present time, the involvement of the regulatory agency in Hong Kong is minimal and relaxed when compared with other countries of the world. To meet the challenge of becoming the leader in the world's pharmaceutical market, extensive upgrading of the regulatory practices with active involvement of the regulatory bodies must be considered.

To establish only one set of standards for all pharmaceutical products manufactured in Hong Kong, the Department of Health should accelerate their involvement to take responsibility for safeguarding quality image. Some exemptions from the current pharmaceutical product registration process such as Traditional Chinese Medicine, drug substance imported for the manufacturing of a finished product and finished product intended to be exported must be reconsidered and removed from the current exemption list.

As evidenced from the confusion of the interpretation of cGMP from one FDA field investigator to the other in the U.S., guidelines in Field Inspection must be established. The process of auditing, reporting on inspection, appeal and corrective action should be published for both the regulator and the manufacturer to follow.

Chapter 18

Patent Hunt: The Story of One Inventor's Struggle to Move from Basic to Applied Biotechnology Research

By

~ Kai-Keung Mark, Ph.D. ~
Retired, Department Head & Principle Lecturer
Department of Science, Hong Kong Institute of Education
&
Retired Professor, Department of Biology
The Chinese University of Hong Kong



***Kai-keung Mark, Ph.D.**, is retired department head and principle lecturer in the Department of Science, Hong Kong Institute of Education and retired professor of the Department of Biology at The Chinese University of Hong Kong. Mark received his B.Sc.Eq. degree in chemistry from Baptist University in Hong Kong. He holds an M.A. in biochemistry from the University of California, Berkeley, and a Ph.D. in molecular biology from the University of Oregon in Eugene. Mark holds three U.S. patents related to biotechnology and environmental protection and has published 49 papers in the fields of virology, molecular biology, biotechnology, and environmental protection.*

A Shift in Research Emphasis

Being a molecular biologist by training and having worked on mutants, screening for bacterial or viral mutants became my basic trade. However, as biotechnology became popular in the '80s, I also made a slight switch in my research interest and started cloning genes and looking for opportunities in this area. On the other hand, being a conservationist, I saw the gradual deterioration of the environment, and I started doing more environmental work, such as water pollution surveys, starting in 1973, in order to attract the attention of the government and the general public.

By the mid-'80s, I had surveyed most water bodies in Hong Kong, such as streams, wells, reservoirs, beaches, and harbors. I became quite popular in the news media, and I used this microbial system to train many successful molecular biology scientists. I then looked for a more positive side to the issue. Instead of reporting and complaining about how bad our environment is, I tried to find solutions for the problems. My first success was the design of chironomid farming to convert chicken manure into expensive blood worm as fish feed.[1] The system was so successful that Hong Kong has been exporting blood worms since the '80s.

Background on Dye Pollution

Once I become environmentally conscious, the dye pollution in Fo Tan (next to The Chinese University of Hong Kong campus) challenged me daily and, around 1988, it led me to pick dye pollution as my research target. Hong Kong has been a major textile center for a long time (at least 40 years) and, thus, the dye-polluted environment contained many strains that can utilize dye molecules as nutrients over the years, making Hong Kong a rich place for a strain hunt.

In Hong Kong, Indigo and sulfur black are the two most heavily used dyes. In 1990, Hong Kong imported 4,000 tons of Indigo and utilized 2,000 tons of sulfur black dye.

Due to my research background and sensitivity to the dye pollution problem, I ventured into the strain hunt to degrade Indigo, or its soluble derivative, Indigo carmine. Later, after my success with Indigo, I went on a strain hunt to degrade sulfur black.

Strain Hunt

Because Indigo is the key dye in Hong Kong's textile industry, with an import of 4,000 tons in 1990, it was picked as the first target. As Indigo is not water soluble, its water-soluble derivative, indigo carmine (Indigo 5.5' disulfuric acid), was used as key substrate for the strain hunt. Samples from dye-polluted areas (Tuen Mun, Tsuen Wan, Tso Kung Tam, Sai Kung, and various water treatment works) were added to bacteria culture medium supplemented with indigo carmine, to test whether there were indigo carmine-degrading bacteria under aerobic conditions. We were surprised to find that indigo carmine-degrading strains are not at all rare in the natural environment. We then proceeded to isolate a large number of such strains by spreading diluted samples atop agar medium supplemented with indigo carmine (0.5g/L) to give a deep blue background on a nutrient agar plate. The trick is that those indigo-degrading strains should also degrade the indigo carmine and produce a clear ring around the bacterial colony. We call this the "halo" screening method. The halo of strain H-12 is given in **Photo 1**.

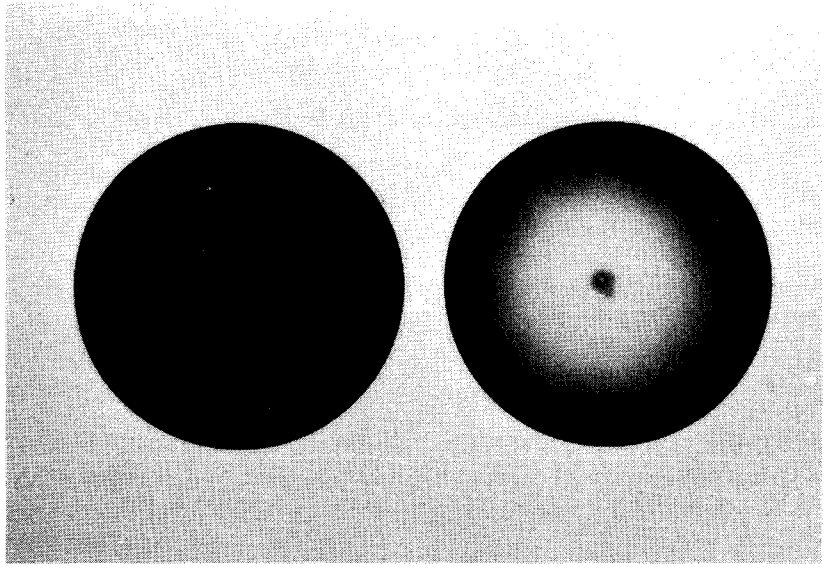


Photo 1. Halo formation by strain H-12 on IM agar plate with 0.5g/L indigo carmine.

Several hundred other strains that produce halos were also isolated. Their actions were compared with respect to the size of the halo produced. We managed to narrow down to five the strains that form the largest halo around the colony. Finally, strain H-12 was found to be suitable for further study.

With the success of the indigo dye, we started a similar screening operation for sulfur black dye with Sandoz's soldyesul, a soluble form as substrate. Again, we isolated many halo formers, and W3 and L5 where chosen for further study (**Photo 2**).

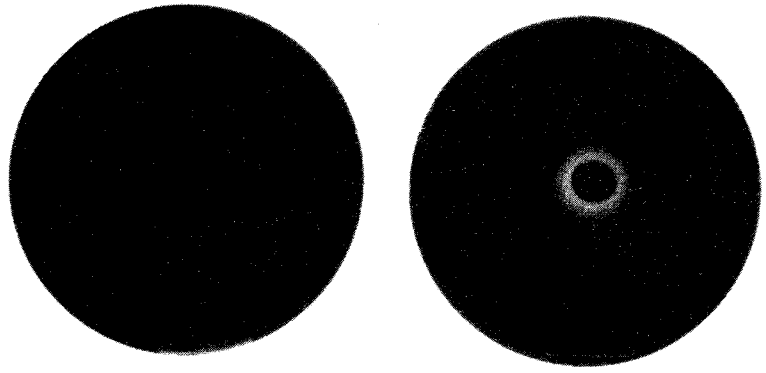


Photo 2. Halo formation on an IM agar plate supplemented with sulfur black dye 0.5g/L by strain W3. Left is control plate, and right is strain W3 spotted in the center, and s clear zone (Halo) around the colony after incubation.

As the screening method is efficient and very easy to perform, progress was fast, and undergraduate students were fascinated by this type of operation. My laboratory was full of students during the summer, and several of them later got Ph.D.s in biotechnology.

My success in obtaining efficient strains was mainly due to my success in designing a simple and easy screening method, as well as having many such strains exist in the local environment.

Potential Use for Indigo and Sulfur Black Bio-Degrading and Bio-Adsorbing Strains

Indigo is very stable and does not fade, even after repeated exposure to strong sunlight, and this makes it the major dyestuff in the denim industry. Indigo is also very safe because its soluble derivative, indigo cermine is a U.S. FDA-approved dye for use in food and drugs.[2]

In 1988, annual worldwide production of indigo reached 14,000 tons, with a market value close to a quarter billion U.S.

dollars.[3] In the same year, one billion pairs of blue jeans were sold, suggesting a market value close to US$54 billion for denim products. Now denim products are even more popular, and the market size has grown even further.

This big denim industry produced many environmental problems. Together with the tightening of environmental regulations in industrialized nations, the handling of dyestuff has created a great demand for biotechnology. Some needs that biotechnology can help meet are outlined below:

- **The creation of a bio-degradative or environmentally friendly system to replace the bleaching reagent, i.e. hypochlorite.** A bleaching step is usually required after the stone-wash process, but hypochlorite is very harmful to the environment and is prohibited from being discharged into the sewage in many countries.

- **The development of a biodegradable or bio-adsorbable and environmentally friendly system to remove indigo or sulfur black as well as other textile industry dyes in the waste water.** The denim industry is unwilling to adopt the currently available methods, e.g. coagulating with alum/lime and ozone reaction, because they are too expensive and time consuming.[4]

- **The replacement of the stone-wash step with a biodegradable and environmentally friendly system to produce a stone-washed effect.** Consumers love the used look so characteristic of denim products. One way of removing the dye that adheres to the cotton fiber is to degrade the cotton such that both the cotton and the attached dye can be removed partially. This approach was achieved by the use of cellulase. Alternatively, any enzyme that can degrade the dye (indigo, sulfur black and other dyes) would also lead to similar consequences. This alternative has not been achieved so far, but is the target of my approach.

- **The removal of useful chemicals contaminated with dyes.** One standing problem is the recovery of sodium thiosulphate that was contaminated by sulphur black.

- **The isolation of bacterial strains for the cleanup of environments polluted by textile dyes.** Due to the extensive use of textile dyestuff in very large quantities over a long period, vast areas were polluted by such dyes, especially the very stable types, like indigo, which can deposit in streams and sea beds for a long period of time.

With this background, it is obvious that indigo and sulfur black biodegrading enzymes or strains will find applications to address these needs. For example, sulphur black bioadsorbing strains can be used to recover sodium thiosulphate.

Strain Characterization

Strain H-12 secretes a low molecular weight (14K. similar to RNase A) protein from the cell in late log phase, and can completely decompose indigo carmine even at blue black concentration (500ug/ml,O.D. 609=4.2) within 24 hours just with resting cells (**Photo 3**) and can decompose indigo itself to some degree.

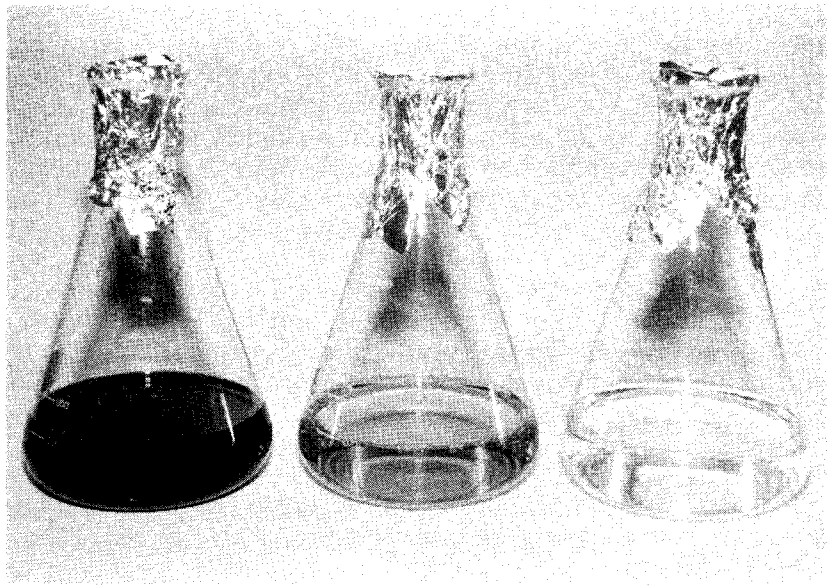


Photo 3. Bio-degradation of indigo carmine (500 ug/ml) in 0.05M citrate buffer pH4 by resting cell of strain H-12. The mixture was incubated at 37°C, shaken at 200rpm for 24 hours under dark conditions.
(a) left: uninoculated control was still in blue in color after incubation;
(b) center: inoculated with resting cells of strain H-12, the indigo carmine was decolorized to a yellow product;
(c) right: supernatant of strain H-12 in 0.05 citrate buffer pH4.

he degraded products were proved to be non-toxic by three different toxicity tests. This enzyme, indigonase, has acidic pH optimal (-pH4), high heat resistance, and a michaelis-menten constant (Km) of 0.17um (with crude preparations). Its low molecular weight, and high heat resistance led to the speculation that the catalyst is not an enzyme, but this was later proved to be wrong by: inactivation by heat; sensitivity to protease; and inhibition by urea, EDTA, and mercury ions. Due to this mistaken assumption, much effort was made to prove it correct, and thus progress was significantly slowed. In the enzyme activity assay, degradation of indigo carmine can be easily followed by optical measurement at O.D.609, but the existing procedure for measuring indigo is complicated and slow.[5] A significantly improved indigo assay system was developed as this work progressed.[6] The recent discovery that this enzyme requires a metal co-factor also significantly improved enzyme activity, purification of the enzyme, and the enzyme's potential.

Strain W3 was first discovered as a bacterial strain that gave a significant halo. It was later found that the halo was formed by adsorbing the surrounding soluble black dye onto the bacterial surface instead of degrading such dye, as expected. After many twists and turns, we also found that this bacteria produced a much higher level of sulfur black dye binding element (We thought it was a protein.) and reached its maximal level at late log phase, or about 50 hours of culture, with vigorous shaking in rich medium at 37°C. With such cells entrapped in polyacrylamide gel (We tried many entrapment systems and faced many difficulties.), we eluted the column with high dye solution, such as 2.44mg/ml (O.D. Log = 1.0 X 40). Clear solution was eluted out, demonstrating that the cells can attain a binding capacity of 1.6mg dye/mg dry W3 cells. We were also amazed by the fact that a sudden and dramatic drop in adsorption was noted when the binding capacity was finally saturated. The cell immobilization process would be made cheaper by floculation with aluminum sulphate in the removal of sulfur black dye from sodium thiosulphate from the Sandoz process. So we are close to designing a system with economic value.

Strain L5 and others strains can decompose sulfur black under aerobic or anaerobic conditions similar to that described for H-12. Although less effort was focused in this direction, the potential has been clearly demonstrated.

All the useful strains were sent to be micro-checked for strain identification based on fatty acid profile. However, complications appeared for H-12, so a complete analysis based on many classification criteria was used and was carried out by the Food Industry Research and Development Institute, Hsinchu, Taiwan, ROC. H-12 was identified as Claribactor michiganense; W3 was identified by micro check as Bacillus circulars GC subgroup B; and L5 was identified as Enterococcus durans.

Patent Application

Literature and Patent Search

A DIALOG worldwide computer literature search of the past 25 years (1969-1994) found no reference for any micro-organism able to degrade indigo or indigo carmine. With this knowledge, we began our efforts and eventually found the indigo and indigo carmine bio-degrading strains. When we started our work on sulfur black dye, we again performed a DIALOG computer search and found that, from 1963-1994, there also were no references for micro-organisms able to bio-degrade or bio-adsorb sulfur black dye. We knew, therefore, that we could claim this scope. Thus, we put all our effort in it, and found several useful strains.

When we started our work in 1989, computer literature searches were not common and quite expensive, but we completed it at the CUHK Central Library with the assistance of library staff. One usually stumbles when venturing into new areas, so it took us some time to realize that computers can be very stupid (For instance, the computer did not know that "sulfur" equals "sulphur" in search terminology.). By the time we found the H-12, W2 and L3 and were impressed by their ability to the extent of thinking about applying for a patent, we were quite familiar with the online computer search and had effectively mastered the use of keywords. Patent searches for both the indigo/indigo carmine and sulfur black areas were very satisfactory. Not a single patent fell near these areas. We were excited at the time, knowing that we had a novel discovery, no previous patent claims and strains that showed promise, but please do read on to understand the problems I faced.

Extra Work for a Front-Runner

Being the first patent application for the CUHK and Hong Kong Institute of Biotechnology (HKIB), I helped draft the cooperation agreement between CUHK and HKIB, the patent policy

of CUHK, and the agreement between inventor and the university. HKIB was established by the Royal Hong Kong Jockey Club as an independent Institute on the CUHK Campus to promote the development of biotechnology in Hong Kong. A big budget was shared between HKIB and HKUST, and HKIB used the budget for the construction of the HKIB building and its initial running cost, with Professor Dominic Lam and Dr. Siu Leung Lee as the first director and associate director, respectively. Since Dr. Lee was my former student, I dealt mostly with him, and we have maintained a close and good relationship ever since. Professor Charles Kao, vice-chancellor (VC) of CUHK, also the founder of HKIB, wanted to promote applied research and patent applications. With this background, I managed to strike attractive terms for the staff of CUHK, where inventor and university shared equally (50%) the net profit from HKIB, and HKIB and CUHK made a 30/70 split on a carefully defined net profit definition. I revised the terms for the inventor to make them more favorable legally (Many of these arrangements were changed to less favorable terms after my times.).

The Patent Application and The Disaster

Anyone with some business sense and an applied research background, could see the novelty, large market value, and potential for application and development of our research, but pushing this case through the department and university patent committee was a difficult job. The patent attorney chosen for the indigo patent knew very little about biotechnology and microbiology (compared to Dr. Bertram Rowland, who filed the sulfur black patent application), so I had to learn the concept and practice of patents from scratch, with help from Dr. Lee, and drafted and revised the patent application myself. To my surprise, the indigo patent application turned into one big disaster. Professor Lam, with his background in applied science, released our concepts and discovery to the news media, and they were published in **Women Wear Daily** on June 4, 1991. Even worse, this careless and unnecessary mistake could have been saved by filing the patent within one year after the news release. HKIB should have been looking after this case, and should have had the experience and knowledge to sound the alarm, but this obvious action was again ignored. As a result, the patent for the concept and application was rejected by the U.S. Patent and Trademark Office (as well as by the patent offices of other countries), and the patent examiner restricted the claims to H-12 only. Two U.S. patents,

microbial degradation of indigo and indigo carmine with bacterial strain (U.S. Patent No. 4,418,161); and degradation of indigo and indigo carmine with an enzyme isolated from bacterial strain ATCC 55396 (U.S. Patent No. 5,547,043) were completed, but contained only 1/20 of its original value because others now can isolate other useful strains for the same purpose.

Failures like this are truly unbelievable to anyone with some applied research understanding.

The patent for the sulfur black invention was easier because of the experience gained from the first invention as well as having a competent patent attorney, but there was another surprise for me. HKIB abandoned the patent application on the last day of a deadline, when the patent application was close to completion. Luckily, I had the confidence and the resources, and thus could take up the patent application from HKIB immediately when this decision came up. The U.S. patent for bacterium useful in the removal of sulfur black dye from a substrate (*U.S. Patent No. 5,610,064*) was completed by me. However, with such a track record, I wonder if any inventor will ever again entrust his/her discovery to HKIB for patent filing.

Constraints on Scientific Publications

Due to the confidentiality requirements for filing patents, an inventor cannot publish the scientific results obtained. Pushing through on two fronts, I got interesting results on:

(1) Strain hunt;

(2) Strain characterization;

(3) Enzyme or protein purification or enrichment;

(4) Application of bio-degradation and bio-adsorption of major industrial dyes;

(5) Adaptation for industrial applications; and

(6) Waste treatment system.

A total of 19 confidential reports were written for HKIB.

This publication restriction had a significant impact on my publication schedule, research grant application, promotion and retirement. There was a big personal sacrifice, even through I got a lot of personal satisfaction out of this.

Industrial Development of the inventions

Dr. Lee and Dr. Albert Chang (the fourth director of HKIB) did contribute to the industrial development of my novel ideas and useful strains for indigo/indigo carmine bio-degradation and sulfur black bio-adsorption and bio-degradation.

We contacted many denim producers, biotechnology companies, enzyme producers, and dye producers. We thus attracted a lot of interest, and entered into nondisclosure agreements with many large, internationally known companies. NOVO NORDISK, an international enzyme-producing company, even entered into an option agreement which would have yielded considerable compensation, but the failure of the U.S. patent application blew away most of this interest. It is a pain in the neck for a scientist to learn this lesson the hard way, especially when it is not his fault.

Since the outlook for novel ideas is attractive, even with the publication restrictions, due to the restriction, one still must secure considerable research and development grants. My development received HK$1.3 million from the Industrial Development Grant of the Industry Department, half a million (HKD) from Croucher Foundation, two small RGC direct grants, and three private research grants.

These developments also forced me into applied research. Besides the troubles and hard work, I now realize applied research and basic research are two different worlds with totally different rules, attitudes, and value systems. Therefore, my experience in spanning these two worlds should be valuable for those basic scientists who look to the applied research side for opportunities. At least my experience can be shared with newcomers, hopefully reducing their chances of falling into the traps and false expectations I ran into.

Reality and Problems

I now realize that a patent application requires a lot of professional knowledge on the part of the inventor, as well as big changes

in thinking and practice as one switches from basic science to applied research. I did not expect in the beginning that the confidentiality requirement for patent applications could have such a bad effect on my academic career. I eventually prevailed, but what would have happened if I was not so lucky?

Inventors must make many important decisions in order to succeed. However, to be competent, one must master the very-complicated patent system. Lots of times, I had to make decisions in the dark, without knowing the consequences of my choices. Professional advice in this area is needed most if Hong Kong is to have some success in biotechnology.

At the beginning, I, as well as others, had the impression that as soon as one obtained results that were sufficient to apply for a patent, one should file the patent as quickly as possible for fear of being taken over by other scientists in this highly competitive world. We also were fed stories about big companies fighting in court over filing dates and invention dates. On the other hand, no one mentioned to us the problems or disadvantages of early filing. I discovered later that for those not-so-dramatic inventions, late filing has a lot of advantages. The Patent Cooperation Treaty (PCT) gives U.S. patent applicants a one-year grace period to obtain worldwide coverage. Such coverage is expensive, with payments due for each country, thus placing it beyond the means of individuals or small institutions. Normally, the company that takes over your invention will fight with the U.S. and other patent offices over patent claims and the arrangement for worldwide coverage. Late filing allows you time to find a company to take up the patent and development role as well as allows you to further build your invention to attract companies to take over development on a shared-benefit basis.

Therefore, determining the proper time for filing a patent is a hard decision, even for good patent attorneys. If you ask an ordinary patent attorney, he probably would advise you to file it immediately so that he can secure you as a client. This problem is the inventor's concern, not the patent attorney's. First-time inventors do not realize such traps and sail along, just as I did.

Most scientists, myself included, tend to dream about making a big discovery, getting a patent, and becoming a billionaire who can sponsor his own research. This perception exists because of the heavy publicity surrounding a few big discoveries. This causes most scientists to overlook the outcome for the ma-

jority of inventions. I must discourage my fellow scientists by revealing that royalties from successful inventions are low.

Scientists are smart and calculating and are attracted to incentives. I shifted my focus from basic to applied research because Professor Kao, advocated the virtues of applied research, but the CUHK system did not recognize the potential nor did it offer incentives in this direction. As a matter of fact, during Professor Kao's term as VC, there was a big punishment for the shortage of publications that came about as a result of the patent restriction. Even patents that were completed did not count as equals published papers, and I was humiliated to be rated as a non-productive staff member. The only thing that carried me through this situation so that I did not drop the project midway was my bulldog attitude: "Bite to Kill." Once I started the process, I had to see it through, irrespective of effort and sacrifices.

For biotechnology to flourish in Hong Kong, local scientists must play a significant role. Universities should adjust their system to give some incentive to practice applied research.

To be a competent inventor, one must understand the patent system, licensing, industrial development, applied research management, commercialization and legal documents. These are complicated and broad fields, in strong contrast with the highly specialized approach that normal scientists take, so an immense effort is required.

When I ventured from basic science into applied research, it seemed to me that I had entered a new world with different laws, game rules, and virtue systems. It was difficult for me to forget my past (in basic science and the system associated with it), and this created many internal conflicts. I had a hard time trying to accommodate the virtues of the two systems, as many aspects contradicted each other. For example, my bulldog attitude is a virtue in basic science which was built during more than 20 years of experience. In applied research, however, one frequently drops a scientific pursuit half way due to an unpromising outlook. Dr. Albert Chang and I have known each other since our graduate student days at U.C. Berkeley, but when he decided as a manager to drop the sulfur black patent application close to completion to save less than US$2,000, it was hard for me to accept. I was forced to take over the project with a lot of anger. With time, this matter cooled off, and I could attribute the problem to a difference in acceptable practices in basic science versus applied science.

To conclude, I maintained my bulldog attitude in following my project all the way to its successful end, but, given my sacrifices, I would not recommend others take this route. It takes a great effort to achieve very little in Hong Kong, and I find that it is not worth the trouble.

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Chapter 19

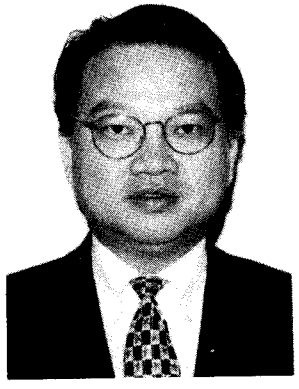
Intellectual Property Protection: The Key to Success for Hong Kong's Biotechnology Industry

By

~ Albert Wai-Kit Chan, Ph.D., J.D. ~
Partner
Cooper & Dunham LLP, New York

Founder
United States-China Intellectual Property Institute
Flushing, New York

Adjunct Professor of Law
The City University of New York Law School at Queens College
Flushing, New York



***Albert Wai-Kit Chan, Ph.D., J.D.**, is a partner at Cooper & Dunham LLP, New York; founder of the United States-China Intellectual Property Institute and adjunct professor of law at The City University of New York Law School at Queens College, both in Flushing, New York.*

Hong Kong is on the verge of deciding whether to merely dabble in biotechnology or to jump in with both feet. Several universities in Hong Kong have set up biotechnology centers, and a number of researchers are stepping up work in this field. Whatever path Hong Kong chooses, it must remember that intellectual property is one of the keys to success in the biotechnology industry.

The United States biotechnology industry has taught the world important lessons about intellectual property, mainly that it should be a focal point, whether planning a project, a company or an empire. U.S. biotechnology companies usually have at least one employee who is responsible for intellectual property matters. A typical start-up biotechnology company spends one-third of its budget on intellectual property matters. If Hong Kong is serious about establishing a viable biotechnology industry, it must be prepared to devote the same amount of time and money to intellectual property.

This chapter will answer the following questions:

1) What is intellectual property?

2) What types of intellectual property protection are available in Hong Kong?

3) How can patents help protect Traditional Chinese Medicine?

4) How can Hong Kong use intellectual property to grow its biotechnology industry?

5) What are licensing and technology transfer and how can Hong Kong benefit from them?

What is intellectual property?

There are four types of intellectual property protection in the world: patents, trademarks, trade secrets, and copyrights.

On June 27, 1997, Hong Kong passed a bill protecting patents, designs and copyrights. A trademark bill was introduced in February 1997 and will not be introduced into the Legislative Council before Autumn 1998.

Patents

Introduction to Patents

Patents provide the strongest and most comprehensive intellectual property protection, but they are also the most difficult protection to obtain. To qualify for a patent, an invention must be new, useful and not obvious. There are different types of patents.

A number of countries issue patents, and there is even the Patent Cooperation Treaty (PCT), through which inventors can apply for international patent protection. Although there are some differences in the patents of various countries, some characteristics are the same. For instance, no matter what the country, every patent application is separated into the "specification" section and the "claims" section.

The specification includes such things as: the background of the invention; a description of the invention; embodiments of the invention; figures and tables; information about whether or not the invention has been disclosed to others; and modes for carrying out the invention.

The claims define the applicant's patent rights. For example, a claim might read: "What is claimed is: (1) A pharmaceutical dosage unit for bolstering immune function in healthy and diseased patients, said dosage comprising a mixture of.... (2) A dosage unit according to claim 1 wherein the dosage form is an orally ingestible capsule. (3) A dosage unit according to claim 2 which comprises 5 mg of ..., 25 mg of ..., and 50 mg of ... (4) A method according to claim 3 wherein said composition is orally administered to the patient in the form of a tablet 3-4 times a day."

Patents in Hong Kong

Hong Kong recognizes two types of patents, a Standard Patent and Short-Term Patent. In both cases, there is no examination of the substantive matter contained in the patent, meaning the intellectual property department in Hong Kong will only examine the form of the patent, not its substance.

The Standard Patent

Hong Kong residents or legal persons (e.g. companies or institutions registered in Hong Kong) can choose to:

1) File a PCT application designating China, the European Patent Office, or the United Kingdom. The Chinese Patent Office is the receiving office for Hong Kong residents and legal persons, according to PCT. Hong Kong residents and legal persons may choose to file their application directly with the International Bureau of World Intellectual Property Organization in Geneva. A PCT application offers a convenient way to temporarily reserve an inventor's right in different countries. The disadvantage of a PCT application is that it delays the process of starting the inventor's patent application in different countries.

2) File a Chinese National Patent Application.

3) File a U.K. application.

4) File a European patent application designating the U.K.

Applying for a Standard Patent in Hong Kong is a two-step process. First, within six months from the date of publication of the designated patent application, the inventor must file a "Request to Record" in Hong Kong with supporting documentation. Second, within six months from the date of grant of the designated patent or the publication of the "Request to Record," whichever is later, the inventor must file a "Request for Registration and Grant" to secure the equivalent Standard Patent in Hong Kong. The Hong Kong Patents Registry will then issue a certificate to the patentee and advertise the granting of the patent. A Standard Patent is good for the lifetime of the patent in the designated country.

There are some key differences in Chinese Patent Law and U.K./European Patent Law. These differences can either help or hinder a potential patent application. Therefore, it is important to seek professional advice prior to making a decision about what route to take.

Short-Term Patent

The Short-Term Patent is the other type of Hong Kong patent. The patent application to for a Short-Term Patent application limits the scope of an invention that can be protected under Hong

Kong Law. In other words, this type of patent restricts what the inventor claims to be his invention. Claims define the protection that is requested. There are two types of claims: independent and dependent. For instance, an independent claim might read: "What is claimed is a method for treating AIDS consisting of..." This independent claim would be Claim 1. Based on this, a dependent claim may follow: "What is claimed is a route of delivery for Claim 1 using an injectable liquid." A Short-Term Patent application is limited to one independent claims and four dependent claims.

The maximum term for Short-Term Patent protection is eight years. The establishment of the Short-Term Patent is intended to protect the rights of smaller businesses but also helps incubate new and developing technology-based companies.

A Short-Term Patent application may assume the priority date of a previously filed application from any PCT country within 12 months. The priority date is the date on a previous patent application. This date is particularly significant in competitive industries because it establishes which researcher or institute was first to claim the invention as his/their own. It might also be useful at a later if there is some dispute over who was first to invent.

The requirements for a Short-Term Patent application are:

- A request for the grant of short term patent;
- A specification in English or Chinese which provides on the face of it for a description of the invention to which the application relates;
- An abstract; and
- A search report in relation to the invention.

Patents and Traditional Chinese Medicine

Traditional Chinese Medicine (TCM), such as herbal medicine, is shaping up to be a major player on the Hong Kong biotechnology scene. TCM can take advantage of Hong Kong two biggest assets, its Chinese culture and its inroads in the Western world. Hong Kong is in the best position to serve as a broker for TCM: It is very familiar with TCM technology and it has the sophistication to sell these technologies to the international market.

In an ideal world, Hong Kong institutes and companies would hold patents to all the varieties of TCM; however, because TCM has been practiced for thousands of years, its "newness" comes into question. Also, the product being patented cannot have been publicly used, as most TCM is. Two common ways that inventors can obtain patents for TCM are if they can:

1) Find new uses for an existing herb or collection of herbs or

2) Isolate a new active ingredient. The basic recipe for most TCM have been known for years and, therefore, is not patentable. Researchers who can find something new about herbal medicines, e.g., a new use for an old compounds, may be able to apply for patent protection.

One problem with patenting TCM is that most of the herbs have been described previously; therefore, they are what people in the patent field call "publicly known." Many of them are also publicly used, i.e. people at different levels have used the herbs for different purposes. A herbal medicine composition, the process of making the composition, and the uses of the composition may not be novel since they are either publicly known or have been publicly used.

Although Hong Kong may have to hunt a little harder for ways to patent TCM, there are a number of big opportunities in the future for patenting things related to TCM and biotechnology.

Since we do not know the active ingredients in TCM, we need indicators to validate each batch of drugs. In the process of achieving this goal, patentable subject matter(s) (i.e., the indicators used to determine the quality of the product) may be identified. Claims may be directed to protect the indicator(s). Standard(s) needed for comparison and the use of such standard(s) may also be patentable.

One characteristic of TCM is that there is a large volume of clinical and/or animal studies for almost every medicine. Having this information on hand, one can determine the effective dosage or the appropriate route of administration. The dose(s) or the effective/appropriate route of administration may not be obvious in light of the prior art and, therefore, may be protected by a new patent.

New formulations which are directed to new dosages and new routes of delivery may be discovered. In the TCM field, things

such as oral drugs, sprays and dermal patches are uncommon forms of drug delivery. Of course, to seek such protection, data must be provided which can show the efficacy of such modifications.

TCM active ingredients, be they single or multiple-chemical entities, also are likely to be patentable.

Another patent focus for TCM makers should definitely be second-generation products. Clearly, those active ingredients which have decoded chemical formulas can lead to second-generation drugs by merely modifying the chemical formulas' functional group.

If we know the active ingredient(s), we may be able to understand the target protein or biochemical pathway the drug is acting on. We can then use such a target protein for screening more drugs.

The cost of TCM can be high, and fake medicine has been manufactured; therefore, the market demands fast and economical ways to authenticate herbs. Authentication kits would allow buyers to test whether or not a medicine is genuine.

I have been involved in prosecuting patent applications which are directed to the authentication of herbs using DNA fingerprinting methodology. Protein fingerprinting may also be another way to authenticate the herb or the medicine.

Copyrights

Article 140 of the Basic Law requires Hong Kong to have its own law to protect the achievement, the lawful rights and the interests of authors and artists in their literary and artistic creations. Hong Kong follows the copyright obligations of the: (1) Berne Convention; (2) Universal Copyright Convention; (3) Phonograms Convention and (4) The Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIP) of the World Trade Organization. Copyright violations carry both criminal and civil sanctions.

The term of a Hong Kong copyright is the lifetime of the author plus 50 years, except for typographical arrangements, which are protected by copyright for 25 years. The following are protectable subject matters under Hong Kong copyright law:

- Original literary (including computer program), dramatic, musical, or artistic works;
- Sound recordings, films, broadcasts and cable programs; and
- The typographical arrangement of published editions.

The Hong Kong biotechnology industry might use a copyright to protect a computer program used in the practice of an scientific invention. It might also find shelter in copyright law for books detailing how a particular biotechnological discovery was made and for a documentary film which follows the inventors from university start-up to the Nobel Prize.

Trademarks

A trademark is a unique mark (i.e. the name of the product presented on signs or packages) which can be used to protect an biotechnology invention's reputation. Manufacturers identify a registered trademark with the ® symbol. Trademarks are consumer oriented. They offer the end user a guarantee of quality, service, and product image. This is the reason that many diners choose McDonald's over other fast food restaurants. The trademark next to the McDonald's name assures consumers that the hamburgers will taste the same in Beijing as they do in New York.

A trademark must be distinctive and must be used continuously in order to be deemed valid. Trademarks also must be in use at the time an application for trademark is submitted. An applicant may file an intent to use the trademark up to three years prior to actual use, but he must provide proof that the mark is used within the time period indicated.

It is worth spending a generous amount of time choosing the right trademark for a product. Any trademark applicant needs to make an effort to understand the culture of the market to which it is directed and to pick a mark which will be acceptable to the end user.

Hong Kong trademark law protects "Any sign capable of being represented graphically which is capable of distinguishing goods or services of one undertaking from those of other under-

takings." It is possible to protect designs, letters, numbers, colors, sounds, and smells. The Hong Kong biotechnology industry can use trademarks to protect the way an invention is packaged, marketed. Trademarks can help guarantee the quality of biotechnology goods and establish a certain reputation for the company. Trademarks protect against consumer confusion, and consumers are the intended benefactors of trademarks. Trademark law is written to prevent consumers from being misled, from thinking that they are buying one product when they are in fact buying a cheap imitation. If consumers look at a package, a name, or a sign and immediately associate them with a certain product or company, then that trademark is successful.

Owners of well-known trademarks, such as Coca-Cola, can protect their marks in Hong Kong, even if they have no business or goodwill in Hong Kong and the mark is not registered in Hong Kong. Several things can lead to a Hong Kong trademark being revoked:

- The trademark is not used for five consecutive years;
- The trademark has become generic in meaning (This would be the case if Xerox allowed its name to be used as a synonym for photocopying, i.e., people commonly say, "I want to make a Xerox" rather than "I want to make a photocopy.")
- The trademark is misleading;
- The trademark is contravened;
- Someone successfully applies to have the trademark declared invalid because it was registered in bad faith or because the application did not comply with the registration criteria.

Trade secrets are the final form of intellectual property protection. Trade secrets afford protection for guarded things such as secret ingredients and recipes. Coca-Cola's formula is one of the best examples of a trade secret. Trade secrets are not registered with any agency; they are maintained within a company, institute or person's head. The most difficult part of maintaining a trade secret is keeping its secret limited to a small number of loyal people.

In order to determine whether an herbal medicine invention, which could qualify for a patent should instead be maintained as a trade secret, the following questions should be considered:

- If patented, can the invention be easily enforced?
- Can the patented invention be easily circumvented?
- Is the life of the patented invention relatively short?
- Does the patent disclosure give competitors an edge?
- Does the inventor want to publish the invention?
- Will it be difficult to maintain the trade secret?
- Is the invention in an active area of research?

There are a number of advantages to trade secret protection:

- The expenses of obtaining patent protection and enforcing patent rights are not encountered when trade secret protection is used.
- There is no a time limitation for trade secret protection. The only limitation is that secrecy must exist.
- Competitors are not apprised of the trade secret, as contrasted to the full disclosure required for a patented invention.
- A trade secret does not have to be a patentable invention; it just must be unique and secret.

Intellectual Property Attorneys

While inventors themselves can file their own patent applications in Hong Kong, most turn to patent attorneys who are familiar with the process and the international ramifications of a patent. In Hong Kong, it is difficult for a good patent attorney to

survive and do well because there is no substantive examination with the Hong Kong intellectual property department. The current system relies on Chinese national, United Kingdom national or the European Patent Office's examination machinery. The practitioner in Hong Kong is simply filing formal papers to fulfill the formal requirements. In a way, it makes sense for a relatively small place like Hong Kong not to invest effort in training a body of "Examiners" and establish substance law. However, also because of that, it is hard to find professionals locally who can give valuable opinions and substantive advice.

Moving Technology from Universities to Industry

In biotechnology, most of the research which leads to the development of products usually takes place in universities rather than commercial laboratories. There are two ways to transfer the technology from university to industry. One is licensing the invention, and the other is forming a venture for the sake of commercializing the invention. Licensing is the process of selling the rights to use an invention. In the U.S., the most common licensing action is universities conferring licenses to biotechnology companies that are shopping for new products or technologies.

To determine whether licensing is preferred over business ownership, inventors should examine the return on investment, or the risk/reward ration. For instance, if the risk too great or the projected return too low, the product(s) may not be a viable foundation for a new company. Another factor to keep in mind is the product's uniqueness. Is the product a breakthrough item or an improvement on an existing product? If it is only an improvement, the technology owner may want to choose licensing over starting a new company. A start-up company might be right for a product that is capable of spawning a family of related offerings, but licensing might be more practical for a single product with no possibilities for expansion. Licensors should choose a partner who can bring their invention to market. Since the risks are high for such an undertaking and the product may not yet be defined, negotiations focus more on the financier's commitment to the scientific talent or to a broad-based technology rather than a specific project. Financiers must see a long-term return before investing in this type of agreement. Potential licensees should have:

- A record of commercializing inventions;
- A plan for developing and marketing the product;

- Experience in the field of invention;
- Someone who has the power to lead the development of the invention;
- Sufficient funding to further the invention;
- Consulting contracts for the most important researchers; and
- A long-term view of the relationship.

Hong Kong technology owners face special obstacles in licensing their inventions or technologies. First of all, there is a shortage of good licensing personnel. A licensing agent must have a technical background (i.e. They can appreciate the invention/technology.) and know how to protect intellectual property. She must also be connected in the industry because she will be the salesperson for the technology.

Another problem that I have come across in my dealings with Hong Kong universities is that the patent policy in some of these institutions is not clear or not encouraging to potential inventors. The patent policy spells out a university's rules regarding what is patentable and what a staff member should do if he thinks he has invented something. It should define what things are patentable; give the name and phone number of an in-house person in charge of patents; and give the percentage of profits the inventor would earn from commercialization of the invention. Without a solid patent policy, inventors do not know who to report the invention to, and they may be so discouraged by the small financial incentives listed in a patent policy that they never pursue commercialization.

The first step toward a good patent policy is the establishment of a university licensing office staffed by a person or persons who have a background in science. This office can be called the "business development office," among other things. In the U.S., Memorial Sloan-Kettering calls its licensing office the Office of Industrial Affairs. Columbia University refers to its licensing center as Columbia Innovation Enterprises. In addition to setting patent policy, the office would be responsible for visiting different departments monthly or every several months and collecting invention disclosure reports (The reports should state the nature of the invention.) prior to publication of the discoveries. The licensing office should organize seminars to educate sci-

entists about the intellectual properties that should be protected and publish a handbook that answers questions such as: "How do you know if you have an invention?" and "What steps should you take if you think you have invented something?"

While licensing is the most popular way for a technology to move from universities to industry, sometimes new ventures are created to commercialize inventions that surface in the university setting. These ventures draw heavily on university professors to serve as founders, consultants, and members of scientific advisory boards. Many university professors, after negotiations, own percentages of these newborn companies. One common scheme is that the professors who create a useful invention establish a paper company. Their institution may help establish this company or may even contribute seed money to give the new company a head start.

The next phase in the life of a new biotechnology venture is usually a move toward a larger-scale operation which involves increased capital. At this point, financing is often provided by venture capitalists. While venture capital for biotechnology in Hong Kong is immature (See Chapters 15 & 16.), it is important that the region's inventors and institutes understand how venture capital arrangements operate. In a typical venture capital setting, serious negotiations with potential investors and the choice of a proper partner help determine the fate of this new venture. The end result is that the venture capital investor may own 40-70% of the venture, with the founders retaining 10-40%.

Corporate partnering (i.e. teaming up with large pharmaceutical companies) may provide a source of second-round financing for the venture's promising projects. In this arrangement, the biotechnology partner gains access to the pharmaceutical company's manufacturing or regulatory expertise. This partnership allows pharmaceutical companies to become involved in biotechnology projects without investing very much of their own time and money.

Another approach to financing is for technology owners to launch a start-up company to market products which use their technology. Before they do this, they should ask themselves whether the market can sustain all the products generated from their technology. They also must realize that the entire company, not just the R&D arm, must be built to support the development of technology. Those who decide to start a new company based

on their technology should be ready to invest five to 10 years in this venture.

Conclusion

Hong Kong is on its way to establishing a competitive biotechnology industry. As long as the region focuses on its strong points (its Chinese history and new closeness with China, and its base of internationally trained scientists), it can mold itself into Asia's biotechnology center. The important thing for Hong Kong to learn now is how to protect its intellectual property rights and how to commercialize the many inventions that are sure to emerge from its universities.

The Significance of China

Chapter 20

Hong Kong as a Gateway for China Biotechnology

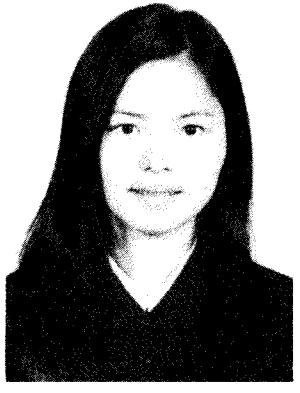
By

~ J. Tze-Fei Wong, Ph.D. ~
Professor, Department of Biochemistry
&
Director, Drug Delivery Centre
The Hong Kong University of Science and Technology

~ Anna Nga Yee Lee ~
Hong Kong Representative
China Innovation Center for Life Science
State Science & Technology Commission of China



***J. Tze-Fei Wong, Ph.D.**, is a professor in the Department of Biochemistry and director of the Drug Delivery Centre at The Hong Kong University of Science and Technology.*



***Anna Nga Yee Lee** is the Hong Kong representative for China Innovation Centre for Life Science of the State Science and Technology Commission. She holds an MBA from Macquarie University in Sydney, Australia.*

Gateway Function

In considering Hong Kong's present and future role as a gateway for Chinese biotechnology, the first question to ask is: Why does Chinese biotechnology require a gateway?

China is a major country in terms of R&D effort and performance and has vast biological resources in the fields of agriculture, forestry, aquaculture, and medicinal herbs. Above all, it is determined to develop a strong biotech industry. Despite these favorable factors, its biotech industry is only starting to build, and biotech exports are still minimal. It is therefore useful to examine the nature of the bottlenecks in the growth of biotechnology in China, and the ways Hong Kong can provide a gateway to help overcome such limitations.

Biotechnology, like other high technologies, requires the coming together of a spectrum of resources — research, development, intellectual properties, investment, and commercialization. Deficiency in any one aspect will seriously hamper the dynamics of the field. Of these resources, China's research strength is widely acknowledged. The calibre of its scientists is top notch in the hundreds of research institutes and universities. While their work can undoubtedly benefit from better equipment and increased funding, research output in either quality or quantity is by no means a major limiting factor. The many scientific accomplishments that have not been transformed effectively into technologies of international commercial value are, in fact, the most telling reminders of how much more facilitation is needed in order to attain a pace of development merited by the breakthrough discoveries of China's scientists.

The Story of Insulin

Human insulin consists of two separate polypeptide chains, A and B, held together by two interchain disulfide bridges between two Cys (cysteinyl) sulfhydryls on the A chain, and two on the B chain. Another pair of Cys sulfhydryls on A-chain form an internal disulfide bridge. The chemical synthesis of insulin was first accomplished by Chinese scientists. In the last step of the synthesis, the six sulfhydryls on the two chains have to be paired off correctly. Given one A chain and one B chain, this requires choosing for one Cys a correct partner out of the remaining five Cys: the probability of correct choice is 1/5. Having formed one correct disulfide leaves four unpaired Cys. To choose

the correct partner for the next Cys out of the remaining three entails a probability of 1/3. Once two correct disulfide bridges are constructed, the two remaining Cys will find one another. The overall probability of all six Cys pairing with the correct partner is therefore (1/5)x(1/3) or less than 7%. Of course, during the reaction one cannot be assured of a single A chain interacting with a single B chain. Instead, there may also occur assemblies of A+A, 2A+B, A+2B, B+B ...., all acting to lower substantially the yield of correctly bridged, active insulin.

Assembly of natural A and B chains into active insulin was first achieved by Professor Gordon Dixon, who obtained less than 1-2% active insulin, and Professor Du Yu-Cang and co-workers at the Shanghai Institute of Biochemistry. One day in 1965 Professor Dixon walked into the laboratory of one of the authors, on the same floor as his at the University of Toronto, holding in his hand the latest paper from China and exclaiming:

"Now the Shanghai workers are getting 50% yield! Is this believable?"

This incredulity was understandable, because the 50% yield of the Shanghai group, made possible by a combination of special experimental conditions (*"Conditions for Successful Resynthesis of Insulin from Its Glycyl and Phenylalanine Chains,"* Du Yu-Cang, Jiang Rong-Qing and Tsou Chen-Lu, **Scientia Sinica** 14, 229-236, 1965), defied all probability calculations. However, their method withstood the test of time, and the strategy of super-yield assembly was followed by Eli Lilly & Co. in 1982 in the manufacture of recombinant human insulin.

To make recombinant insulin, Lilly required two methods, one for cloning the A and B chains, and one for assembly of the two chains. Since the Shanghai method was published unpatented, the cost to Lilly for the use of high-yield assembly is zero. For the cloning of the chains, Lilly employed a recombinant DNA methodology which in the view of University of California at San Francisco (UCSF) infringes on a UCSF patent. UCSF recently lost the seven-year court case, and in so doing suffered a financial loss of US$12 Million in legal bills. However, as **Science** (*"A Bitter Battle Over Insulin Game,"* 277, 1028-1029, 22 August 1977) commented, if UCSF had won, it would have gained financial compensation of several hundred million U.S. dollars from Lilly. Since the cloning and the assembly of the chains are both essential to the manufacture of recombinant insulin, the financial value of the Shanghai super-yield assembly method, freely given away for lack of patent protection, could be comparable to that of the cloning method. Yet even today many worthy Chinese biotech inventions are still not patented outside of China.

International Commercialization

Development of high-tech products requires the making of high-risk investments, which as a rule can be justified only when backed by intellectual property protection in the form of patents or trade secrets. For most biotech inventions, a patent provides the most effective means of protection. Investment in patents, however, is a two-fold risk, incurring first the uncertainty of winning a patent, and secondly the uncertainty of the patent finding useful application, which for pharmaceutical products is often attained only after prolonged and expensive regulatory testing at both the preclinical and clinical levels. Successful international commercialization thus depends on ready access to a complete set of key capabilities:

- Availability of risk capital;
- Due diligence for evaluating the potential of technologies;
- Efficient prosecution of patent applications in key countries;
- Commissioning of GMP manufacture recognized by key countries;
- Design and performance of preclinical and clinical studies to meet regulatory requirements outside of China; and
- Effective marketing of products outside of China.

China is making important progress in the patent process, but still lags behind with regard to the other requirements. The acquisition of strength in all the capabilities will take time, and in the face of fierce and fast-paced international competition in biotechnology having to wait is extremely costly. Hong Kong, as an international financial center with a fine corp of scientists and engineers having long standing ties to all parts of the world, is

exceptionally well equipped to complement the R&D strength of mainland China by speeding up such acquisition. In so doing it stands to partake in the immense rewards of a thriving world-class Chinese biotech industry. This is a precious opportunity, and Hong Kong must move quickly to furnish an effective gateway for the international commercialization of Chinese biotechnology. If Hong Kong acts too slowly, and Chinese biotechnology falls further behind that of the developed countries, catching up will become that much more difficult.

Setting of Targets

Some progress is being forged. Hong Kong venture capital firms are now active in the area of biotechnology and a number of key patents for China inventions have been issued or are pending through the efforts of Hong Kong companies **(Table 1)**. Thus Professor Du Yu-Cang's invention of Memory Enhancing Peptide, in contrast to the super-yield assembly of insulin chains invented by him and his co-workers years ago, is protected by both U.S. and U.K. patents. Biotech products invented/manufactured in China are also being marketed through Hong Kong **(Table 2)**. These are encouraging examples. The CARDS, or Cooperative Applied Research & Development Scheme, of Hong Kong Government Industry Department also directly aims at promoting Hong Kong-mainland complementation. However, in terms of the vast gap China has to bridge to become an important international player in biotechnology, the present efforts represent only a useful beginning. Much greater resources have to be allocated by both China and Hong Kong, and key targets have to be set to develop more fully the gateway functions of Hong Kong. Two foremost targets are readily identified.

First, the Hong Kong SAR Government is encouraging the Stock Exchange of Hong Kong to study the feasibility of establishing a venture board to help high-tech start-up companies raise capital. This will facilitate the transformation of Chinese biotechnology into a major global presence, and deserves the earliest implementation. Given the abundant pipeline of China biotech inventions, availability of start-up capital in the entrepreneurial environment of Hong Kong undoubtedly will unlock a vast outpouring of biotech enterprises.

Secondly, China, recognizing that it takes substantial corporate strength to compete in the international arena, has announced

plans to encourage the formation of ten major biopharmaceutical corporate groups on the Mainland. Because the Mainland groups cannot gain international corporate expertise overnight, sizable pharmaceutical corporations need to be established also in Hong Kong. Specializing in international drug development and commercialization, these will cooperate with Mainland corporations. Complementing one another's strength, the Mainland and Hong Kong corporate groups will be able to build up international competitiveness quickly based on Mainland R&D, Mainland markets, and Hong Kong's gateway assets. The objective will be the emergence within a decade of several Mainland-Hong Kong conglomerates among the top 30 in the world in the biopharmaceutical field. With one-quarter of the world's population, this objective is both achievable and necessary.

With the setting and attainment of these and other worthy targets, we may look forward to the day when Chinese biotechnology becomes a major global player, and not a single Chinese biotech invention fails to receive the international development it deserves.

Table 1. Foreign Patents on China Biotech Inventions Applied for Through Hong Kong Companies

Invention	Inventor(s)	Hong Kong Company	Foreign Patent
Recombinant Vaccinia Virus	Zai-Ping LI, Yuan WANG	Sarrus Biomedical Group	US Patent 5,077,213
Memory Enhancing Peptides	Yu-Cang DU	Sarrus Biomedical Group	US Patent 5,618,791 UK Patent GB 2,269,821B
A Composition for Preventing and Treating Motion-Sickness Syndrome	LIU Chuangui, YUN Liuhong, WEN Guangling, ZENG Fanghong, YU Ruiqi, YU Guihua	Sarrus Biomedical Group	Pending

Table 2. China Biotech Products Marketed in International Markets Through Hong Kong Companies

Product	Inventor	Hong Kong Company	Manufacturing Site
Infinitus	First Military Medical University	LKK Health Products Group	China
NDA	Robert KM KO, Hong Kong University of Science & Technology	LKK Health Products Group	China, Hong Kong
PSP	Qing-Yao YANG, Shanghai Teachers University	Lanford PSP Ltd	China
King Drink	Shengzhen Neptunus Pharmaceuticals	Sarrus Biomedical Group	China

Chapter 21

An Entrepreneur's Viewpoint of the Future of Biotechnology in Hong Kong and China

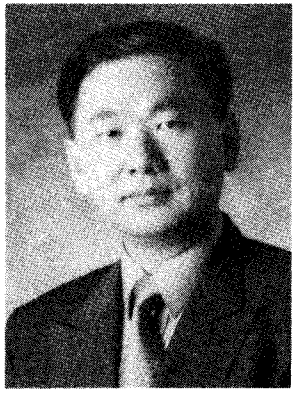
By

~ Patrick S. Ko, Ph.D. ~
Guest Professor
Feed Industry Centre, Ministry of Agriculture, China
South China Agricultural University

~ Kong-Hoi Wong ~
Project Manager
Sarrus Biomedical Limited, Hong Kong



Patrick S. Ko *is the chairman of one of the world's leading anminal feed ingredient trading companies. He received his Ph.D. from the Kennedy-Western University. Ko has more than 20 years' experience in fishmeal and related feed ingredients trading. For the last five years, he has focused on applying biotechnology to the animal feed industry in China. Ko is an adviser to the Hong Kong Baptist University's School of Business and a fellow of the universitiy's Internaional Institute for Business Development.*



Kong-Hoi Wong *is project manager for Sarrus Biomedical Limited in Hong Kong. He is also vice president of the Hong Kong Baptist University Alumni Association and a part-time postgraduate student specializing in communications at Hong Kong Baptist University. Wong holds a B.A. degree from Hong Kong Baptist University, where he studied Chinese language and literature.*

The widespread and in-depth application of biotechnology is destined to sweep the world. Under such circumstances, what might Hong Kong be able to do?

Some years ago biotechnological research began very quietly. Many scientists labored day and night, hoping to launch through their tireless endeavor one by one the fruits of biotechnology into wide-ranging applications for the betterment of the quality of life of all mankind, achieving greater ease and happiness. Herein lies endless business opportunities for businessmen with vision and foresight.

Population problems have brought with them heavy economic burdens. In the case of China, even with very severe population control policies, the population constantly increases. Experts estimate that by 2010 China will have a population of 1.3 to 1.6 billion.

Providing a population of 1.6 billion with sufficient food is difficult enough, but this expanding populace is sure to demand superior food. China is undergoing a transition from a basic, adequate mode of livelihood, with an emphasis on starch consumption, to a middle-class mode with an increasing desire for protein consumption. The Chinese population is, unlike decades ago, no longer merely concerned with just filling its belly. Instead, consideration has been extended to wholesome nutrition and a balanced diet, to the well-being of both body and mind, to growth and good health, even to body esthetics, including skin conditioning and smoothing.

Under these circumstances, China's current reliance on traditional methods of intensive agriculture, unplanned fishing, and passing-grade animal husbandry certainly does not equip it to cope with the combination of population growth and constantly upgrading market demands.

The application of biotechnology to agriculture, aquaculture and animal husbandry represents a sure solution to the problems at hand. In this regard, there is ample room for Hong Kong to contribute its planning strength, its special talents and many other advantages.

Our company has spent the last 16 years addressing some of these problems. When the company first started, we concentrated mainly on animal feed trading, in particular, fishmeal trading. Within five years, the company's turnover increased from HK$3 million to HK$100 million. We foresaw a niche market in China. The com-

pany then extended its business to Taiwan and Southeast Asia. In 10 years' time, our company's turnover rose to HK$200 million.

Our company helped advance the Chinese animal feed industry from a labor-intensive one to a technology-intensive one. We bought back aquaculture products plus value-added products from China and exported them to the United States and Europe.

Let's take a closer look at biotechnology and agriculture. The goal of cross-breeding is to attain new varieties with more beneficial traits is, as in the case of rice, a time-honored and productive approach. However, because variety improvement through hybridization is too slow and its effects unpredictable, gene transfers are now utilized to accomplish faster, more-predictable improvements. Thus, the appearance of boll weevil-resistant cotton is an exceptional achievement, a herbicide-resistant rice strain represents a grand discovery, and the production of plastics from plants is practically a fairy tale. Yet these research results keep tumbling forward, making plain the notion that biotechnology is an enterprise that is just beginning to show its power.

Good plant growth requires the application of fertilizer. In recent years agriculture's dependence on chemical fertilizers has become so overwhelming that it has become unhealthy. The use of chemical fertilizers such as urea causes the soil to clump and turn acidic, and crop quality to decrease year after year. If this continues, no usable soil will be left.

The advent of microbiological fertilizers is a timely solution to this problem because it alleviates soil acidity and reduces energy consumption. These fertilizers employ microorganisms to fix nitrogen, release potassium and phosphate, and, consequently, enhance the soil's growth-supporting capability. They enable plants to absorb adequate nutrients and grow stout. The action of the microbiological fertilizers enhances plant quality as well as yield. In terms of quality, fruits are sweeter, the flowers more colorful, and leaves greener. In terms of yield, productivity can increase as much as 20-30%. In addition, microbiological fertilizers only need to be applied once per crop, in comparison to the multiple applications per crop required with chemical fertilizers.

Hong Kong can establish a gene bank and an experimental farm to specially serve China's present and future agricultural needs. Working hand in hand, China and Hong Kong can create agricultural miracles together.

A Hong Kong plant gene bank would enable the collection of the genes of all plants growing or cultivated in China, including grains, fruits, vegetables, flowers, trees, herbs, etc., stored by category for use in gene improvement and distribution. This bank also could facilitate the exchange of materials with other regions of the world. This would serve to introduce into China plant varieties suited to, but so far not cultivated in, China. The gene bank could very likely render China the largest base in the world for natural medicinal herbs, with Hong Kong being the window for modernization and the distribution center for this base.

Hong Kong also could set up an experimental farm to grow its own native plants and plants transplanted from elsewhere for trial purposes. Microbiological fertilizers rather than the usual chemical or traditional organic fertilizers would be employed. Selection of renowned, high-quality, and high-performance varieties will close the gap between China's standards and that of the rest of the world.

Exemplary applications will demonstrate that the combination of modernized economic crops and modernized microbiological fertilizers will create new economic benefits. Hong Kong can engage in large-scale enterprises, generate great economic returns, supply China with many employment opportunities and help solve the food supply problem.

Next, let's talk about aquaculture.

Everyone agrees that the world's fish resources are becoming increasingly depleted. Each year the catch is less and less, and the fish caught are diminished in size and weight. If such uncontrolled fishing continues, one day soon there will be no more fish for anyone to eat.

Action to protect and enhance fish resources must not be delayed any longer.

In the meantime, steps need to be taken to better utilize fish resources, stop excessive fishing, and allow the oceans to naturally come back into balance, increasing the quantity of fish.

To resolve or ameliorate the problem of inadequate ocean fish, penetrating research is needed on aquaculture in the ocean or in high-tech factories. We need to minimize the calculated risk of ocean aquaculture so that it can generate huge profits.

To have successful aquaculture, the following five problems must be resolved:

1. **Improved fish variety.** Use DNA selection and transfer to select the best varieties to enable large-volume growth. Here, the creation of a fish gene bank is also urgently required.

2. **Growth hormone.** To speed the growth rate, the use of harmless growth hormone from fish brains is essential.

3. **Vaccine.** These would help prevent fish diseases.

4. **Water quality control.** This would be used to simulate optimal natural conditions and allow rapid fish growth, avoiding the effects of "red tide" and dirty water.

5. **Manufacture and application of good, quality fish feed.** Quality fish feed is very carefully designed and specially formulated. First the feed's digestible protein ratio and the conversion ratio must be considered. The approach is to add growth hormone, vaccine and amino acids to fishmeal of an appropriate grade to achieve a balance, followed by nutritive and beneficial additives. The mix is rendered through a vacuum expansion technique with a semi-floatation density that gives fish adequate time to ingest, thereby preventing waste and environmental pollution.

If the fish feed is poor in quality, important damages will result:

- The fish will be unable to digest the feed, or even get sick.

- The fish will need to expend additional energy to digest the feed.

- The indigestible residue excreted from fish can support the growth of bacteria and, thus, cause the depletion of dissolved oxygen.

- The inability of the fish to transform what it is supposed to eat into weight gain represents a waste of money.

Biotechnology must target these problems and produce various high-quality feed tailor-made for different types of fish.

The harvesting of food from the ocean is an unavoidable trend. Various marine algae are very useful to man. For example, Spirulina is extremely rich in protein that is very easily digested. It can be directly consumed, added to other foods, used as feed for small fish and shrimp, or employed as a cosmetic ingredient for beautifying the skin. Biotechnology can be applied to control the algal variety and the quality and temperature of the water in order to greatly increase the yield of Spirulina, so that it can become an abundant source of protein from the sea. Hong Kong's biotechnology R&D, and institutes and companies engaged in product development will find great opportunities here. Hong Kong can choose the best technologies in the world to grow and produce the algae; offer technical support and financing; provide high-level management; conduct marketing research; planning and off-shore trading; and serve as a transportation center.

The applications of different grades of fish oil are another worthy subject of research. Fishmeal production has always had an important by-product: fish oil.

Use of deep-sea fish to produce fishmeal results in better fish oil. This type of fish oil contains EPA and DHA, which effectively control fat and cholesterol levels in the blood.

Fish oil, through different refining procedures, can be separated into refined grade – for human consumption, reduction of cholesterol, and reduced heart and brain blood vessel disease; semi-refined grade – for animal consumption, to control the proportions of fat and lean meat and support good health; and crude grade – for coating and dyestuff manufacture.

Freshwater aquaculture is another important item. In the interior provinces of China, only freshwater fish can be grown, and the methodology is almost the same as for ocean fish.

As long as the fish is well cultivated, people can derive from it a source of easily digested protein. However, freshwater fish lack UGF (Unknown Growth Factor), which is obtainable only from marine fish. Fish oil would bring the huge benefits of deep-

sea fish to people in interior regions. All Chinese must be able to partake of a relatively complete and balanced diet. This is essential for the attainment of equitable intellectual and physical development which, together an emphasis on education, will help elevate the economic and cultural standards of the disadvantaged regions.

Importance of ecological balance:

The food chain consists of interlocking links. A rational distribution and scheduling of feed makes possible the collection of animal waste for useful transformation, an example being the use of chicken and pig excrement for marsh-gas generation of electricity, or for fuel, with further processing yielding a new convenient form of natural fertilizer.

Hong Kong, now that it has been returned to China, plays an ever more important role because it can fulfill the function of an integrated intermediary between China and the rest of the world. Hong Kong possesses an effective legislative system, e.g. corporate laws and patent laws, a stable financial setup for the provision of capital, and a highly developed information transmission system. The people of Hong Kong are creative and daring, ideal traits for managing the application of biotechnology in China.

Made by Hong Kong (Berger, Suzanne and Richard K. Lester, eds., Hong Kong: Oxford University Press, 1997) is the inevitable path. Biotech initiatives can be registered and embodied in limited companies in Hong Kong. This will make possible participation by Mainland China, Hong Kong and other countries with clearly defined rights and obligations. Market research can help guide commercial decisions regarding the choice of a location for factory construction in China. With rigorous efforts in quality control, marketing and advertising, the manufactured products will enter smoothly into world markets, making it possible for the entrepreneur to choose between expansion of the existing enterprise or diversification into other industries. Only by following all these steps will Hong Kong business and industry be ensured an invigorated and better tomorrow.

Biotechnology's Future in Hong Kong

Chapter 22

Developing a Biotechnology Industry in Hong Kong

By

~ Thomas Tsun Yung Cheung ~
Founder
Innomed Group Limited, Hong Kong

~ Abigail Yu-Fang Jung ~
Assistant to the Director
Innomed Group Limited, Hong Kong

Thomas Tsun Yung Cheung *is the founder of Innomed Group Limited in Hong Kong. After graduating from the University of Wisconsin at Madison with a B.S. in mathematics, computer science and statistics and from Cornell University with a Master of Engineering degree in operations research and industrial engineering, Cheung joined Arthur Andersen & Co. in Hong Kong. An active biotechnology player in Hong Kong and China, Innomed engages in projects such as molecular diagnostics, DNA fingerprinting, cord blood banking, stem cell research and applications of cell therapy technology. Cheung believes that in order to maintain its competitive edge, it is essential that Hong Kong develop its own high-tech industries with high value-added products and services. He envisages biotechnology as the most challenging and promising industry for the region in the immediate future.*

Abigail Yu-Fang Jung *is the Assistant to Director of Innomed Group Limited. She graduated from the University of California at Berkeley with a degree in Molecular and Cell Biology, with an emphasis in Neurobiology, and a minor in East Asian (Chinese) Studies. Jung was with Andersen Consulting LLP in San Francisco prior to joining Innomed Group Limited in Hong Kong. She hopes to improve healthcare in Asia by contributing to the development of biotechnology in Asia.*

During a recent interview for a position at my Hong Kong based biotechnology company, I questioned an American expatriate candidate regarding her purported interest in biotechnology when all her other job interviews were in the finance and management consulting industries. To her response, "Well, I didn't know Hong Kong had a biotech industry," I had no answer. Her simple response unfortunately zeroes in on the situation in Hong Kong today. While a small number of small biotech companies do exist, there really is no biotech industry in Hong Kong.

And why not, you ask. That is a valid question, considering the budding biotech industries elsewhere in the region, particularly Taiwan, Singapore and China. Even Japan and South Korea, with their troubled economies, maintain biotechnology research and development as priorities. It appears that of the more developed economies of the region, Hong Kong alone remains impervious to the increasing importance of biotechnology in Asia.

Current Biotechnology Situation in Hong Kong

The biotechnology industry is not susceptible to the same economic cycles experienced by many other industries. In the United States, where the biotechnology and healthcare markets are highly developed, demand for drug and other biotechnology products increases at a fairly constant rate year after year. Although the industry is populated with companies that remain unprofitable and continue to struggle for financing, industry reports predict that the biotechnology industry is poised for solid, long-term growth. The biotechnology industry has been said to be in the same position that the high-tech industry was some 30 years ago.

One would hope that after watching the extremely lucrative high-tech revolution of the '90s bypass Hong Kong, the government would be on the alert to ensure Hong Kong does not miss out on the next profit-generating revolution. Unfortunately, this is not the case. As Hong Kong attempts to climb on the current high-tech bandwagon with the local government's encouragement of hi-tech development, it is allowing the next wagon to roll on by. And that wagon, of course, is biotechnology.

In Hong Kong the biotechnology industry is in its nascent stage; very few companies offer biotechnology-related products or services. One reason is that the concept of biotechnology is still somewhat foreign to the Hong Kong general public, neither

well understood nor viewed as an essential component of basic healthcare. The lack of emphasis on biotechnology combined with the business-oriented culture of Hong Kong serves to work against biotech entrepreneurs. The Hong Kong people have very little exposure to biotech concepts, products or services; hence, there is not widespread demand for biotechnology. While the medical and academic communities may understand the impact and benefits of biotechnology, the Hong Kong Government does not. As a result, the Hong Kong people do not. The consequence is that few biotechnology companies exist in Hong Kong, as not many entrepreneurs are likely to set up operations in such unfavorable conditions.

Another reason for Hong Kong's absence from the biotech scene is that Hong Kong is still very technologically behind when compared to neighboring countries such as Japan, Singapore and Taiwan. Japan and Taiwan's well-developed electronics and high-tech industries and Singapore's biotechnology and information technology industries continue to show signs of growth and success.

Examination of the obstacles encountered by Hong Kong biotech entrepreneurs show governmental, infrastructure, financial, and educational problems. Of the many hurdles, the lack of government support is by far the most serious problem. Proper government action would mitigate most of the other obstacles. Currently, the government does not play an active role in supporting biotechnology in Hong Kong. However, without government-sponsored funds to encourage emerging biotech ventures, local entrepreneurs are unable to grow and expand. Without strong government emphasis on research and development (R&D), scientists are not encouraged to carry out innovative biotechnological research. Without private funding from industry, researchers at universities are dependent on government grants for research funding. However, scientists are often so involved in securing the much needed government grants that their research suffers. At the moment, not many science-related employment opportunities are available to university graduates. The few biotechnology companies currently in Hong Kong are more involved in trading and providing healthcare services than in new drug development and other biotechnological products.

Aside from those found in academic institutions and at the Hong Kong Institute of Biotechnology, few research-related positions are available to university graduates with science degrees. Nontechnical positions can be found in hospitals, pharmaceutical companies and medical equipment companies. Unlike the plethora of research and technical jobs generated by the booming biotechnology industry in the United States, Canada, Europe, and Australia, Hong Kong's job market remains distinctly bereft of such positions. Because of this void in the job market, many university students choose not to major in the sciences. This contributes to the difficulties experienced by biotechnology entrepreneurs in finding technically qualified people to staff on their ventures.

A lack of proper facilities containing current medical equipment and research technology is another problem. The Hong Kong Institute of Biotechnology (HKIB) is the only government-sponsored institution dedicated to biotechnology research and development. While HKIB does sponsor an Incubator Program fostering biotech development, the facilities are unable to fulfill all the needs of the program participants.

In addition to the lack of an academic and research infrastructure, Hong Kong also lacks the financial infrastructure necessary for encouraging entrepreneurial development. Currently, there is no venue in which small companies are able to raise the capital needed for growth and expansion. While they rely heavily on personal savings, friends and family to set up operations, they are often unable to expand due to the lack of funding.

The formation of a Second Market, or Second Board, to the Stock Exchange of Hong Kong would partially alleviate the effects of government inactivity while providing a partial solution to the industry's financial problems. A Second Board, with less-stringent listing requirements than that of the Main Stock Exchange, or Main Board, would allow entrepreneurs from all industries and sectors to raise much-needed capital for growth and expansion. Venture capitalists seldom invest without an assured means of exiting from their investments, especially high-risk, early-stage investments such as biotech ventures. In addition to raising capital from direct investment firms, a public listing on a Second Board would allow biotech ventures access to public funding. As abundant as venture capital funding is in Hong Kong at the moment, biotechnology companies looking for funding are at the mercy of direct investment firms and private investors wary of getting involved with long-term, high-risk investments in developing industries. Since this is the primary source of expansion funding for most small companies, many are unable to continue operations beyond this point.

Despite these challenges, a number of entrepreneurs have formed small biotechnology companies in Hong Kong. Excluding the pharmaceutical and medical equipment factories already successfully manufacturing goods, a few biotechnology service-oriented companies have set up operations in Hong Kong. An example is Cell Therapy Technologies Centre Ltd., a healthcare services company that provides cord blood banking services to expectant parents. This service allows parents to store cord blood, or blood derived from the umbilical cord connecting newborns to their mothers, for possible future use by the infant and family members. Studies have found cord blood to be rich in stem cells, the fundamental building blocks of our blood and immune systems that form our bodies' red blood cells, white blood cells and platelets. Since these regenerative stem cells are the underlying reason behind bone marrow transplantation, cord blood can be used to treat any cancer or genetic disorder currently treatable by bone marrow transplant. Another company applying biotechnology to everyday life is Molecular Technology Innomed Limited (MTI). MTI uses molecular analysis of genetic information for DNA fingerprinting, DNA HLA-typing, PCR, parental and neonatal diagnosis. MTI also offers oral fluid HIV-antibody testing. These tests are used in blood typing, family planning, paternity disputes, criminal investigations and AIDS testing.

Importance of a Biotechnology Industry to the Hong Kong Economy

The far-reaching effects of a biotechnology industry on the Hong Kong economy should not be underestimated. While the current economic situation in Asia poses a significant problem to biotechnology advancement at the moment, once the region recovers economically, biotechnology will undoubtedly gain prominence as a key industry in Hong Kong's future development. Not only would the industry create much needed employment for the Hong Kong people, especially for fresh university graduates, its success would help the economy stabilize itself.

While Hong Kong is still the region's premier financial and trading center, its heavy reliance on service industries, such as finance and real estate, make it vulnerable to currency and economic crises, as demonstrated in 1997. In an attempt to diversify its economic scope and establish a more balanced economic portfolio, Hong Kong must move into other promising industries such as high-tech and

biotechnology. A brief review of the development of Asia's high-tech industry can provide a good reference for those interested in the development of Asia's biotechnology industry.

High-Tech Revolution

Asia has become a major global player in semiconductor production in the past several years, turning out roughly half of the US$151.3 billion worth of chips produced worldwide every year. With chip-fabrication labs located throughout Asia, from Japan down to Thailand, most of Asia has reaped significant profits resulting from its participation in the high-tech revolution. Japan's dominance in high-tech manufacturing is irrefutable. China's numerous manufacturing plants provide leverage in manufacturing labor-intensive low-tech and mid-tech products.

Singapore's government-supported high-tech industry continues to attract foreign interest and investment. The niche that Taiwan created for itself in its efficient high-quality high-tech enterprises substantiates the government's earlier investment by helping keep the Taiwan economy steady during times of turmoil. In recent years, Taiwan has demonstrated its strong presence in the electronics development and manufacturing industries. Producing goods for global export has allowed Taiwan to remain relatively stable despite the currency devaluation taking place all around the region. Even now, there is still a worldwide demand for Taiwan's products.

And what has Hong Kong been doing amidst its neighbors' hi-tech activity? Unfortunately, Hong Kong, the strategically located international finance center where East meets West and a prime candidate for a strong technology presence, has been absent from the high-tech frenzy. For years, many of Hong Kong's business elite argued that the government should actively promote a high-tech industry to replace the declining manufacturing industry; however, the British colonial government convinced of the success of its laissez-faire "positive non-interventionist" style of governing, chose not to actively support the development of a high-tech industry in Hong Kong. Hong Kong's first chip-fabrication factories were set up in the early '80s, like its counterparts in Taiwan and Singapore. But the Taiwan and Singapore governments, viewing the high-tech industry as a key industry of the future, gave support to the developing industry in the form of tax

breaks, land and capital. Hong Kong's chip makers, on the other hand, with no support from their government, were left floundering in the wake of their well-supported competitors.

Should Hong Kong wish to get into the potentially lucrative, but risky, high-tech industry this late in the game, the government would need to provide significant advantages over those being offered by the governments of Taiwan and Singapore. These include unequivocal government support and advocacy, public education, capital, facilities, and favorable taxation laws. Tung Chee-hwa, Hong Kong's Chief Executive, in his maiden policy address announced his goal of building Hong Kong's presence in Asia's booming high-tech industries, which are forecast to grow to US$1 trillion a year by the year 2010.

Hong Kong's mistake of missing out on the high-tech revolution would not be as serious if the lessons learned were evident in light of the growing significance of biotechnology and related healthcare fields in Asia. The healthcare sector is expected to continue its modernization in Asia, with an increasing demand for medical services. The Health Industry Manufacturers Association of the United States says Asian demand for medical technology is expanding 19% a year, three times faster than the rate in the United States, Europe and Japan. The European pharmaceutical giants have long realized China's immense market potential and have already begun establishing their heavyweight presence in China. If Hong Kong wants to remain competitive in the global emerging markets, it cannot afford to miss out on the advent of biotechnology in Asia.

Asian Biotechnology

Biotechnology ventures in neighboring Asian countries have a much easier time getting started than their counterparts in Hong Kong. Singapore, especially, has a significant head start over the rest of the East Asian region in biotechnology development. The Singapore Government sees technology as a key factor in Singapore's future economic success and has acted accordingly. In answer to Singapore's vision of being the region's leader in science and technology in the 21st Century, the government has made significant contributions to funding research and development, establishing international relations with important international industry hubs, promoting science education, emphasizing innovation, creating funds to sponsor entrepreneurial activities,

developing greater depth in technological capability, and encouraging foreign investment. Taken altogether, the Singapore Government's supportive attitude toward biotechnology fostered innovation and promoted entrepreneurial activity.

Taiwan's commitment to the biotechnology industry is demonstrated by the selection of the biotechnology and pharmaceutical industries as two of the top 10 "star" industries chosen by Taipei authorities for an intensive program of promotion and development. The Ministry of Economic Affairs of Taipei is counting on local entrepreneurs putting US$278.6 million into the industries over the next three years.

A pharmaceutical industry is taking off in China as international pharmaceutical and medical equipment companies attempt to tap into China's important emerging market. With annual growth rates expected to exceed that of other Asian countries, China will be an important market well into the next millennium. With a gross national product (GNP) increasing approximately 10% each year, China's national health expenditure is projected to be US$48 billion by the year 2000, a 400% growth over 1992. Pharmaceutical product sales will be close to US$19 billion by 2005, of which 67% of the sales will be for Western medicines.

China's surge of biotech companies began in 1986, after the late Chinese leader, Deng Xiaoping, specified biotechnology as an important part of China's high-tech growth and development. Around 600 biotech companies have been incorporated since then. Not only does the Chinese Government give its blessing to the pharmaceutical industry; it actively funds research institutes and other related facilities. Foreign medical equipment and medical device companies are also being granted coveted entrance to China's vast market and resources as the government attempts to bring China technologically into the 21st Century.

International pharmaceutical companies are helping the Chinese Government's efforts to turn Shanghai into the region's predominant pharmaceutical and biotech center. Many have set up joint ventures to manufacture generic forms of drugs developed in North America and Europe. Others have chosen Shanghai as the base of their Asian operations. A number of foreign biotechnology companies have obtained approval from the Chinese Government to set up operations in China. Some sample operations follow.

Sinogen, a San Francisco-based biopharmaceutical company with Mainland joint-venture partners, has secured rights to manufacture and market alpha interferon (hepatitis treatment), interleukin-2 (cancer treatment) and recently, recombinant erythropoietin (treatment of anemia associated with kidney dialysis). What is significant about Sinogen is not only its success in China, but its impressive list of investors, including Boeing, Aetna Insurance, Monsanto Pension Fund, and Vertex Technology. The substantial investments of these major American corporations demonstrate their belief that China's healthcare and biotechnology industries will achieve significant and sustainable growth.

Quintiles Transnational Corp. announced the opening of an office in Shanghai. It plans to work with China to help China advance as both a high-growth market for pharmaceutical development and as a source of new therapies derived from Traditional Chinese Medicine.

Sino Pharma International Limited (SPI), a British Virgin Islands company, with investors from Hong Kong, Singapore and China is completing clinical trials of its inactivated Hepatitis A vaccine. The vaccine is scheduled to hit the market by the middle of 1999. The biopharmaceutical company also plans to introduce a rabies vaccine, an interferon ointment as well as various diseases diagnostic kits by 1999.

China's pharmaceutical and medical equipment sectors are expected to continue to generate annual growth rates of over 10%. Demand for better drugs and medical equipment is driving these markets and will increase as the country moves to modernize and provide healthcare to a population of nearly 1.3 billion.

A number of different cities throughout China have already launched pharmaceutical joint ventures with foreign investors. Jilin Province aims to fully utilize its advantages in herbal resources and biotechnology as well as its electronic and mechanical technology to support the development of a provincial pharmaceutical industry. Some of the bioengineered medicines developed in Jilin are recombinant human insulin glucokinase and genetically engineered interferon. Some examples of Jilin's provincial medical devices include: degradable orthopedic material, orthopedic steel plates, novel medical catheters, and tumor diagnostic kits.

Even countries with crippled economies, such as Japan and South Korea, view biotechnology development as a priority. Despite the continuing economic struggle in Japan, which spurred the government to reduce the budgets of most of its ministries considerably, support for biotechnology is still on the rise. South Korea, which cut at least 10 trillion won ($7 billion) from its 1998 budget, still approved a five-year science and technology innovation plan designed to promote government-funded research and development in an endeavor to improve the nation's economic growth.

The Singapore Model

Singapore's well-developed biotechnology industry did not evolve overnight by itself. The Singapore Government, particularly the Economic Development Board (EDB), played a critical role in its development and nurture. While Hong Kong differs from Singapore in many fundamental ways, the Hong Kong Government can make note of Singapore's success in terms of industry development.

The Singapore Government has long identified biotechnology as an industry critical to Singapore's economy. In the mid-'80s the government put together a strategy to launch a successful biotechnology industry. The master plan included the promotion of biotechnology research, the building of a biotechnology infrastructure conducive to the development and nurture of a local biotechnology industry, the development of the work force at all levels, the formulation of economic policies conducive to biotechnology cultivation, the promotion of biotechnology understanding among the general public, particularly among venture capitalists and entrepreneurs, and the promotion of biotechnology investment in Singapore.

Singapore's biotechnology industry is as successful as it is today because of the government's intimate involvement in each of these targeted areas. To promote biotech R&D and build a biotech infrastructure, the government built the Institute of Molecular and Cell Biology (IMCB), a state-of-the-art research facility currently housing over 200 scientists. With many major programs dedicated to molecular and cell research and numerous business deals with American and European biotech giants, it is

no wonder that, since its completion in 1987, IMCB has gained world recognition as an excellent research institution.

To ensure there is adequate manpower to support continued biotech development, the Singapore Government invested in the recruitment of overseas scientists, the training of local scientists and the education of university students.

In establishing a legal and regulatory environment conducive to general industry development including biotech development, the government implemented Good Manufacturing Practice (GMP) certification schemes, ISO 9000 certification schemes and patenting schemes.

To educate the general public about the benefits of biotechnology as well as to arouse the interest of Singapore's younger generation, the EDB-sponsored biotechnology awareness programs and events such as fairs, exhibitions and conferences. The government felt continued support of the younger generation to be especially important in sustaining the momentum of biotechnology development in Singapore.

Future of the Biotechnology Industry in Hong Kong/China: Personal Viewpoint

Due to the different stages of the biotechnology industries in the U.S. and Hong Kong, the future of Hong Kong biotechnology companies lies along a different path than that of the U.S. biotechnology industry. Without subsidized land and facilities, the high costs of land and labor in Hong Kong make it an impractical site to house large-scale biotechnology operations. Instead, Hong Kong's future in biotechnology ties in very closely to that of China's. Hong Kong's free market economy, advanced financial system, mature legal system and low taxation base complements China's wealth of land, labor and talent.

Hong Kong is long overdue for an actual value-added industry. The two primary industries are financial services and real estate, both of which are simply paper-generating industries. Manufacturing in Hong Kong has long been replaced by manufacturing in China and Southeast Asia. A key reason behind the push for biotechnology and information technology industries in Hong Kong is the belief that, in order to remain competitive in the global marketplace in the next century, Hong Kong must be

able to sustain itself against outlying forces. One prime example of this is the current currency crisis that has devastated many of the region's economies.

A biotechnology industry in Hong Kong can only become a reality with the active collaboration of China. The Hong Kong government needs to take more interest in developing biotechnology in Hong Kong in relation to China. China's biotechnology industry cannot grow to its full potential without the help of Hong Kong, and Hong Kong can only benefit from China's involvement in the biotechnology and healthcare industries. Not only will these industries create employment and generate revenue, they will also create new industries. All this is essential to Hong Kong's economic future, as both the stock and property markets remain volatile.

Under the new Prime Minister, Zhu Rongji, China is gearing up for the next millennium with the slogan, "science development followed by education means prosperity for the country." The government is finally loosening its reins on foreign investment and businesses to promote economic development. Shanghai is well on its way to becoming the primary Asian pharmaceutical center with many multinational pharmaceutical giants moving in and setting up operations. Hong Kong needs to seize the opportunity to help China achieve its goals while, at the same time, helping itself develop a value-added and productive industry.

Hong Kong has long been the gateway between China and the rest of the world. Despite China's open door policy and various other economic reforms opening it up to foreign companies, Hong Kong has remained the principal link between China's business and trade interactions with the West. Over the past decade as the return of Hong Kong to China drew to a close, there has been a significant increase in business interactions between China and Hong Kong. Hong Kong companies established manufacturing companies across the border, while the Chinese Government invested in Hong Kong's economy. It is from this prime position that Hong Kong will be able to help develop China's budding pharmaceutical and biotech industries. Hong Kong's long association with the West will prove useful in modernizing and guiding China into the 21st Century. China will need Hong Kong's expertise in building a stable infrastructure and market economy, developing a stable legal system, gaining access to Western technology, and managing businesses. In return, Hong Kong's status

as a Special Administrative Region of China gives it a higher priority and a greater access to China's resources compared with foreign countries.

Hong Kong and China should prove to be excellent business partners, complementing each other's strengths and compensating for the other's weaknesses. While China supplies land and human capital, Hong Kong should make use of its well-known financial service management and coordination abilities to assist China in funding its biotechnology and pharmaceutical ventures. Hong Kong would serve well as the liaison between foreign capital and Chinese operations, providing intimate knowledge of how to do business in China. In addition, Hong Kong could provide distribution and marketing services to Chinese joint venture partners. The combination of foreign biotechnology, Hong Kong management skills and China resources has great potential for success.

As we have seen, Hong Kong's role in the development of biotechnology in Asia is a fundamental part of China's plan to vitalize its economy. However, at the present time, neither China nor Hong Kong has the resources to develop a biotechnology industry similar to the one in the United States. The developed U.S. biotechnology industry took decades to develop, not to mention billions of dollars to finance. While China and Hong Kong can look to the U.S. biotechnology industry for direction, they must develop their own means in building a biotechnology industry.

Stages of Biotechnology Development in Hong Kong/China

Even with Hong Kong as a gateway to China's resources, certain issues deter potential investors from venturing into China. The lack of an established legal system, infringement of intellectual property rights and inadequate patent protection are the sources of many misgivings. Without a sound legal system to enforce regulations, many foreign companies are hesitant to establish operations in China. Intellectual property issues and patent protection are a source of aggravation. Another important element is the issue of quality control of products produced in China. In a pharmaceutical or biotechnology industry, these issues are of paramount importance. The last cause of concern at the present time is China's economic and financial stability in the currency crisis. While China's renmenbi has not devalued, despite pressure from neighboring countries, its devaluation could cause systemic damage throughout the region. Although China is considering a number of aggressive measures to reform the floundering state-owned enterprises and the inefficient banking system, many fear the reforms may not take effect quickly enough.

China's problems, however, will not last forever. China is directly addressing the challenges of shifting from a centrally planned economy to a market-oriented economy. China's first step in developing a globally competitive market economy will be to address all issues concerning international business standards. With his grasp of both local and global economic situations, Zhu Rongji is helping to instill confidence in both his own people and the international community. China is quickly conforming to international standards of quality control and business transactions. In fact, as the government slowly loosens its grip on a socialist-based economy and the Chinese people experience more and more of what a market economy has to offer, efforts to achieve international business standards will increase as well. Little by little, reforms and competition are loosening the Chinese Government's grip on creativity and independent thought. To gain an edge over competitors, many firms are now paying more attention to research and development than ever before. China is beginning to realize that the key to growth is no longer solely investment, but also technology and talent. Growing collaboration with overseas companies provide technology and capital, while Western-trained scientists and businessmen are being lured back to set up research facilities and start-up companies.

The next step, after properly addressing internal issues, is to introduce Western pharmaceutical products and biotechnology services to China and Hong Kong. China is not ready to develop new biotechnology or pharmaceutical goods at this time. It must start with low-end pharmaceutical and biotechnology products before moving onto more high-end research and development. Although a number of Western drugs and vaccines are already available on the Chinese market, there are many more that would benefit the Chinese people. However, these Western products come with hefty Western price tags. One way the local industry has found to circumvent this problem is to develop the local version of these drugs or vaccines locally and then sell them at local prices. This way, both the local pharmaceutical industry and the general public benefit.

Low-end biotechnology services, such as antibiotics, vaccines, DNA fingerprinting, HLA-typing and molecular diagnostic kits

would also prove beneficial to Asian consumers. Many rural parts of China still lack basic vaccines and primary forms of healthcare. Immunizations and other preventive medicines important in eradicating diseases would help China take better care of its people while their production would generate revenue for its budding biotechnology industry.

Another way to add value to China's healthcare industry is to address indigenous diseases with Western medicines. A number of U.S. or European drugs treat diseases that either have been wiped out in industrialized nations or simply are not as prevalent. However, these drugs can still help Third World nations such as China. A typical example is nasopharyngeal carcinoma (NPC), or cancer of the nasopharynx. The incidence of NPC is significantly greater in southern China alone than in the entire United States. The higher incidence of hepatitis and consequent liver disease in Asia compared to developed nations creates a much larger market for hepatitis vaccines in Asia. Asian nations would benefit from the availability of drugs that have already been proven effective in other countries.

China is also exploring other applications of biotechnology, such as in agriculture and the environment. With 23% of the world's population (1.3 billion people) and only 7% of the world's arable land, it is important to improve the production and nutritional content of its agricultural products. This is especially important as China's population continues to grow and the land continues to be overworked. Another major concern is the rapid desertification of China's farmland. In northern China, the desert is reclaiming more and more land each year. Agricultural biotechnology and nutritional research would be able to partially help mitigate these effects. China's multiple industrial centers and projects, such as the Three Gorges Dam, as well as numerous nuclear power plants all over the country are generating incredible amounts of pollution and industrial waste. Short of banning cars and stopping industrial manufacturing, China needs to find alternate ways to reduce the harm it is causing to both the local and the global environments. Environmental biotechnology and bioremediation should be able to provide some sort of relief to China's damaged environment.

Laying the Groundwork

While many medical personnel, such as doctors, hospital administrators and public health officials, are interested in biotech

products and services of all types, there is presently no means by which to obtain them. As private healthcare becomes more and more prevalent in Asia, people will require more of the sophisticated treatments currently available in North America and Europe. The demand for Asian biotechnology will also increase. It is up to Hong Kong to respond to the demand for biotechnology by taking advantage of its relationship with China. Because of China's many assets, including the government's interest in biotechnology, it is presently an ideal site for setting up biotech operations. If the Hong Kong Government does not choose to participate in biotechnology development in China, many other governments will take up the slack. Hong Kong would once again miss out on a high-value industry that could potentially provide immense benefits to its economy.

Hong Kong must nurture the growth of biotechnology by taking a more active and aggressive role in its development. The government's role is especially crucial in this time of economic crisis. The Hong Kong Government spends less than 1% of its gross national product on development, compared to countries such as the United States and Japan, which spend between 5% and 7%, respectively. With one of the largest monetary reserves in the world, this should not prove difficult for Hong Kong, even during periods of economic uncertainty.

There is a two-step process by which the government can actively support the development of biotechnology in Hong Kong. The first is to provide the means by which small businesses can secure loans. This can take the form of low- or no-interest loans through a government-sponsored small business loan program or commercial loans backed and guaranteed by the government. These loans would provide small biotechnology companies with the seed or startup capital they need to commence operations. From the government's perspective, loans are the ideal way to support small business development. While not all ventures will be successful, the enduring long-term value (employment, better healthcare and a stronger economy) created by the ones that do succeed will more than compensate the government for its losses.

The government would not need to provide funding for the loan guarantees; only the small business loan program requires active participation. To establish a loan program would require an evaluation committee to determine which companies receive capital. Loan decisions should be based on the concepts behind the proposals or projects and should be given

with a frequency and amount considerable enough to provide significant value to the companies.

While the government does provide grants to academic institutions, grant funding serves a totally different purpose than loan funding. Grants given to scientists and academics are often used to conduct theoretical research that has no immediate applications. While this type of research is extremely important to the progression and development of science, it could last many years. Loans to be repaid, on the other hand, subject borrowers to a pressure that grant recipients do not encounter. Biotechnology entrepreneurs are also not pure scientists, they are businessmen interested in making a return while providing invaluable products and services to their community. Hence, biotechnology entrepreneurs would more likely conduct research on immediate applications of biotechnology rather than more theoretical applications. The loan funding would then be channeled in the direction of products and services that could potentially generate revenue for the company and the industry.

The second action the government needs to take to help these beginning-stage companies obtain needed capital is to establish a Second Market, or Second Board, to the Stock Exchange of Hong Kong and support programs providing capital to companies trying to commercialize innovative technologies. The existence of a Second Board would allow small private companies to list, or undergo initial public offerings (IPO). The Second Board, with its less-stringent listing requirements, would provide venture capital firms with a channel from which they can exit from their investments. This exit avenue is a crucial factor in many investment decisions. As a result, small biotechnology companies would be able to obtain much-needed expansion capital from venture capital firms. Once these companies become successful, not only will they be able to repay their loans; they will be creating value for Hong Kong's economy in the form of products and services, employment and revenue. A few successful companies would then encourage the development of many other biotechnology companies as others jump into the fray hoping to gain a portion of the biotechnology pie. This would then be the start of a biotechnology industry in Hong Kong. The Second Board would provide the capital biotechnology and high-tech companies need in order to grow and expand in Hong Kong, in the same way Nasdaq in the United States provided the means for these same industries to develop in the United States.

Venture capital financing for seed and startup companies in Hong Kong is difficult to come by, even in the best of times. Inherently at this stage, they contain the highest risk compared to the later stages of development. With increasing numbers of established companies in trouble, more venture capital is being funneled into buyouts and leveraged buyouts, resulting in even less seed and startup capital available to small companies. This is precisely the point at which the government's loans would prove most useful. The loans would provide the financing small biotechnology companies need to set up operations. Once past the startup stage, they would be able to approach venture capital firms for expansion financing. Only when there are proven track records, high growth potential and possible future stock exchange listings, would venture capital firms be convinced to invest in the expansion of the companies.

Considerations in developing biotechnology in Hong Kong and China, other than financial support, involve the building of a biotechnology infrastructure in Hong Kong. Biotechnology cannot exist without the brainpower and manpower to drive and support its development. To this end, the government needs to invest more aggressively in research. Government-funded research institutions need to be established. Scientists at these research institutions would be able to devote their time completely to research and development of science and technology. The research that comes out of academic institutions, while very important, trails behind the type of cutting-edge research that can be found in private research institutions around the world. However, scientists at universities are often unable to concentrate solely on their research due to a number of mitigating factors, such as politics and grant applications.

The other key source of innovative research is private-industry biotechnology companies. Many top scientists prefer to work in private industry rather than in government-funded research institutions for various reasons, including bureaucracy and compensation issues. In private industry, scientists are able to concentrate solely on their research without having to worry about government politics or teaching obligations.

The final element of a successful biotechnology industry in Hong Kong is a skilled work force. Vocational training needs to be provided in order to train thousands of technicians and support personnel to work in the industry. Biotechnology courses

should also be taught at universities to emphasize biotech's importance and encourage students to consider biotechnology as a viable career. High skill levels can lead to high productivity and cost-effectiveness that is beneficial not only to individual companies, but to the industry as a whole. A biotechnology industry does not consist solely of scientists; it requires skilled professionals from all different sectors, such as strategic business planning, marketing, legal affairs, and information technology.

The government's dedication and commitment to developing this industry would help convince the public of its importance as well as educate people of its many relevant applications. Following Singapore's example, the Hong Kong Government could promote fairs, exhibitions, seminars, career fairs, workshops, and international and national conferences on biotechnology. Public support would have a substantial effect on the industry, as many overseas-trained scientists would be enticed to return, university students would be motivated to study the biological sciences, and workers would have an incentive to obtain medical laboratory training. At the same time, the venture capital community would be more inclined to invest in industries where the government has shown active involvement and commitment.

Hong Kong's inability to progress in biotechnological development can be attributed to the current stalemate between its strengths and weaknesses. While on the one hand, Hong Kong appears to possess all the necessary ingredients for success (entrepreneurs with global vision and ambition, a stable government with ample capital, a well-developed financial center, an established legal system, a good relationship with both China and the West, and a large local Asian market for biotechnology products, hurdles that continue to obstruct progress are a lack of government support, investment community support, research infrastructure, and general awareness. On the surface, it would appear that given the many factors and conditions that must take place before a real biotechnology industry in Hong Kong is possible, Hong Kong's role in the overall development of biotechnology in Asia remains to be seen. But with the passion and perseverance found in local biotech entrepreneurs, there is no doubt that biotechnology will become an important and crucial industry in Hong Kong.

Chapter 23

Biotechnology in Hong Kong: A New Alliance Needed

By

~ King L. Chow, Ph.D. ~
Assistant Professor, Department of Biology
The Hong Kong University of Science and Technology

~ Lillian L. Wong ~
Operations Director
New-Alliance Management (Asia) Ltd.



***King L. Chow, Ph.D.**, is an assistant professor in the Department of Biology at The Hong Kong University of Science and Technology. He received his B.Sc. in biology from The Chinese University of Hong Kong and his Ph.D. in cell biology from Baylor College of Medicine in Houston, Texas. Chow completed postdoctoral training in the Department of Molecular Genetics at Albert Einstein College of Medicine in Bronx, New York. In 1996, he was awarded the Teaching Award in the School of Science at The Hong Kong University of Science and Technology. Chow holds one U.S. Patent for "Mutated skeletal actin promoter" and has a U.S. Patent pending for "Uses of mab-21."*



***Lillian L. Wong** is the operations director at New-Alliance Asset Management (Asia) Ltd. in Hong Kong. She holds a B.S. in Finance with Accounting from Baruch College, The City University of New York and an MBA from the University of Manchester/University of Wales. Wong has worked in the Hong Kong offices of a number of other companies, including Jardine Fleming Holdings Limited, Peregrine Asset Management (Hong Kong) Limited, Aetna International Inc./Aetna Investment Management (HK) Ltd., Schroders Asia Ltd., and Wardley Ltd.*

A Planned Economy

In the 20th Century, we have seen nations from time to time make efforts to improve the economy with policies from the top down. It is perceivable that is why many governments seek industrial development in order to improve their situations and accomplish their goals in a short time using a rational design. But which rational design best suits a particular country? Since there exists no model historical experience, the choice of the proper road for accelerated and sustainable development cannot be made easily.

Hong Kong is currently in a transition phase where a new government administration, executive offices and committees are evolving to address an ever-changing and complex political and socioeconomic climate. One of the greatest challenges is maintaining and expanding our economic and industrial strength under the pressure of growing international competition. Can a rational design provide the solution?

Influential ideas can expand our knowledge, shape the development of our culture and move our society forward in the hope that it will eventually lead us to prosperity. Very often, such ideas come from an elite group within or sometimes outside the circle. What about the future of Hong Kong? What is a good way to charter our road into the next millennium at this special moment? Contracted by the Hong Kong government, an elite team of professionals headed by Massachusetts Institute of Technology professors provided a recommendation last year on the future establishment of Hong Kong so as to keep it as a competitive player in the global economy (**Made By Hong Kong**, edited by S. Berger & R.K. Lester. Hong Kong: Oxford University Press, 1997). A recommendation for developing the biotechnology industry was made. Biotechnology will be vital to our ability to meet the health, environmental, and economical challenges that lie ahead. This projection has also raised eyebrows of academics in this community. The fact is biotechnology is here to stay while other manufacturing sectors may move north to the peripheral industrial areas around the Pearl Estuary, or even to other parts of China or to other Asian countries.

Biotechnology and Its Impact on National Development

Biotechnology derives from decades of research on basic biology and biochemistry. Biotechnology uses living cells and

materials produced by cells to create pharmaceutical, diagnostic, agricultural, environmental, and other products to benefit society. The science of biotechnology is also used to alter genetic information in animals and plants to improve them in some way that benefits people. Because biotechnology essentially uses the basic ingredients of life to efficiently make a product or generate new products, it is both a cutting-edge technology and an applied science. Over the years, such an endeavor has extended beyond the field of medicine to other fields, such as agriculture, energy and environmental protection.

Analysts from financial and investment communities in the West have predicted that biotechnology will be one of the most important applied sciences of the 21st Century. Worldwide sales of biotechnology-derived products have grown from zero in 1980 to US$6 billion in 1997, and are projected to be US$50 billion by the year 2000. Biotechnology will follow the industrial revolution and computer technology to be the next driving force for the prosperity of mankind in forthcoming years.

In fact, this observation and prediction has transformed the strategic planning of countries in their overall economic policy, infrastructure and education over the past two decades. In North America, biotechnology became an important industry in the '90s. Its contribution parallels that of the electronic industry, though it is still not comparable in scale. This industry's well-being has already played a pivotal role in the ups and downs of the Wall Street stock market. It is also a major employer in the U.S. We should realize that all this impact has been produced at a stage in which biotechnology has not yet developed to its full potential.

The same thing happened in European countries which would like to see themselves competing with their North American counterparts. For example, the German government has pledged to make its country as competitive as the United States in the field of biotechnology. It has already established a number of first-class universities, major research institutes and research-oriented corporations with highly qualified personnel. The German government is determined to make biotechnology one of its national prides. It has social stability and a geographical situation with access to the most important markets, and it is putting in place an infrastructure for industrial activities.

In Asia, Singapore sees biotechnology as a strategic industry to meet the demands of a growing Asia. Its effort to set up education and research institutions to cultivate the next generation of young scientists, initiative to attract biotech companies, and strengthening of its R&D branch has lured corporate investment of more than US$1 billion in its pharmaceutical, healthcare and biotechnology industries over the years. Though the industry is taking shape only now, the future is promising.

Is Hong Kong Ready for the Game?

Hong Kong, in its geographically important location, has always been in competition with other East and Southeast Asian economies. Head to head with the other three dragons, Taiwan, South Korea and Singapore, it is thriving, with its top performance in finance and business. Nonetheless, industry in this city, particularly heavy industry, has never been competitive. This was partly due to the lack of natural resources, land, infrastructure, and government investment as well as political uncertainty. Nowadays, a regional economy can seldom evolve without global outlook. Hong Kong is not only facing the challenge from its regional competitors but also international rivals. In this regard, high-tech industry may be an alternative niche which can make Hong Kong feel less disadvantaged and in which it can excel in the coming decades, provided that a favorable climate is cultivated. Making it or breaking it awaits to be seen, but biotechnology is certainly a good choice for industrial development.

The establishment of a biotechnology industry is no simple matter. Neither an industry nor a company can stand alone in the community and function by itself. Involvement at different levels is critical to keeping it alive. Taking the United States, Europe and Singapore as examples, one can see immediately the extensive range and mega scale of investment this new industry needs in order to make it thrive. The participation of academia, the financial and business communities, and the government plays a crucial role in the sustainable development of the biotechnology industry in these countries. Sometimes, an aggressive biotechnology program may require legislative mandates to overcome hurdles and to gain inertia in the community. In addition, these key players alone will not be sufficient. One may find that a strong biotechnology industry demands a strong educational system, technical support and the public's understanding. The question is: Is Hong Kong prepared for the move?

Government Sets the Pace

Hong Kong has gone through the transition to realize that high-tech industry is necessary for the survival of its economy. However, our leaders and elite scientists alike may or may not fully understand that industrial development, such as that required by biotechnology, demands a modern industrial system and education. The social infrastructure required is fundamental, not peripheral. The transition of this city from one developed stage to another is a complex process that demands facing up to the established interests in the community, and the impetus for this must come from all social sectors.

Once Hong Kong identifies as a goal the building of a strong biotechnology sector, government funds will be essential for getting the machine rolling. Government spending in this regard will keep the wheel rolling for some years to come. The important question is: "How many years?" One should realize that a brief injection of money can power the initial stage of an industry's development, but there is no guarantee this early funding will lay the foundation for a sustainable industry. As we all know, biotechnology is a long-term investment which could give a high yield but involves a high risk. Once the ball is rolling, it does not mean that taxpayer support is no longer necessary. Is our government committed to this venture, and is it willing uphold its share of the responsibility in the coming decades? Or does it simply see biotechnology as a trial industry? Without some long-term logistical planning, we may have a rocky road ahead of us. Moreover, monetary contributions from various private sectors will be essential to getting things scaled up. Are these private investors fully aware of the risky nature of this industry?

In America and in Europe, government's role in developing biotechnology is always instrumental. Government investment is needed not for the setup of the industry, but to provide an incubator to nurture its growth and to help establish a network to safeguard its well being. Developed Western countries have found national research centers that are exclusively dedicated to biotechnology development. These centers provide competent scientific infrastructures that are recognized internationally and whose relations with industrial research are given a high priority. These initiatives nurture and develop the investment attractiveness of a region as a research and production base for biotechnology companies and academic institutions. What they are targeting is a continuous infusion of capital and human resources to support an expanding enterprise.

At the same time, the government needs to raise its R&D budget and establish promotional programs designed to stimulate innovations, bench science know-how and technology transfer in the most strategic scientific areas. These include, for example, molecular natural substance research, environmental biotechnology, molecular bioinformatics technology, techniques for designing state-of-the-art bioproduction facilities, and agricultural programs. Preferential support can be offered to associated research projects in which scientists from universities, other research facilities and industry cooperate. The ultimate goal of all these activities is to reinforce basic biological knowledge as the common and integrated foundation for applications, be it in agriculture, industry, medical science or the environment.

Emphasis should be placed on basic research projects which deliberately combine the contributions of different disciplines and techniques through efforts intended to remove important bottlenecks resulting from structural and scale constraints. They will foster the formation of laboratory clusters which address in an integrated manner highly specific research issues where an impact is to be expected. Should biotechnology take root in Hong Kong, concerted action must be taken to create community networks of competency and skill where funding from the Hong Kong Government or even the Chinese Government is available. Such structural planning should serve as a blueprint, though on a different scale, for shaping the biotechnology industry in Hong Kong.

The Participation of Academia

In recent years, there have been dramatic changes in Hong Kong's research community. The Hong Kong Research Grant Council, as well as the Industry Department, is actively promoting research activities. Applied projects, as well as those offering fast reward, have been encouraged. This effort, to some extent, has successfully linked the industrial sector with research units in our higher education institutions. It also has changed the government's perspective on the overall development of Hong Kong.

A market-driven economy works well in this arena. Education, secondary and tertiary alike, is just another investment business. The change in directives and emphases of these government agencies, and an increase of funding in this area, immediately resulted in a change in attitude at our local universities. All of them are trying their best to boost research activities. At the same time, while a biotechnology initiative will eventually con-

stitute a substantial share of future funding in biological sciences, universities are working hard to reallocate resources into specific areas so as to prepare themselves to bid for the money available in this biotechnology category.

In order to further improve their competitiveness, individual universities are organizing efforts to increase their academic and research reputation locally and internationally. An emphasis on research activity and associations with industry and business enterprises are two key areas of their money and manpower investment. For example, the Hong Kong University of Science and Technology has built a network with renowned research universities in China, Taiwan, Japan and South Korea in order to promote intellectual exchange, communication and research collaborations. This Association of East Asia Research Universities (AEARU) was organized to establish a research-intensive environment in the hopes that it will eventually lead to the blooming of a high-tech culture.

The Hong Kong University similarly formed another group called "Universitas 21" with 14 universities from Australia, Britain, Canada and China. This alliance is an association of major, research-intensive, international universities, aiming to assist its members in becoming global universities and to advance their plans for internationalization.

These efforts spell out a clear message: Research activity would be one major target for Hong Kong's higher education institutions. However, one should not forget that emphasizing the formation of an alliance based on research without considering the fundamental need for quality research as well as quality education is shortsighted. While Hong Kong's tertiary institutions are looking outward for partnerships, they should also look inward to make sure that sufficient resources are dedicated to maintaining their own research activities and education quality. A strong high-tech industry cannot take off with only facilities and capital. Without human input, the most important factor, the best machine will not run by itself.

Bridging the Business Community and Academia

The resources available in universities can precipitate the development of a small biotechnology community (mostly academic) in this region. The connection between academia and the business community is not a small task to be accomplished next. The setting up of organizations, such as a biotechnology council or association, would be instrumental in channeling the efforts of various constituencies having an interest in developing a strong biotechnology program in Hong Kong. This organization should assume the role of helping academic and industrial researchers identify economic benefits that can be gained from research projects. It can organize activities, including regulatory review, legislative advocacy, public education, and periodic publications so as to nurture interaction between these two groups.

The primary goal of this establishment is to provide links to bridge the gap between the commercial world and its counterparts in the Ivory Tower. Without a proper mutual understanding, this match initiated by the government will not last for long. The difference in mentality between the two sectors would probably lead to more conflicts, not collaboration, and the partnership will contribute little to the future growth of this industry.

Are There Investors in Hong Kong?

For most venture capitalists and investors in the Asia market the ability to efficiently spot a profitable return is the key to success. Most fund houses and investment bankers look for opportunities to put money in stock or property markets that can generate high yields in short periods of time, ranging from a few months to a few years. Long-term investment plans of a decade or longer are not appealing to most entrepreneurs and speculators. With that mind set, would biotechnology be an attractive business for them?

There are a few factors that can be considered in measuring the potential of a biotechnology company. These include its pattern of management, product pipeline and financial support. For most biotech companies, it takes years for the release of a commercial product. Thus, they burn cash in their ongoing research and development. The "burn rate" is a critical measure of a company's longevity. This same criterion can be applied to the biotechnology industry as a whole. The existing and prospective financial support this industry can secure are key to determining its survival. In addition, the management team and the types of products are critical parameters to examine. On top of this, an inextricable collaboration between a corporation and its academia

partner can often reflect an industry in good health. Using these yardsticks for assessment, do we have an optimistic outlook for biotechnology companies and the biotechnology industry in Hong Kong?

Let us examine more developed biotechnology communities, such as the one in the United States. Over the past 15 years, all U.S. biotech firms combined (There currently are over 1,000.) have successfully commercialized only over 40 products. The outlook is not bright in this regard. In addition, while many biotech firms are still in their infant or juvenile stage, their fortunes are largely determined by investor perceptions of the relative merits of their research and development pipelines. The scarcity of earnings becomes one of the most striking aspects of the biotech industry. Most biotech companies carry losses for years, even after they have launched a new commercial product. Thus, succeeding in the biotechnology industry is a difficult goal, and it is often impossible to predict, even in the U.S., not to mention that such industry is not even in the infancy stage in Hong Kong. With these facts in mind, biotechnology in Hong Kong is just not a business as promising as it presents itself to be, particularly for local investors. So the issue is not the availability of money, but the attractiveness of the business for the financier, from a business point of view.

Investing in biotechnology is a study in long-term growth rather than quick profit making. That being the case, investing in biotechnology is not for everyone and is best suited for risk-tolerant investors who are seeking abnormal capital gains from long-term investment. In Hong Kong, projects of this nature are scarce, and investors of this type are few. At this early stage, the government, being the biggest investor in Hong Kong, is probably in the best position, in spite of the high risk as well as return, to invest in this industry. Moreover, the government is best suited to set the pace of the development and to create a favorable environment for strong academic-industry-investor alliances. Such an establishment is made and the industry continues to take shape, the reduced risk and increased potential for profit making may bring in a second wave of local and foreign investors. Participation by the private sector will then more likely be assured.

Has Biotechnology Investment Been Profitable?

Reviewing what a government can do to nourish an industry, we wonder whether such an approach will lead us anywhere. We

know that only a few hundred American and European biotechnology companies may be left in 10 years' time as a result of the rest going broke or being sold. At the moment, only a handful of companies is making a profit. Should we then see biotechnology as a viable investment for an economy like Hong Kong? The answer is certainly dependent on how much progress we have made toward building a productive environment, which is not something we can guarantee now. What we should notice, however, is that while most companies may not be delivering what they promised to their investors, the biotechnology industry as it is now has already jump-started a large number of biotechnology-affiliated businesses which are providing supporting services. This subsidiary industry comprises companies churning out products like research equipment, PCR machines, microscopes, laboratory consumables, plasticware, glassware, enzymes, chemicals, and reagent kits. Over the years, these companies have flourished, and this service market has grown several fold in the past few decades. In recent years, these companies have bloomed and now cover a wide range of services. They are feeding on increased funding from the government and on healthcare expenses. With an annual increase in the R&D budget there will certainly be a growing appetite for the products they provide.

The whole scenario resembles that of the gold rush in American history. The people who made a lot of money out of gold rush were not those who rushed in to find gold; instead, they were those who sold picks, shovels and tents to those who dug for gold.

Unfortunately, most of these service companies in Hong Kong are not manufacturers themselves, so they cannot generate jobs and products. They are simply trading companies or agents for manufacturers in Europe, the U.S. or Japan. Most of them are providing a one-time service. Once the product is delivered and the profit is made, the deal is over. Few would provide extensive coverage for maintenance, technical services, etc. In addition, highly qualified service personnel are lacking, such that most technical service personnel are only flown in from time to time to deal with situations as they arise. If Hong Kong is to develop into a competent biotechnology research center, we should consider establishing a local service and manufacturing sector, i.e. one that makes the shovels and tents. We may even have the potential to act as a center for this region, serving nearby cities. However, we need to ask ourselves whether we are unique in this position. If such a service sector is dependent on users, do we have a large enough pool of users to support these service companies?

Well-Being of the Industry Relies on Basic Research

In science-based research, we have no doubt that Japan is the leader in industry development in Asia. As China catches up based on sheer numbers and the economic reform, it provides a good test market and intellectual pipeline for the future of science in Hong Kong. As stated in the recent People's Congress in China, strengthened R&D investment and streamlined management will be the focus of the next five years. Education and scientific research will help lead China into a developed economy. All these emphases, will only serve to benefit Hong Kong, whatever high-tech direction it is moving in. Should Hong Kong pursue biotechnology, central government backing, be it only in the ideological stage, will be important.

Biotechnology will transform some aspects of our society in the next millennium. It will exert major cultural influence in the coming decades. In this regard, Hong Kong has a remarkable opportunity to become a regional leader. However, in the long run, a viable biotechnology industry will depend heavily on a balanced and interactive development of applied research and the creation of an active academic research team with critical mass in the long run. After all, biotechnology is an applied science built on the fundamental principles of biology, a basic science derived from a solid foundation of basic research. The product or the fruit of biotechnology, its end product, will not come suddenly. It comes with our thorough understanding of the basics of biology. Proper establishment of a strong academic environment will play a strategic role in the continued growth of biotechnology. Ultimately, a sound educational system with strong basic research capability will be necessary to provide quality education and training to both the basic and applied sectors, and facilitate their interdependent growth. Therefore, the development of an evolving, dynamic base of knowledge through sustained investment in fundamental research is central to our ability to pursue an understanding of medical, agricultural and environmental applications in biotechnology.

Basic Research: An Economic Good

Few scientists would doubt the value of basic research. From the perspective of politicians, the economics of basic science may be dismal. Thus, respect for science can only soar when government indicates that support for basic science is economically sound. If Hong Kong is to reap the economical benefits offered

by biotechnology, support for basic research must increase. We can envision that the knowledge that emerges from basic research is its principal. The firm belief remains that the economic returns on society's investment are substantiated and substantial and that a percentage of most companies' profits would not have been achieved without university research in basic science. More progress has been made by the impact of basic research on the ability of businesses to find new solutions to technological problems. In biotechnology, this impact is even more direct.

Throughout this chapter, it has been emphasized that strong basic research is indispensable for the development of biotechnology industry in Hong Kong. Oftentimes, universities are referred to as "incubators" or "playing fields" of basic research. We may wonder whether Hong Kong has reached a critical mass in this area. The answer is simple, "No." Currently, there are only six institutions in Hong Kong with biological science or medical science programs. The total number of faculty members and researchers that can be classified as biotechnologists is still low, and these people have not yet evolved to a point where they can generate momentum. While there are some large groups that may have substantial manpower to undertake ambitious biotechnology projects, most research groups here are still small, with principal investigators operating in mentor-apprentice settings. It is nowhere near anything industrial in scale. Such a workforce will be severely stressed if it is asked to back up a biotechnology initiative.

Apart from academic departments, there are a few research institutes affiliated with universities. However, their capability for supporting a strong biotechnology program is still limited. If the determination is there to foster a strong, viable biotechnology industry, the Hong Kong Government must establish additional research institutions to attract competent workers to this area and then to focus their efforts on mission-oriented biotechnology research. Universities, meanwhile, should be left to produce and retain a continuous supply of competent personnel to satisfy the expansion of this industry-based research activity. This layering of research activity can be cultivated as an industrial-academic collaboration and network. An economy that wishes to stimulate high-tech industrial growth would do well to encourage strong regional networks among players, both industrial and academic. To get the best out of such networks, companies must support research themselves and be in close contact with the university community. The idea is emerging that the research network itself should be seen as a significant unit of economic public good.

Quality Education is the Key to a Sustainable Industry

Both biotechnology and basic research rely on human resources. An abundant supply of dedicated and talented people is essential. In the past two decades, a scarcity of scientifically competent people who were willing to stay in their Asian motherland has always held back high-tech development in Asia, including Hong Kong. Many excellent Asian scientists remain abroad because of freedom, better pay, living conditions and facilities. Will this change in the future? In the case of Hong Kong, the emphasis on research in higher institutions in recent years has lured back some of these well-trained scientists, technologists, technology marketing experts, and management talents. They have brought with them their experience in research settings. In a more-familiar academic environment, their training would prepare them to effectively cope with circumstances that arise in daily research operations. However, some of these talents, who may have little experience in biotechnology, will need to learn on the job in order to make biotechnology succeed in Hong Kong. It is still uncertain whether this approach is the best, but we must do it with what we have.

As the second-tier workforce, technical personnel are abundant in Hong Kong. From the late '80s to the early '90s, plenty of students left Hong Kong and studied abroad majoring in biological science-related disciplines. Many of these people have returned to Hong Kong. These technical workers have been exposed to the research environment abroad and can easily fit into the infrastructure that Hong Kong is trying to build. The major obstacle then lies not in the education system, nor the research environment, but in the opportunities presented by society. Hong Kong is a dynamic city with an emphasis on trade and commerce. Job opportunities are plentiful for qualified personnel. A well-trained person can easily move from job to job without much difficulty, securing a salary increase with each move. That is something that a research setup can hardly match. While research work demands dedication and long-term commitment these out-of-the field opportunities are just too tempting, so the retention rate of technical employees in Hong Kong is usually low. In some research labs, this shortage has reached a devastating level and has become a formidable task for administrators to handle.

A constant supply of well-trained workers is further provided by tertiary institutions where biotechnology degree programs have been set up to train both undergraduate and postgraduate students. Hundreds of qualified students will enter this field in the next few years. Together with existing programs in biology and biochemistry, the supply of manpower should not be a major set back. On the other hand, while we do see a need for these trained technical workers, do we know how many and how urgent? Are these training programs designed with a projected need in mind? Are we overproducing graduates for a biotechnology industry that is only in its fetal stage? Is the industry expanding at a rate that can guarantee employment to these graduates? It may be dangerous for an industry to seek its way without carefully addressing these questions. If our graduates are turned into victims of such ill-planned efforts to boost biotechnology, there is no way can we say that biotechnology is serving our community well. Without employment opportunities and a good coordination of these educational programs, it would appear that the government is mistakenly channeling money to the wrong pool. The biotechnology industry would not benefit from this well-trained workforce and more social economic problems will follow.

Rally for Public Support

Biotechnology is not something that should be confined to an elite group of scientists, nor should it be limited to political leaders when planning the future of our society. It is a technology that we should feel comfortable with in our daily lives. Citrus fruit that can stand up better to shipping and resist rotting, and cattle that grow faster than normal are some of the wonders genetic engineers can generate in their laboratories. Not all consumers, however, are well informed. Should they know how these engineered products are created, they may query whether these genetically engineered marvels are really safe to eat? Are they being given to unsuspecting customers without proper warning?

One can still remember the response from restaurants in New York City when engineered tomatoes were introduced in 1993. There was a boycott from the restaurants, their chefs and customers. This example vividly illustrates that technological advancement is one thing, its acceptance by the public is another. Acceptance, however, can come with promotion, education and reassurance. Issues as simple as convincing people to accept engineered food in the market may take years. Fortunately, Hong Kong people are quite different from those in the West. They are more receptive to new technology, and they are less resistant to scientific advancement and scientists. Thus, hopefully, acceptance and support from the public may not be such a difficult task.

Of course, skeptics abound. In the days when an airplane was unthinkable and a refrigerator was still a novelty, nobody could imagine what life would be like with these machines. In the days when everybody was still proud of Edison's introduction of electricity, no one would consider the necessity of having alternating current. We should ask ourselves: "Is it necessary to have these machines today?" and then ask ourselves, "Do we need biotechnology in the future?" We will have our answer only when we realize what will happen without biotechnology. This process of educating and understanding is important. Without the appreciation of automobiles, there would not be an automobile industry in Detroit. Without experiencing the benefit of generators churning out alternating current, there would not be a Westinghouse in Pittsburgh. Without a proper understanding and appreciation of what biotechnology can bring to society, this industry will never receive enough public support to have a place in Hong Kong's history. It will forever be confined to research parks and university campuses as the toy of a bunch of crazy scientists.

The Media and the Promotion of Science

When the name "Dolly," and later "Polly," came up last year, these English ewes were welcome with enthusiasm by most scientists and looked upon skeptically by the public. It generated hype that the age of custom-made genes and magic-bullet drugs is here to lead us into the future and to demonstrate how technology can dramatically improve the quality of life. It has also generated fear that the doomed end of mankind is finally here, all thanks to the media. The public is entering the uncharted future and yet is not aware of the fundamental impact of this success story, the significance of basic research in animal systems and its impact on biotechnology.

On the other hand, excitement brought about by the media can be an effective way to convey this new development to the public. Putting aside issues concerning the ethical aspects of cloning, we should take this opportunity to re-examine what biotechnology is about. Applied as it is, biotechnology never would have reached this stage if scientists had not paved the road with decades of hard work in fundamental research, in this case a replication of a frog cell transplantation experiment. The bits and pieces that science practitioners put into place may not hint to the public the full significance of this development; however, when ideas are connected, marvelous products and a significant impact will

be made on our society. It is important that such a moment be allowed to happen in a protected environment with academic freedom. It is also important that such a notion is conveyed to the public, not just to investors. Only when the public sees tax money spent for the "right" purpose will they will feel comfortable with their government's decision to support education, research and various development initiatives.

An Alliance Needed

The establishment of biotechnology may represent the shattering of the ideology of pure science under the impact of economics and politics. It also marks the rebirth of biological sciences in an era of renewal. The synthesis of a biotechnology industry is the result of many rational and dedicated scientists being swept into the whirlwind of a socioeconomic transformation. Scientists, educators, university administrators, government officials, entrepreneurs, mass media executives, and political leaders, as well as their voting constituents – all act in a world that is only partially of their own making. And, yet, one should not forget that the survival of the biotechnology industry in Hong Kong relies on all these units properly interacting with each other. In order to advance our society on the right track, none of them can be missed out from the scene. Only when education, basic research, biotechnology, socioeconomic infrastructure establishments are properly put into place by our leaders and brought together as a new alliance, can this high-tech-based economy move forward at a healthy pace.

[NOTE: The opinions expressed in this chapter do not necessarily reflect the viewpoint of New-Alliance Management (Asia) Ltd.]

Chapter 24

Education, R&D and the Biotech Industry in Hong Kong

By

~Wai-Yee Chan, Ph.D. ~
Professor, Departments of Pediatrics, Cell Biology Biochemistry & Molecular Biology
Georgetown University, Washington, D.C.



***Wai-Yee Chan, Ph.D.**, is a professor in the Departments of Pediatrics, Cell Biology, Biochemistry and Molecular Biology at Georgetown University, Washington, D.C. He obtained his B.Sc. in chemistry from The Chinese University of Hong Kong and his Ph.D. in biochemistry from the University of Florida in Gainesville. Chan is a member of the Lombardi Cancer Center and director of the Molecular Genetic Diagnostic Laboratory at Georgetown University Medical Center. Chan served in Study Sections of the National Institutes of Health in the U.S. and as reviewer of research grants for the Research Grants Council of Hong Kong, the U.S. Department of Agriculture and the Health Research Council of New Zealand.*

Introduction

In his speech at the ceremony to celebrate the establishment of the Hong Kong Special Administrative Region (HKSAR) of the People's Republic of China, Chief Executive Tung Chee-hwa announced that the Hong Kong government will "facilitate the development of value-added and high-technology industries" and that the "vision of Hong Kong is a world-class cultural, education and scientific research center."[1] This was the first time a firm commitment to the development of high-tech industries is made by the head of the government of Hong Kong. This was also the first time that Hong Kong, a world-class financial center, vowed to also strive to become a research center. This came in marked contrast to a previously held view that technology development to improve the business infrastructure and business processes would have a greater positive impact on the economy than the promotion of high-tech industries.[2] This demarcates a change in government policy from that of the British-ruled colonial Hong Kong.

Industry occupied a special position in the economic landscape of Hong Kong prior to its becoming a commercial and financial center. It is fair to say economic development in Hong Kong after 1949 was brought about by its industrialization.[3] Light industries, including garment, textile, plastics, toys, and electronics, constituted the backbone of the economy of Hong Kong until 1979, when there was a massive movement of manufacturing industries northward to China following economic liberalization of the country. The recent economic crisis in Asia and its effect on Hong Kong expose the danger of over reliance on the finance and service sectors. Diversification of economic activities appears to be the only guarantee of Hong Kong's long-term vitality and competitiveness in the world market. The development of high-tech industries is one policy most suited for Hong Kong. Hong Kong offers favorable conditions for the development of high-tech industries, such as that of telecommunication, computer, and biotechnology. These industries require few natural resources, produce high-value products, and can make strategic use of Hong Kong's global business networks.

It is often quoted that the "laissez faire" and "positive non-interventionism" policies of the government are keys to the economic success of Hong Kong. However, it is becoming increasingly apparent that even though "positive non-interventionism" contributed to the past economic success of Hong Kong, it is no

longer sufficient if Hong Kong is to remain competitive in the present world economic market. Certain interventions by the government, such as policies encouraging research and development (R&D), might be necessary.[3] Indeed, a brief look at the development of high-tech industries in the neighboring "dragons" (Singapore, Taiwan and South Korea) and Japan reveals varying degrees of government involvement in the planning and facilitation of growth in high-tech industries, including the biotech industry. One characteristic of all high-tech industries is their heavy reliance on R&D. Thus, besides building the infrastructure and providing incentives to encourage entrepreneurs to invest in these industries, the government plays a critical role in the key element of R&D, namely, education.

Building the Foundation – The Role of Government

Science Education in Elementary and Secondary Schools

The best way to stimulate the economy is through education. This was the unequivocal conclusion of the U.S. Government's council of economic advisers in its 1995 report "Supporting R&D to Promote Economic Growth – The Federal Government's Role." The biotech industry, similar to other high-tech industries, is heavily dependent on research and a highly skilled and well-trained work force. Without exception, biotech centers in the U.S., Europe and Japan are always found in areas with a high density of universities, research institutes or science parks. The government of the other Asian "dragons," namely Taiwan, Singapore and South Korea, recognize this fact and have spent the past decade investing heavily in building new research facilities and revamping their policy on R&D. Hong Kong lags behind these countries. In the beginning of the 20th Century, the Hong Kong government started making strides in science and technology and developed new policy designed to foster greater growth in R&D. The government of the HKSAR takes an additional step: Mr. Tung stressed the importance of improving the education system at all levels, including primary, secondary and tertiary schools and vowed to make Hong Kong a scientific research center.[1]

Education has played a critical role in the success of Hong Kong. The government spent a significant portion of its capital expenditure on public education. In the 1996-1997 financial year, 21% of the government's total recurrent expenditure and 8% of capital expenditure was on education.[4] Human resources has always been a successful factor in the development of Hong Kong.

However, different from the traditional labor-oriented low-tech industries and the finance- and service-oriented industries, the biotech industry is heavily research oriented and requires a highly skilled and well-educated work force of administrators, scientists, technical and other support staff. Besides ensuring a supply of appropriately trained personnel for the industry, education is also an important factor that can attract companies and qualified individuals to Hong Kong. In view of this new challenge, a careful re-examination of the education system as well as how the resources are allocated is appropriate.

In spite of the fact that Hong Kong students often score high in international mathematics and sciences competitions, education in Hong Kong lacks the component that encourages critical thinking and innovative problem solving. Students tend to be examination oriented and choose to avoid risk-taking. Curiosity, creativity and self-motivation are qualities required for success in a career in science and technology. These properties must be cultivated very early on. The structure of the primary and secondary school curricula leaves very little room for the development of these qualities in students.

Another problem with the curriculum is the over emphasis on textbook knowledge and shortage of hands-on experimentation. Even though natural sciences are taught in primary schools, very little hand-on experimentation is encouraged. This is also true for secondary schools. In the past, with the exception of a few elite secondary schools, the majority of schools in Hong Kong taught science as a textbook subject only. This was partly caused by the limitation of resources, namely, space and equipment, and partly by the structure of the curriculum. The result is that students are often well versed in textbook knowledge but are poor in practical experience. A rethinking of the science curriculum and a reallocation of educational resources may be necessary to better prepare students for a career in the biotech industry. The skills of data collection and analysis are useful for everyday life as well as for working in science. These skills should be introduced to students very early on in primary school using everyday examples. Simple hands-on experiments should also be introduced. For secondary schools, a stronger emphasis on the practical aspects of the sciences will encourage schools to pay more attention to laboratory instructions. The government can also earmark funds for the building of laboratory facilities as part of its subsidization to secondary schools. Furthermore, universities, industries and government institutions should be encouraged to

open the doors of their laboratories to high school students. A closer partnership between university/industry/ government institutions and high schools is found to be very helpful in encouraging the best and the brightest students to pursue a career in science. For example, the Computer/Math/Science Magnet Program at the Montgomery Blair High School in Maryland, which sends a number of semifinalists to the Westinghouse Science Talent Search every year, has a very close relationship with local universities, industries and government laboratories. Students often spend their summer doing research in the laboratories of government institutions, such as the National Institutes of Health and the National Aeronautic and Space Administration; local universities, such as Georgetown University and American University; and local industries, such as IBM. It is the often the experience that the students have during their research with established scientists that inspires them to pursue a career in science. Universities should also be involved more in providing career guidance to high school students.

Special Programs and Center Schools – Cultivation of Special Talents

Even though scientists can be hired from overseas, the long-term growth and success of the biotech industry depends upon Hong Kong's ability to produce quality scientists locally. For example, Singapore's own students make up the biggest source of scientific talent in its biotech companies. In spite of the fact that almost the same percent of the budget is allocated to education in Singapore as in Hong Kong, Singapore is more successful in training local scientists to fuel the biotech industry. This is the result of the difference in how educational resources are allocated by the two governments. To encourage students to pursue research, Singapore even provides full scholarships right through graduate school.[5]

In the U.S., especially in areas with prosperous high-tech industries, such as the Boston-New York area, the Silicon Valley, the Houston-Dallas-Austin triangle, the 270-corridor in Maryland, there are special programs in regular schools or center-schools created to train students with special talents in the natural sciences along an accelerated path. A survey of the list of finalists of the Westinghouse Science Talent Search, a very successful program in the U.S. that identifies high school students with special talents in the sciences, shows that many of these individuals come from schools or programs which emphasize

computers, mathematics or the natural sciences. Schools such as Bronx High School of Science, Stuyvesant High School in New York, Thomas Jefferson High School in Alexandria, VA, and special programs in regular high schools, such as the Computer/ Math/Science Magnet Program in Montgomery Blair High School in Silver Spring, MD, are well known for the performance of their students in competitions such as the Westinghouse Science Talent Search, the Student Space Science Involvement Program, and the Duracell Science Competition. In such schools or programs, students with special talents in science or mathematics are given accelerated instruction. They are often given the flexibility of designing their own curriculum of study based on their ability. Such schools or programs also maintain close ties with university, industry or government laboratories so that their students have the opportunity to work with scientists very early on. The majority of the graduates of these schools or programs end up pursuing a career in physical sciences, biomedical sciences or engineering. The pilot project School-Based Program for Academically Gifted Children and the Fung Hon Chu Gifted Education Center are examples of similar efforts by the Hong Kong government.[4] However, more innovative approaches to educate students with special talents should be encouraged.

Training of Technical Staff for the Industry – Some Examples

Headlines are made by researchers who discover new genes and create exciting new drugs, but skilled laboratory technicians are the mainstay of daily manufacturing operations. A steady supply of well-trained technicians who can meet the demands of the growing number of new firms is essential for sustaining growth in the biotech industry. Graduates of local technical colleges usually constitute the majority of these individuals. Traditional departments in the majority of post-secondary institutes or technical colleges throughout the world do not provide training tailored to individuals working in the biotech industry. Thus, a number of colleges in the U.S. are designing new programs for training workers with entry-level biotechnology skills. A good example is the New Hampshire Biotechnology Technician Education and Training Center based at New Hampshire Community Technical College in Portsmouth. In this institution, a technician-in-training may earn a two-semester Biotechnology Certificate, a one-year Biotechnology Diploma, or a two-year Biotechnology Associate in Science Degree. Uniting all programs are cornerstone courses in biotechnology research and manufactur-

ing, which are taught in a fully equipped, state-of-the-art laboratory that simulates a multifunctional biotech company.[6] An example closer to home is Singapore. The two polytechnic institutes of that country are training technicians to fill the growing demand from biotechnology laboratories and industries.[5] In Hong Kong, under the auspices of the Industry and Technology Development Council (ITDC), there is a committee for biotechnology.[7] However, the seven technical institutes and two technical colleges under the Vocational Training Council (VTC) which aim to provide well-trained manpower at the technician level do not offer programs for training technical staff for the biotech industry. Whether the planned Hong Kong Institute of Technology, the formation of which was announced in October 1997, will change this is unknown.

Hong Kong has invested heavily in human resources in the past and it continues to do so in the present. This policy apparently will remain unchanged in the future because it has proven to be very successful. However, to cope with the changing nature of the economic make-up of the region, education policy must be revised accordingly. A lag in the modernization of the education policy leads not only to a waste in resources but it also drags down the future economic development of the region.

Executives and Scientists – The Role of Universities

Training for a Career in the Biotech Industry – A Multidisciplinary Approach

The biotech industry needs not only individuals with training in the technical aspects of the industry but also those with training in management, marketing, finance, law, etc., and a solid knowledge in the sciences. Before the implementation of the credit system, similar to that practiced by universities in the U.S., the undergraduate curriculum in the universities in Hong Kong followed the British system and was quite rigid. Training was provided in the classical disciplines, such as chemistry, biology, and physics. Very few interdisciplinary programs were available. The choice of subject areas was also limited by the size of the faculty. Adopting the credit system allows some flexibility in the training provided to students. However, programs aimed at training science graduates with knowledge of the business world are still lacking.

Interdisciplinary programs that provide training for individuals who plan a career in biotech that are worth examining. At Georgetown University, the Department of Biochemistry and Molecular Biology offers a Certificate Program and a M.Sc. Program in Biotechnology. Students of these programs, besides taking courses in biochemistry and molecular biology, also take a course in entrepreneurial biotechnology, which introduces topics such as venture capital, intellectual property, problems and opportunities in start-up biotech companies, with lecturers from the law school and different biotech companies. Students are also offered opportunities to intern in law firms, the Federal Drug Administration, and local companies. Turku University in Finland offers a program of Bioeconomics to undergraduates with courses in biotechnology and economics. In the U.K., Nottingham University offers the Biotechnology Young Entrepreneurs Scheme (Biotech YES) for both undergraduate and Ph.D. students. This program gives students the opportunity to establish a simulated company consisting of five biotechnology scientists from anywhere in the U.K. Four of them take on the roles of finance director, marketing director, head of human resources, and chief scientist, and the fifth is appointed their managing director. The teams attend a weekend workshop at which they are taught fundamental business skills, including business planning, intellectual property management, and fundraising and marketing strategies, by the industrial sponsors of the scheme, consultants, and biotechnology executives. The team then composes a business plan that they present to a judging panel. In Italy, the National Program of Research offers programs to prepare undergraduates for management in the biotech industry. Students divide their training between academic centers and industry. During both these periods the participants working in laboratories, acquiring skills and knowledge in molecular biology, biochemistry, immunology, combinatorial chemistry, etc. Then in the last three months of the program, participants manage a research project. This exposes them to subjects such as finance, industrial organization, project management, quality and certification, licensing, maintenance, and safety.[8]

The biotech industry has its unique needs. Universities are responsible for developing programs that will train graduates who are equipped to meet the demands of the industry. The government needs to facilitate this by allocating additional resources to universities.

Graduate Science Education – Training of Scientists in R&D

Graduate science education is not well developed in Hong Kong. This was especially true of the period before 1990. Traditionally the majority of university students in Hong Kong regard the undergraduate degree as a terminal degree. The pursuit of a graduate science degree and a career in scientific research is a choice for only a few students because most students are attracted to careers that are less technically demanding or more rewarding financially, such as high school teaching or business. Research job opportunities are rare. There are no research posts in industry. Because of the small number of faculty positions in universities, academic jobs are limited to a select few. Furthermore, a university education is reserved only for select high school graduates. An undergraduate degree guarantees a well-paying job; therefore, there is very little incentive to pursue a higher degree after undergraduate work. Similarly, for engineering and medical graduates, a bachelor's degree guarantees good employment. There is no particular reason to encourage anyone to pursue a career in research. Most students who pursue graduate education go overseas. The majority of this crop of students stay behind after graduation and do not return to Hong Kong. Among the universities in Hong Kong, only The Chinese University of Hong Kong (CUHK), Hong Kong University (HKU) and the Hong Kong University of Science and Technology (HKUST) have appreciable graduate programs in science and engineering. Graduates of these programs are very small in number. Thus graduate education, even though in existence in Hong Kong for a number of years, has not produced a large enough mass to advance Hong Kong's research enterprise.

In order to provide quality scientists for R&D in the biotech industry, postgraduate science education has to be strengthened in Hong Kong. Furthermore, thought must be given to luring more students to scientific research careers. For example, Singapore, like Hong Kong, lacks a tradition of pursuing graduate studies in science and engineering. To overcome this problem, the Singapore Government, besides recruiting overseas both for academic staff and graduate students, also lures promising young scientists into a research career by providing ample funding and salaries to principal investigators.[4,9] The Japanese Government, in hopes of boosting science and technology, unveiled a plan in 1997 to double the number of postdoctoral fellows to 10,000 by the end of the decade and to increase the number of postgraduate students from 170,000 to 300,000 by 2010.[10] Hong Kong has made a number of changes in graduate science education since 1990. The first was

the establishment in 1991 of HKUST, which has graduate education as one of its primary goals.[11] Funding for research has also been increased significantly. This change stimulates research among faculty members and creates a demand for more graduate students and postdoctoral fellows. The recent elevation of several other institutes to university status opens university education to a larger number of students. Less than 5% of the 17-20 age group received a tertiary education in Hong Kong 10 years ago. By 1994-1995, the seven higher education institutions together allowed 18% of this age group to receive tertiary education.[12] This will unquestionably make the undergraduate degree less attractive as a terminal degree. With this increase in university graduates, the number of students entering graduate school is also expected to increase. Therefore, if the Hong Kong Government continues its policy of encouraging research, graduate science education should be expected to expand in the foreseeable future. This is a favorable factor in the future development of high-tech industries in the region.

The China Factor in Education and R&D

Mainland China affects the development of the biotech industry in Hong Kong in a number of ways. Besides providing the raw materials and the market for the products, more importantly, Mainland China will be a source of scientific personnel needed for the biotech industry. In the past, the tie between institutions of higher learning in Hong Kong and those in Mainland China was very weak. The number of Mainland scholars working in Hong Kong universities was very small. In spite of the presence of some students from Southeast Asia, there were almost no students from Mainland China attending universities in Hong Kong. The impact of China on higher education in Hong Kong was almost nonexistent. With the reversion of Hong Kong to Chinese sovereignty on July 1, 1997, interaction between universities in Hong Kong and Mainland China is expected to increase. The exchange of personnel and collaborations will have a positive impact on the research community in Hong Kong. Chinese students and scholars have contributed significantly to scientific development in the West. They provide a valuable source of graduate students, postdoctoral fellows and research associates. Similarly, Mainland Chinese scientists can help fill the gap of postdoctoral fellows in research institutes in Hong Kong. Also important is the opening up of another pool of students for undergraduate and graduate programs in Hong Kong. Hong Kong has already increased the quota for undergraduate students from

Mainland China. Even though the majority of these students and scholars are expected to return to the Mainland after their tenure in Hong Kong, they will, at the minimum, provide the "fuel" to keep the research engine in Hong Kong running. The proper use of the China factor is the key to a successful launching of high-tech industries in this region.

Academic Scientists in R&D - Past and Present

At the center of the biotech industry are the scientists who supply new products to sustain the continuous growth of the industry. Since industry-based research is almost nonexistent in Hong Kong, university-based scientists will play a key role in R&D. In fact, even in regions where the biotech industry is relatively well established, university-based scientists still play a significant role. For example, a recent analysis of patents of human DNA published after filing (About two-thirds were Patent Convention Treaty applications; the remainder were applications with European Patent Office, U.K. Patent Office and U.S. Patent and Trademark Office.) showed that 40% of the 652 patents originated from public-sector institutions, mainly U.S. universities and medical charitable foundations. Only half the patents were filed by the private sector. Despite the huge R&D spending by the world's multinational companies, they have been able to claim only 26% of this patent total.[13] Because economic pressure makes it so difficult for industry or government laboratories to undertake long-range economically oriented research, most Asian nations, Hong Kong included, look toward universities to perform cutting-edge research. For the universities in Hong Kong to take up this responsibility, a major adjustment in academic policy and government funding will be required. The primary mission of universities in Hong Kong, similar to most universities in Asian nations, is to educate undergraduates, not conduct research. As such, professors are not well equipped to train Ph.D.s. Most faculty members carry a very heavy teaching load, resulting in little time to pursue scientific investigation. Only in the last few years has the government had a policy on research by university faculty. Funding for R&D was low, estimated to be at 0.05% of the gross domestic product (GDP). A comparison of Hong Kong R&D expenditures and that of other Asian countries reveals that this figure is extremely low (Malaysia 0.4%, China 0.51%, Taiwan 1.6%, Australia 1.6%, South Korea 2.3%), in fact, one of the lowest in the world.[2,11,14-16] Because of the lack of funding, most faculty members did not have dedicated technicians or research

associates. Postdoctoral fellow positions were virtually unknown. Because of the size of most graduate programs, there were also not enough graduate students to share the research load. Thus, the part that university-based scientists played in the R&D of the biotech industries was minimal. This phenomenon was not only typical of Hong Kong but was, in general, true of the other Asian "dragons" as well.

The scene appears to be changing. To encourage productivity and competitiveness in university scientists, Asian countries have established systems for evaluating the performance of individuals and institutions. For example, Taiwan, uses the number of SCI papers (papers registered in the Science Citation Index) and their impact to assess individuals and institutions, giving bonuses based on these assessments. One criticism is that the system is over-reliant on Institute for Scientific Information (ISI) statistics. Many suggest that it needs a stronger human factor, i.e. reviews by an external, international panels of experts. Taiwan's Academic Sinica, has for many years placed overseas Chinese scientists and even non-Chinese scientists in advisory positions. Singapore uses external panels extensively. Hong Kong stands out for having the only centralized system for external assessment of research quality in every department of its universities.[17] The University Grants Committee monitors quality assurance in all publicly funded tertiary institutions. The committee has undertaken a series of teaching and learning quality process reviews as well as assessments of research output performance which started in 1996.[4] Such monitoring of faculty activities is important for maintaining the vitality of the university system.

Asian countries are putting more money into R&D, boosting research in recent years. Industry, which accounts for the lion's share of growth in R&D spending worldwide, supports little basic research in Asian countries. Governments must bear the burden of supporting basic research. The most typical example is that of Singapore. The Singapore government attempts to use high technology to strengthen its economy. It spent US$13.8 million to build the Institute of Molecular and Cell Biology (IMCB), as well as to provide the funds of about US$17.5 million a year to operate. Underpinning this effort is a strong push in basic research at the National University of Singapore (NUS), which houses the IMCB. The university conducts one-third of Singapore's R&D, and NUS scientists have made their mark in several high-tech industries, such as material technology, microelectronics and information technology. Other efforts include

establishing the Bioscience Center, to provide core facilities for researchers at the NUS; the Food Biotechnology Center; the Bioprocessing Technology Unit, to improve purification, synthesis and fermentation methods for commercial products; and the National University Medical Institute, modeled on the National Institutes of Health in the U.S.[5]

In Taiwan, a number of research institutes were established in the Hsinchu Science-Based Industrial Park to conduct cutting-edge research. In 1993, 50% of the National Science Council (NSC) grants, about US$200 million, was delegated to support university-based research in Taiwan.[18] In South Korea, the government launched an initiative called the Highly Advanced National Project, and built a 227-acre science park modeled on the research park at Japan's Tsukuba Science City.[19]

Since 1980, R&D spending has grown at annual rates ranging from 15.8% in Taiwan to 23% in South Korea. Research support in Hong Kong has also grown very rapidly in recent years. In 1985-1986, grants earmarked for research was about $2.6 million.[11] In 1996-1997, the Research Grant Council disbursed $42.5 million in grants for academic research.[4] In the last few years, the Industry Department also awarded grants to support applied research and product development projects. In 1996, $10.9 million was given out by the Industry Department to support projects in the fields of biotechnology, telecommunication and robotic engineering.[4] This is a very significant change from just a few years ago.

The results of changing academic policy and increasing research funding are reflected in the dramatic increase in the number of scientific papers produced by the region stretching from Japan to Singapore in the past few years. The output of papers leapt from just over 50,000 in 1989 to more than 90,000 in 1996, according to the ISI. Hong Kong has tripled its output while Mainland China has doubled its production of scientific papers. South Korea recorded a five-fold increase, and Taiwan has nearly quadrupled its output, while Singapore has tripled its output. Rapidly growing government investment in science and technology is a major factor behind these increases.[17] The quality of research also improved tremendously. A survey of the citations per paper (a measure of the quality of papers), shows that Hong Kong recently crept into the league of top-30 nations at Position 28, with a citation impact of 1.94, an achievement better than other

"dragons." Japan has an average of 3.18 compared with more than 5 for U.S. papers and close to 4 for the world average.[17]

Albeit improving, the research output of Hong Kong universities is still behind the world average. Research is a long-term investment. It is a crucial factor affecting the future prosperity of high-tech industries in the region. In view of the changes in neighboring countries, Hong Kong must continue and expand the policy of supporting R&D in order to be competitive.

Other Factors Affecting Development of the Industry

Technology Transfer – The Role of the Government and the University

It was long held among traditional Asian academians that academic pursuits and business pursuits are two distinct tracks. This separation of scholarly work from profit-generating commercial products is still deeply rooted in many scientists' minds. However, research cannot have an economic impact if scientific discoveries are not translated into marketable goods and services. The easiest way to channel scientific discoveries into marketable goods is by patenting the discoveries. This concept of patenting of technologies or research products is still foreign to many academic scientists in Hong Kong and other Asian countries. Because of this cultural tradition, there is often minimal collaboration between academic investigators and the industry. For example, U.S. universities obtained 1,900 patents in 1994, while Japanese universities gained only 130 in the same year, according to Japan's Ministry of International Trade and Industry (MITI).[20] Furthermore, most academic scientists lack the legal experience to know whether a particular research finding is worth patenting. Even though patent-worthy technologies or products are discovered, they are often not patented at the right time. Consequently, industries do not invest to develop such technologies or products into marketable forms.

Nowadays, in most U.S. institutions, researchers are more conscientious about the patenting of their research products. In some institutions, the administration even sends attorneys to laboratories to talk to investigators in order to identify patentable technologies or products. This helps scientists package their work to make it more attractive to the industry. Thus, on one hand, it helps the industry to identify potential products for the market in

the future. On the other hand, it helps scientists to translate their work from the bench to products that can benefit the society because this usually generates more support for their work. To make this happen, scientists must feel comfortable moving their technologies out of universities. In recognition of this fact, the MITI and the Ministry for Education, Science, Sports and Culture (Monbusho) in Japan are considering setting up technology liaison offices to help improve collaboration between universities and industry.[20] In Hong Kong, the establishment of The Hong Kong Institute of Biotechnology (HKIB) apparently also has this function in mind. However, the affiliation of HKIB with CUHK limits its accessibility for scientists in the other universities. This situation can be improved either by setting up institutes similar to HKIB at other universities or by establishing technology liaison offices similar to those in Japan. A closer relationship between universities and industry will facilitate the discovery of valuable products as well as provide additional sources of funding to support research for universities.

Recruitment of Overseas Scientists – Positive and Negative Factors

One way of jump-starting the research engine is by recruiting scientists from overseas. The migration of scientists can have a profound influence on the economic and technological development of nations. Most notably, the impact in the U.S. of central European emigrants from the 1940s onwards is well documented. More recent examples are seen in Hong Kong, Taiwan and Singapore. New institutions such as the ICMB in Singapore, the Hsinchu Science Park in Taiwan, and HKUST are staffed mainly with overseas recruits. These new institutions and recruits have helped boost the output of papers from the region. Papers in Science Citation Index for Taiwan, Hong Kong and Singapore more than doubled between 1989-1994. The impact on industry has also been profound, particularly in Taiwan, where both scientists and business people from the U.S.'s Silicon Valley have set up venture businesses in Hsinchu Science Park for integrated circuits, computers and telecommunications that are competing successfully on the world stage.

The lack of a tradition for pursuing graduate studies in science and engineering in Singapore and Hong Kong has meant that new institutions tend to recruit overseas, both for academic staff and graduate students.[9] The majority of Hong Kong academic staff, especially in science and engineering, are recruited

from overseas. Traditionally, individuals originally from Hong Kong make up the bulk of these recruits. More recently, however, a large number of these individuals originated from Taiwan or Mainland China but went abroad for graduate education. What makes a job in Hong Kong so attractive to them? Faculty jobs are harder to find in the West because of financial constraints in the U.S. and Europe. The terms offered by universities in Hong Kong are very attractive, compared to those offered by universities in China or even Taiwan. The closeness of Hong Kong to Mainland China and Taiwan is another advantage; the cultural and language barriers are almost nonexistent. Therefore, working in Hong Kong is an alternative, in some cases even a better alternative, than working in their place of origin. There are, however, also factors that may deter individuals from coming to Hong Kong. An important factor is the political uncertainty after July 1, 1997. Many people are still concerned about the practicality of the "one-country, two-systems" philosophy. However, with time, this suspicion will be proven either true or false. The other factor is the availability of research support. This is especially important for younger investigators who want to establish a career in scientific research. Unless continuous stream of research funding is available, young and productive scientists will be very reluctant to relocate to Hong Kong. Another factor is education for children. A lot of the potential recruits in high-technology industries will consider educational opportunities for their children one of the major factors affecting their decision to relocate. Similarly, companies, especially high-tech companies, look at access to transportation, local tax rates, as well as other community assets such as the quality of cultural offerings, education, etc., which will help them recruit high-quality employees and decide where to build plants. The major centers of biotechnology in the U.S., such as Silicon Valley, the Boston-New York area, the I-270 corridor in Maryland, and the Houston-Austin corridor, all offer good living environments, demonstrating the importance of these factors in recruiting. The infrastructure of Hong Kong certainly provides these assets well. Thus, if Hong Kong continues to maintain a favorable living environment, recruitment of overseas scientists should not be a factor deterring growth of the biotech industry.

Networking and Continuing Education of Scientists

Biotechnology is an ever-evolving field. New technologies and new research findings turn up every day. To be at the cutting edge of the field is vital for a biotech company or scientist. One obvious disadvantage of Hong Kong is its geographical location,

being relatively isolated from centers with vigorous research activity, such as North America, Europe, and Japan. Geographical isolation results in limited accessibility to scientific conferences, which offer valuable opportunities for the continuing education of scientists and the discussion of new discoveries. Hong Kong's location also limits networking with scientists in other regions through participation in activities of scientific organizations. This is partially solved by advancements in communication technology. In the past, scientists were often impeded by the lack of current literature in Hong Kong libraries. Prior to the telecommunications boom, even current scientific literature searches could be formidable tasks for researchers in Hong Kong. This prevented the acquisition of cutting-edge information and technologies. With the help of the Internet, this is no longer a problem. Even though communicating through the Internet is commonplace nowadays, electronic mail cannot replace face-to-face meetings with fellow scientists. Many Asian scientists are aware of this fact, and regional scientific organizations are attempting to bring more meetings and conferences to the region. For example, the Asian Pacific Society of Bioscientists serves as a medium for interaction among Asian bioscientists. There is also the International Molecular Biology Network (IMBN) for Asian and the Pacific Rim countries which aim to increase interaction among molecular biologists in the region.[21]

In 1996, an Asian-Pacific conference of science and technology leaders was held in Beijing to talk about the potential of science and technology to improve the socioeconomic situation in the Asia-Pacific region and identify the major constraints on the collaboration necessary to realize this development. The conference identified specific areas of collaboration that should receive increased support and new communication technology strategies for enhancing overall regional cooperation. Conference participants proposed the Asia-Pacific Science & Technology Organization (APSTO) as a non-governmental forum for enhancing science and technology collaboration in the region.[22] The outgrowth of this conference is the Pacific Rim Initiative (PRI), a program of the American Association for the Advancement of Science of the U.S. which aims to engage the nations of the Asia-Pacific region in greater cooperation with each other, particularly with the American science and technology community. PRI is intended to build cooperative relationships between the U.S. and scientific communities in the Asia-Pacific region. It aims to facilitate the exchange of scientific information and the development of technology, in particular, telecommunications and biotechnology, between U.S. and Asian Pacific Rim countries. Another goal of the PRI is to facilitate the communication between scientists and entrepreneurs in order to enhance collaboration between industry, government and scientists in the Pacific Asian countries.[23] It is hoped that such attempts will enhance regional collaboration. Geographical isolation will no longer be a hindrance to the development of the biotech industry in Hong Kong.

Conclusion

1997 marks a turning point in the history of Hong Kong. It also marks a turning point in the philosophy of the government regarding to the future economic development of Hong Kong. With the recent crisis in the Asian financial marker, it is becoming apparent that over-reliance on the financial and service sectors is not beneficial for the long-term economic health of the region. The Hong Kong Government recognizes the importance of technology-intensive, high-value industries in the future economic growth of the region and has taken a turn in its policy. Some in Hong Kong believe the territory missed the opportunity to develop high-tech industries in the 1970s and 1980s, when neighboring countries made massive efforts to attract or build such industries.[2] With its global connection and its highly motivated population, however, there is no reason to believe that Hong Kong will not be able to catch up with its neighbors in developing high-tech industries, including the biotech industry. The key to the success of such efforts is education. It is of utmost importance that the education policy at all levels be carefully examined and revised such that future generations are provided with cutting-edge knowledge and the best available techniques. It was human resources that made Hong Kong so successful in the past. It will be human resources that make Hong Kong equally successful in the future.

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Chapter 25

Biotechnology for Hong Kong
A View from Afar

By

~ Hardy Chan, Ph.D. ~
Chairman
ScinoPharm International, Ltd., Mountain View, California



***Hardy W. Chan, Ph.D.**, is chairman of ScinoPharm International, Ltd., in Mountain View, California, and a member of the board and executive vice president, R&D, for ScinoPharm Taiwan, Ltd., in Taipei.. Chan received his B.S. in chemistry at University of Wisconsin in La Crosse, Wisconsin, and his Ph.D. in biochemistry from the University of Wisconsin in Madison, Wisconsin. He is also executive vice president of research & development and a member of the board at ScinoPharm Taiwan, Ltd., in Taipei. Chan is the principal of Bio/pharmaceutical Consulting in Belmont, California. He has worked at Syntex Corp., Palo Alto, California, where his most recent position was vice-president & director of biotechnology. Chan holds two U.S. Patents.*

Modern biotechnology was born about 20 years ago when commercial applications of recombinant DNA and monoclonal antibody technologies were first recognized. Since then, over 1,200 biotechnology companies with total market capitalization exceeding $80 billion have been established in the United States. In Europe, though the total number of companies is much smaller, the biotechnology industry is growing with unprecedented momentum.

The establishment of The Hong Kong Institute of Biotechnology (HKIB) and the Biotechnology Research Institute (BRI), within the Hong Kong University of Science and Technology (HKUST), marked the earliest attempts to develop a biotechnology industry in of Hong Kong. Hong Kong has targeted this industry for close to 10 years. So far, Hong Kong can hardly boast that biotechnology is its star industry. In fact, Hong Kong's biotechnology industry lags behind that of neighboring countries such as China, Taiwan and Singapore.

Does Hong Kong have the ingredients necessary to become successful in biotechnology? Should Hong Kong even be engaged in biotechnology? If so, in what form and shape?

Many have attributed Hong Kong's lack of success in biotechnology to its shortage of capital. A common argument is that Hong Kong's investors lack the sophistication or vision to appreciate the potential of a high-technology industry such as biotechnology, which often requires incubation periods of years before showing any commercial success. I happen to disagree with that interpretation. A number of venture capital firms set up by Hong Kong business groups are already actively involved in making investments in biotechnology companies located in the United States and Europe. It is true that Hong Kong does not have an over-the-counter stock market, an effective forum through which the U.S. and European biotechnology companies have been able to secure substantial portions of their required capital. Listing on the U.S. over-the-counter market does not require a company to show three consecutive years of increasing profit, something that is required in Hong Kong. An early initial public offering on the over-the-counter exchange is an exit strategy that justifies investments from venture capital groups and is the major mode of financing for the U.S. biotechnology industry. On this point, if Taiwan can consider establishing an over-the-counter stock market to stimulate its nascent biotechnology industry, I do not see any reason why Hong Kong could not follow suit, that

is, assuming the local financial community agrees that Hong Kong's biotechnology industry has a bright commercial future.

A major deficiency in Hong Kong, in my opinion, is its lack of experience in developing novel science or technology into marketable products. This is by no means a condemnation of the caliber of science conducted at the various Hong Kong university campuses. It simply reflects the fact that Hong Kong does not have an existing industry capable of exploiting technology breakthroughs in a timely manner, a reflection of Hong Kong lacking the right kind of professional leadership. The fact that Hong Kong does not have a sophisticated and proactive regulatory agency similar to the U.S. Food and Drug Administration, also makes new drug development and approval virtually impossible.

Why then should Hong Kong be bothered with establishing a biotechnology industry? The paramount reason is that China (which includes Hong Kong) needs to rely on biotechnology to overcome some of the most critical problems that the country is facing in the first part of the 21st Century. Hong Kong could be a great help to China. It is widely recognized that by the second quarter of the next century, China will no longer be able to produce sufficient food for its population, unless new genetically engineered strains of crops are developed to boost harvests. In the healthcare arena, diseases such as liver and nose and throat cancers are affecting a much younger population of Asians. There are no effective medical treatments for these diseases, and Western pharmaceutical companies are reluctant to do anything to combat these predominately Asian diseases. There is no surprise that China put biotechnology as one of the nation's top priorities in its "863 Plan," an initiative promulgated in March 1986 declaring the development of biotechnology as one of China's top priorities. Special funding was allocated to promote research and commercialization of biotechnology products which impact human healthcare and agriculture. The initiative on biotechnology was supervised by the Science and Technology Commission. The introduction of the 20-year pharmaceutical patent protection term in January 1, 1993 further propelled China into a phase in which discovery of new therapeutic entities became a national prerogative. Activities related to all aspects of biotechnology are now carried out by a multitude of government institutes, universities and pharmaceutical companies in China, totaling in the thousands. Yet, most of these institutions are suffering from a scarcity of research funding. Lacking real drug development experience also dampened any real chance of success for many Chinese institutions. For instance, it is not unusual that compounds are developed for the wrong clinical indications, largely due to an insufficient understanding of the compound's true pharmacology. Other drug candidates were abandoned prematurely when the sponsoring institutions ran out of funding.

What can Hong Kong do to assist and complement China? Building a manufacturing plant for biopharmaceutical products is the last thing Hong Kong needs. Hong Kong offers no advantage over the many biotechnology parks that are sprouting up in Jungshan, Pudong, or on the outskirts of Beijing. Neither should the training of research personnel nor the establishment of a sophisticated development infrastructure akin to the Development Center for Biotechnology of Taipei be a priority for Hong Kong. If Hong Kong must invest in a new laboratory, it should consider establishing a mechanistic-based drug screening center. This would definitely complement China's effort in new drug development. The center would screen drugs using a method based on a specific molecular target. For instance, cardiovascular drugs could be ACE (angiotensin converting enzyme) inhibitors, calcium channel blockers or andrenergic receptor antagonists. Each group has its own mechanism of action and also side effect profile. These days, contrary to using whole animals for preliminary drug screening (which gives you no idea of how a drug works), companies are using specific screening methods that decipher the mechanism of action at the onset. This not only increases the potency of drugs but also minimizes the side effects due to the lack of mechanistic specificities.

In my opinion, the perfect role for Hong Kong to play is to become both an investment banker and a management consultant for China's biotechnology industry. True scientific breakthroughs must be of a global nature and have commercial potential which far exceeds the country's borders. There is little question that some good science is being conducted in China. Unfortunately, not all biotechnology projects have been subjected to stringent scientific, patent or commercial scrutiny. When they are, the evaluation might not be from a global perspective. Even good projects receive only very modest funding, a reflection of the financial reality that China's scientific community is currently facing. While many multinational companies have a keen interest in obtaining technology leads from China, scientific results published by Chinese institutions are nonetheless often viewed with a certain degree of skepticism. An excellent opportunity, therefore, exists for any Hong Kong entity willing to search

through the myriad Chinese laboratories to identify the few good projects and endow them with adequate funding. Once these projects are shown to withstand stringent scientific verification, the Hong Kong entity can forge corporate alliances or arrange licensing agreements with major multinational companies.

With a large number of corporate mergers and acquisitions taking place in the West, a large number of overseas Chinese scientists and biotechnology executives are now available and interested in returning to Asia, if the right business opportunity exists. They are representative of the talent Hong Kong should attract to provide the leadership necessary to make Hong Kong the control center of China's biotechnology industry.

Chapter 26

The Hitchhiker's Guide to the Virtual Biotechnology Universe

By

~ Bernard Chan, M.D. ~
Chairman
Phoenix Bioscience Limited, Hong Kong



***Bernard Chan, M.D.**, is chairman of Phoenix Bioscience Limited in Hong Kong. He graduated from the University of London, England and was an Elmore Scholar at the University of Cambridge. A member of the American Societies of Hematology, Clinical Oncology and Bone Marrow Transplantation, Chan was formerly chief executive officer of ProImmune International Limited, a start-up biotechnology company in Nottingham, U.K.*

Hong Kong is a beautiful city with a great entrepreneurial spirit. Here, the density of entrepreneurs per square inch is probably higher than in any other city in the world, with the possible exception of Las Vegas. Most observers believe biotechnology is the next wave. It will replace computer technology as the great engine of growth, and, in the process, produce food to feed billions, clean up the environment and improve our health. One might therefore expect a pairing of Hong Kong's entrepreneurial energy and the opportunity of biotechnology to be a marriage made in heaven, but the two have behaved like male and female giant pandas put into the same zoo enclosure. They studiously avoid each other. What is the problem?

Let us begin by examining what is needed to create the Hong Kong biotechnology industry. There are two possible answers. In one sense, it requires a great deal of resources, such as new buildings on reclaimed land, in Hong Kong's inimitable style, halfway between a stock exchange and a country club, plus grand televised fundraising events, complete with film stars and beauty queens. But what happens if you do not have such resources?

When I was young I did not have a car, but I visited many beautiful places. Now that I have a car I hardly go anywhere. This chapter is about doing biotechnology on a shoestring budget, hitchhiking on the technology superhighway.

When you take a close look you may be pleasantly surprised how little is required to get started. The most important starting material is in the form of intellectual property, which already exists on a global basis. It may be argued that in order to create a new industry we do not start with all or even most of the parts, otherwise the industry already exists. The first thing we need is a concept. I suggest we call this concept "biotechnology with Hong Kong characteristics."

In 1946 an Australian and an American laid the foundation for the Hong Kong airline industry. Cathay Pacific became a great success story, but it did not and does not now, have Hong Kong-designed airplanes with Hong Kong-made Rolls Royce engines. In fact, it did not even have Hong Kong pilots, although these days it has a few. In 1946 the only ingredient from Hong Kong was attractive flight attendants, who were called "hostesses." It did however have a great concept: An airline with Hong Kong characteristics. With the concept and its success came landing and other rights, which are worth a great deal of money. The

entrepreneur begins with concepts and ends with rights. Both are intangible. Of course the entrepreneur may want to build Rolls Royce engines, but then he would have the concept to build Rolls Royce engines, which is totally different from the concept to run an airline. Biotechnology, even more than the airline industry, includes many components which can be virtual, or contracted out. Just as Cathay Pacific, with rights in Hong Kong, has major shareholders in London, repair facilities in Xiamen and a computer center in Australia, the biotechnology company with Hong Kong characteristics can license its technology from the U.S., work with a Contract Research Organization in England and have its production facilities in the Netherlands. In fact it may have no other choice because biotechnology is a global industry, and if it does not have the best strategic partners wherever they may be, it cannot survive. However, its strength will be because Hong Kong is part of China, with its vast market for agribusiness, environment and health care. So, the biotechnology company with Hong Kong characteristics may be compared to the Holy Roman Empire, which Voltaire once described as neither holy, nor Roman, nor an empire. It all goes to show that you do not need everything in order to be something.

A notable guest editorial appeared in the July 1996 issue of the American journal **Science**. Its author was the prime minister of the People's Republic of China. In his message, Mr. Li Peng declared that China, with its vast resources of material and manpower and a potential market of 1.2 billion people, is open for business. China wants collaborative projects with the West, and needs the West's technology and business know-how. This is especially true of biomedical technologies. What better place to develop this collaboration but in Hong Kong, now part of the motherland and its most sophisticated city?

However, the China-Hong Kong connection has its weaknesses. For example, in the pharmaceutical industry, China has a 4,000-year history of producing medicines, but its industry is antiquated and must be brought up to date with a lengthy and detailed drug discovery and development program that is concerned with safety and conforms to international standards. Presently China has more than 5,000 drug companies, the majority of which do not meet any Chinese or international Good Manufacturing Practice (GMP) standards. There is a need to rationalize the industry, perhaps by stages, over the next decade.

The traditional Chinese concept of a pharmaceutical company, or indeed of any enterprise dealing with intellectual property, is that of a family business with a secret formula transferred from generation to generation. Thus, discovery, development, production and marketing, together with the intellectual property rights associated with each stage of the process, remain in the family. The biotechnology company with Hong Kong characteristics must break away from such traditional concepts and weaknesses. Importantly, traditional thinking has given rise to the mistaken idea that the Hong Kong biotechnology industry should keep everything, or most things, "within the family," starting with an invention made by a Hong Kong scientist and funded by the Hong Kong Government. Just like starting an airline with your own Rolls Royce engines, this is unnecessary and may be undesirable.

Over the past two decades most universities and research institutes in North America and Europe have adopted a policy of patenting their scientific discoveries. However, the cost of developing a biotechnology invention is very high. It has been estimated that the cost of developing a new drug is US$300 million, or US$600 million, including infrastructure costs. This means that only a tiny percentage of discoveries ever entered the preliminary development phase. Industry insiders claim that out of 1,000 candidate drugs only one or two will make it to the end user.

There is now a huge oversupply of patented inventions. Most U.S. universities have established technology transfer programs to facilitate the licensing of available technologies. These programs frequently have a list of hundreds of innovations waiting for an interested entrepreneur. In the past two years, I have personally reviewed more than 2,000 technologies available for licensing, including 1,000 from the U.S. National Cancer Institute. For the biotechnology entrepreneur, this oversupply of available technologies represents a vast resource of starting material. I will call this the "Patent Mountain."

For the rookie entrepreneur with minimal start-up capital, another important resource is the "Virtual Office." Globally, the biotechnology revolution has resulted in a major restructuring of the industry. In 1998, biotechnology companies are either very large or very small. The very large companies have been created from mega mergers. An important recent example is that of Amersham Life Science and Pharmacia Biotech, which have merged to form the world's largest research-based supplier to the life sciences. Other notable cases include Glaxo-Wellcome and Novartis (formerly Sandoz and Ciba-Geigy). Nonetheless, the vast majority of the 1,000 or so U.S. biotechnology companies are

tiny. When it comes to innovation in biotechnology, small is beautiful. In the vocabulary of the entrepreneur, the key words are "virtual" and "agile." Virtual because he can outsource almost all his needs. We have already seen that he has a vast supply of technologies available for licensing. He can also contract out his research to Clinical Research Organisations (CRO) and his production to Contract Manufacturing Organisations (CMO). Indeed, CROs and CMOs will beat a path to his door. His enterprise however must remain agile, i.e., highly adaptable. This is because biotechnology, by its very nature, is rapidly evolving, not only in terms of the science but perhaps even more so in terms of the economics, and of the changing rules of the game and the players involved. Thus the qualities of virtual and agile are interlinked.

Let us suppose that our entrepreneur has opened a virtual office. How does he tackle the vast amount of information available on the Patent Mountain? If he is a good entrepreneur, he will not take anything on the patent mountain at face value, e.g., He will not take a technology invented for cancer treatment to make products for cancer treatment. Of course, he might, since people will do anything, but it will be expensive, and there will be a great deal of competition. The inventor might very well want half a million dollars in licensing fees, and there would be hundreds of people trying to make similar products. This is not being agile. Not only that, it is also totally prosaic and lacking in sex appeal. It is like climbing Everest without writing poetry, a form of sub-optimal behavior. Our hero does much better than that. He climbs the mountain and there smells the air and meditates. He picks a piece of the patent mountain and transforms it with his inspiration.

The creative spark in biotechnology involves seeing value where others do not. For example, an outdated anti-cancer drug might be highly effective in treating venereal disease; a molecule which boosts the immune system might be useful in cosmetics; a treatment developed for arthritis might be useful against AIDS. These are actual examples of entrepreneurial insight, only lightly disguised. The process is part science, part inspiration. If you can do that, the original inventor would be so amazed that he would charge you very little for the license, say five dollars. In fact, he might very well give you the five dollars.

Recently I attended a meeting to discuss an immune protein at the Institute of Directors in London. One participant, a well-known professor of medicine, suddenly said: "Why don't we give it to a racehorse?" Now that was a defining moment in entrepreneurship, one that separates the men from the boys. A mere scientist would give the immune protein to a mouse, but an entrepreneur would give it to a racehorse. Some might object that I am advocating an offshore biotechnology industry, one in which the scientific foundation, the discovery and development, and even production, take place outside Hong Kong. This is true, but the innovation, the creative spark, will belong to us, and I believe this is an essential first step.

One only has to look at the advertisements in **Science**, **Nature Biotechnology**, and other journals, or on the Internet, to realize that in Europe and in the U.S., there is a vast network of companies which offer services from custom peptides and antibodies to combinatorial chemistry. One can find service suppliers or strategic partners all the way from the discovery process through to regulatory approval. This network is virtually absent in Hong Kong. I have therefore described an essentially personal perspective of operating under a highly adverse environment, with practically no infrastructure to support a biotechnology industry.

Let us also look at some alternative scenarios. One option is the Singapore model in which, through significant government incentives, major multinational players are encouraged to site their production, as well as some R&D, in the city state. As I am writing, I have in front of me a two-page glossy advertisement from the Singapore government promoting the advantages of being located in Lion City. It is certainly tempting. This, however, would be an inappropriate model for Hong Kong for the simple reason that Hong Kong is not a city state. The vital consideration is that Hong Kong is part of China, which is emerging as an economic superpower. An alternative model which has been talked about is essentially that of a generic industry based on imitation. This would, for example, produce a Chinese version of interferon, a Chinese version of erythropoietin, etc. These could have a substantial market but only under the conditions of restrictive trade practices. With the liberalization of trade and the adoption of international standards for intellectual property, this market will vanish. In the rush to create a new industry, we must not forget that biotechnology is about innovation, and imitation is not innovation. In the long term this strategy would be disastrous. When we talk about the 1,000 or so U.S. biotechnology companies, we are talking about companies with intellectual property rights. The life cycle of a biotechnology innovation is very short. By the

time a technology attracts imitators, it is already half way to obsolescence. If the Hong Kong biotechnology industry is not driven by innovation, we will find in 10 years' time that all we have are obsolete facilities and skills.

Recently the CEO of the New York Academy of Sciences wrote glowingly of the opportunities in technology for Hong Kong and particularly for China in the Academy's bimonthly journal, The Sciences. By the year 2015, i.e., in less than 20 years' time, China (without Hong Kong or Taiwan) is projected to have a gross domestic product (GDP) of 12 trillion of 1997 U.S. Purchasing Power Parity Dollars. China, as an economic superpower, will have a truly vast need for agriculture, environment and health care products. China will be in an excellent position not only to provide for its own needs, but to have a healthy export industry in biotechnology if we act now. A particularly encouraging feature of the worldwide biotechnology industry is the speed of new development. If we look not only at the first wave of successful companies, like Amgen and Genentech, but also at the second wave of relatively new companies, like Isis, Hybridon and Nexstar, we see how rapidly a company can take on a commanding position. Generally this is because they have developed a platform technology which others will have to use, such as antisense or combinatorial chemistry. Biotechnology develops not so much in a straight line but in leaps and bounds. A new platform technology such as SELEX (Selective Evolution of Ligands by Exponential Enrichment), which could be developed by a relatively small company in a short space of time, can launch the whole industry to a new level. This is why I believe that if we have the will, China, including Hong Kong, can become truly competitive.

Much of Hong Kong's success derives from its business culture, which is a mixture of hustle and commitment, with great flexibility and flair for innovation. The government has traditionally taken a laissez-faire attitude. This, however, is not necessarily true of science policy and most certainly not true of policy regarding medical science and health care, where a virtual monopoly by government agencies over many decades has created its own culture, which is essentially conservative.

We have to re-examine our culture and history within the context of Hong Kong's new role inside a reformed and liberalizing China. The negative and conservative attitudes in science and medicine reflect the colonial past, where innovation and scientific discovery took a back seat. The old colonial mind set may

be summed up as elevating mediocrity to a fine art. But I am not the only one calling for a radical change to our cultural values in preparation for a wholly new start. Indeed, the new Chief Executive Tung Chee-hwa has said: "Hong Kong has finally broken free from the psychological constraints of the colonial era. We should have the courage to set aside past modes of thought and plan Hong Kong's future with vision." Nor is the problem peculiar to Hong Kong, for Britain's prime minister Tony Blair recently called for "the chain of mediocrity" to be broken, and to be "free to excel once more."

However, changing cultural values is easier said than done. Because Hong Kong is affluent, there is a tendency to throw economic resources at problems which may inherently require non-economic solutions. There is talk of building more institutes and science parks. As I write this, there are giant cranes outside my window reclaiming more land. Will this effort be enough?

When I returned to Hong Kong several years ago, I had lived one-third of my life in Europe, one-third in North America and one-third in Asia. People asked me why I didn't choose Singapore and other similar questions phrased slightly differently. Some people implied that I must be crazy. I was attracted to Hong Kong because of its proximity to China, which is emerging as a major player economically, with a vast market in healthcare. I think of Hong Kong as the hub of my work, which is essentially a network with strategic partners in the U.S., Europe and China. I found out early on that there are plenty of promising technologies waiting to be licensed and that it is possible to be in the game even though one's company is very small. The right strategic partners are also vitally important. It is true that Hong Kong lacks the basic infrastructure and the investment climate that you have, say, in Europe, and I have had to relocate most research and development to the United States and Europe.

I had been interested for some time in the innate response of immunity which had been neglected in general as being less glamorous, compared to antibodies and T cells, but which I think is important if only because it has been conserved through hundreds of millions of years of evolution. A chance meeting gave me an introduction to a company based at the research park of Northwestern University in Chicago. This company has a product based on an acute phase protein which fit nicely in my general field of interest.

The same contact also led to the development of a treatment device for AIDS. Again, the question is how does one with relatively little resources compete in this large and well-funded field? I happen to have had experience in using extra-corporeal devices (ECDs), and this led to a research collaboration using a fragment of a complement molecule to capture HIV in an ECD.

I now have four products under development, a therapeutic and a diagnostic product based on the acute phase protein, an ECD for HIV/AIDS and a cancer vaccine. However, only the cancer vaccine will be developed in China. I also set up two companies which offer biotechnology-based services, one for immunotherapy and one for the processing and storage of blood cells.

If one person comes to Hong Kong and impulsively starts an R&D biotech company, it may be a mental aberration, but if 100 people do the same thing, it may be considered rightly to be a sign of patriotism. One important plus factor for Hong Kong is that many ethnic Chinese scientists (You only have to glance at **Nature** or **Science** to know there are many of these.) actually would like to live in Hong Kong. If we set up excellent facilities for R&D, I do believe we could attract many first-class scientists involved in the biotechnology industry. I have in mind particularly the people who are in universities and are thinking of joining industry. In many cases these scientists could come to Hong Kong on a leave of absence from their institutions and can train the many excellent young people we have here. I think these scientists would like to live in Hong Kong, whose lifestyle exudes a certain glamour, but they might not wish to live in Shanghai or Beijing, even though personally I consider these to be very attractive cities. In this way, they and Hong Kong together could contribute to the development of biotechnology in China.

Chapter 27

Turn Your Dreams Into Reality: It Is Not Too Late to Capture the Marketplace

By

~ Chris Pak, Ph.D. ~
President & CEO
Molecular Targeting Technology, Inc., Malvern, Pennsylvania



***Chris Pak, Ph.D.**, is the president and chief executive officer of Molecular Targeting Technology, Inc., a privately held biotechnology company in Malvern, Pennsylvania. MTTI develops novel diagnostic imaging agents and has developed reagents that can be used to detect heart attacks, strokes and breast cancer. The company also developed the "Plug Seal" technology that aims to treat other cardiovascular diseases and cancer. Prior to MTTI, Pak was assistant director of research development at Centocor, Inc., also in Malvern, Pennsylvania. Pak holds seven patents in the diagnostic imaging and therapy field and has published more than 40 articles covering the use of antibodies for cancer and cardiovascular disease. Pak is president of Monte Jade Science and Technology Association of Greater Philadelphia and co-chairman of the Chinese Entrepreneur Association.*

Biotechnology generates novel diagnostics and therapeutics, more productive livestock and more nutritious crops, and innovative approaches to remedy pollution through biological methods. Biotechnology companies have proliferated, with 2,000 in existence today in the United States alone (**1997 Genetic Engineering News: Guides to Biotechnology Companies**, Mary Ann Liebert, Inc.). Numerous commercial products demonstrate the field's scientific and commercial potential. By 2007, the market for biotechnological products is estimated to reach $32 billion. This article uses the rise of Centocor, Inc., Malvern, PA, as a model for the successes and challenges that face the industry and illustrates strategies for entrepreneurs and scientists in the field. Hong Kong has a track record of rising from a fishing village into the "Pearl of the Orient" and of turning scars into stars. Hong Kong certainly has the vision and courage to ameliorate human suffering through this new industry, biotechnology.

The Race of the Hare and the Tortoise

As the master general Sun Tzu might advise, one can win the war before it starts by refusing to be intimidated. I was privileged to work for Centocor in the research and development from 1985 to 1993. Centocor is a major biotechnology company, founded in 1979 by scientists and businessmen with vision. The mission statement of Centocor states that it will strive to become a world leader in monoclonal antibody technology and to apply this technology to meet a variety of important medical needs. The projects I focused on were: (a) Imaging agents for detecting deep vein thrombosis, atherosclerotic plaque, acute myocardial infarct and cancer; (b) Therapeutic reagents such as ReoPro and Avakrine, and (c) In vitro diagnostic reagents. Centocor was actively promoting the in vitro diagnostic reagents in Japan. I was involved in promoting certain in vitro reagents in Mainland China together with a few of Centocor's executives.

During my tenure with this company, I witnessed the many ups and downs. In the early years, the company had little revenue and high expenses. The executives, however, attracted financial support from the financial and investment sectors. Most importantly, all the problems and setbacks did not discourage management from reaching their objectives. In 1991, during the clinical trials of two therapeutic reagents, Centoxin (anti-sepsis) and ReoPro (anti-coagulant), Xoma Corp., Berkeley, CA, sued Centocor for infringing their patent on sepsis antibodies. In the

subsequent year, the FDA refused to approve Centoxin after almost 10 years of preclinical and clinical testing. In 1992, Centocor's stock plummeted from $55 dollars to $5. That year, the company was forced to eliminate almost 1,000 employees. Despite tough times and numerous setbacks, the Centocor executives Dr. Hubert Schoemaker and David Holveck remained steadfast and focused. In 1992, Centocor announced partnerships with Eli Lilly, such that Lilly agreed to pay Centocor $100 million in advance for Centoxin and ReoPro, with royalty to be shared equally by the two companies. Centocor continued to pursue the ReoPro clinical trial. Several large pharmaceutical companies, such as Merck, had also embarked on developing similar products, but Centocor, not intimidated by these far larger competitors, pressed on. Finally, a year ago, the FDA approved ReoPro. The pharmaceutical giants are still doing clinical studies. Currently, ReoPro is used in 30-35% of all angioplasty procedures. Analysts estimated the sales of ReoPro at $250 million in 1997, and Centocor stock has, accordingly, returned to $50 (November 13, 1998).

Centocor and other successful biotechnology companies share the following characteristics:

- **Innovation.** The key question to ask before embarking on any new project is: Is this idea innovative enough to succeed in a highly competitive marketplace?

- **Customer Orientation.** For a product to succeed, one must understand the needs and wants of the marketplace: Is there a strong enough need for this product to more than recoup the costs of research and development?

- **Knowledgeable About Regulations.** Most successful corporations follow the rules and regulations as set forth by the FDA and other regulatory agencies.

- **Respect for Others' Territories.** Many companies divert resources into litigation. It is more productive to honor the patents and discoveries of others.

- **Staying Power.** Numerous biotechnology companies have excellent ideas, but many of them do not have the endurance to weather adversity.

In order to capture the marketplace in the 21st Century, qualities other than competitive determination are needed. I have termed them collectively as the "tortoise mentality."

The tortoise has benevolence, courage, direction, endurance and the right attitude. The tortoise did finally win the race in spite of the odds. Just so, the world may laugh at entrepreneurs with the tortoise mentality until they win the race. They are not intimidated by the huge resources of the pharmaceutical giants, and their courage, focus, and endurance carries them through difficulties that would daunt others. Also, benevolence helps win friends, inspire subordinates and avoid unnecessarily creating enemies. These talents help keep resources focused on the goal.

Attitude and Leadership: "Attitude Determines Altitude"

Christian author and motivational speaker Charles Swindoll once said, "Attitude is more important than facts, than the past, than the education, than money, than circumstances, than failures, than successes, than what other people think or say or do...I am convinced that life is 10% what happens to me and 90% how I react to it." If we examine Chinese History, one of the components that determined the successes or failures in a dynasty was leadership. The leader must have a vision, a character that includes credibility and integrity and the inner strength to weather storms and difficulties. I was fortunate to hear George Rathmann, the former CEO of Amgen, speak of his experiences recently. George turned Amgen into one of the leading biotechnology corporations in the world. George's attitude and leadership skills did play an essential role for the success of Amgen. His success might be attributed to his flexible attitude in dealing with the dynamic changes in biotechnology. He focused on the needs and wants of physicians and their patients and persevered in moving the product to the marketplace. Robert Morrison, chairman and CEO of Philip Morris, said of successful entrepreneurs, "They are very smart and have acquired broader and broader experiences through their careers. They have a passion to win and an ability to fire up the people who work for them." Indeed, successful executives like George Rathmann, Hubert Schoemaker, David Holveck, and Bob Swanson (one of the founders of Genentech, Inc., San Francisco) have demonstrated their flexibility, positive attitude, and remarkable leadership skills in keeping their corporations moving forward.

Benevolence

The genuine desire to develop the best medicine through innovation is a hallmark of these entrepreneurs. They are committed to providing better medicines, better nutrition and better health for mankind. They are dedicated to developing new, breakthrough products that enhance, improve and change the way we live. They are focused on fulfilling hope, solutions and health for all people. The Berkeley Study (**The Philadelphia Inquirer**, March 23, 1997) concluded, "The happiest and most satisfied adults scored very high in three areas: cognitive, reflective and affective qualities." Cognitive skills are those related to understanding; reflective skills are those involved in understanding issues from alternative perspectives; and affective skills are those related to feeling sympathy, empathy, and compassion for others. These are essential skills for group leadership, company management, and survival in the competitive marketplace. Roberto Goizueta, the former chairman and CEO of Coca-Cola, reiterated the importance of this quality, "Business now shares in much of the responsibility for our global quality of life. Successful companies will handle this heightened sense of responsibility quite naturally, if not always immediately. I say this not because successful business leaders are altruistic at heart. I can assure you, many are not." (*"Robert Goizueta in his Own Words,"* **The Wall Street Journal**, October 20, 1997). The world would be a better place if we are armed with the unique quality of benevolence.

Courage

Strength is described in the poem of Rabindranath Tagore, a Nobel prize-winning author who had associations with eminent figures such as Gandhi, Nehru, and Albert Einstein, as the state in which "...the mind is without fear" (*"Tagore and His India,"* **The New York Review of Books**, June 26, 1997). Where the mind is without fear, and the head is held high; where knowledge is free; where the world has not been broken up into fragments by narrow domestic walls..." The courage to proceed despite turbulent times is one of the key characteristics that a successful entrepreneur should possess.

I started Molecular Targeting Technology, Inc. (MTTI), Malvern, PA, in 1993. My company is in the forefront for developing diagnostic reagents for rapid detection of cardiovascular disease. I believe that MTTI's lead product, AMISCAN™ will provide early diagnosis of heart attack by providing early rule-in and rule-out diagnosis of acute myocardial infarct within the first few hours after the onset of chest pain. MTTI's role in the therapeutic arena is targeted at the preservation and salvage of the myocardium. A radical technology of cell repair will be MTTI's leading therapeutic reagent. This cell repair technology is applicable to the salvage of neurons in brain injuries. Similarly, it is envisioned that the same procedure is also applicable in the therapeutic intervention of cancer. Currently, MTTI is actively seeking partners in Asia.

Before I started my company, a friend shared with me the story of Rose Kennedy, matriarch of the Kennedy political clan. In the worst moment of Kennedy's life, following the murder of her son, a reporter approached her and asked "Mrs. Kennedy, tell us how you handle the tough times in your life." Kennedy replied, "The wind was so strong last night and almost destroyed the nest of the bird. In the morning the bird sang. Why not me?" (*"The Sorrow and the Strength. Rose Kennedy,"* by Brad Darrach. **Life**, March 1995, Vol. 18, p. 52). Kennedy displayed resiliency during a truly terrible time.

It is not easy to start a biotechnology company in the U.S. New companies are often limited in resources and other support. In fall 1993, a venture capitalist from New York approached MTTI but did not meet the requirements of our company. Despite the temptation to accede to his terms, we turned down his offer. We were fortunate to gain subsequent financial support from the Ben Franklin Center of Southeastern Pennsylvania and the federal government. In January 1997, we won the Ben Franklin Emerging Business Award in the "Most Innovative Product" category. Kennedy's story often reminded me of the need to endure difficult times without compromising standards.

Direction

Life without purpose is like a ship adrift. I am most proud of having had the opportunity to witness the rise of numerous biotechnology companies. These companies, by virtue of their values, practices and success, have made a major impact in medicine, agriculture and the environment. I am also grateful to the successful entrepreneurs who were willing to share their problems, setbacks and experiences with me. Successful, enduring and visionary companies have a clear sense of direction. Most successful companies display a remarkable resiliency and ability

to bounce back from adversity. Their sense of direction guided them when it was too dark to see the way.

Endurance

The enthusiasm surrounding biotechnology has resulted in the formation of close to 2000 new companies. The proliferation of new corporations and the successful launching of commercial products have marked advances in this field. However, only a small fraction of new companies have escaped acquisition, merger or failure. The key strength that sustained the survivors of competitive pressures has been their staying power. Executives certainly need to have a clear picture of how long they can survive on contributed capital before a revenue stream kicks in.

Eric Pierce, staff writer of **BioCentury**, indicated the magnitude of loss that can occur instantly on product setbacks. In the article, *"When Lightning Strikes,"* (September 1997). Pierce compiled 32 cases over three years of the sell-off of biotech stocks following disappointing clinical events. The stocks fell an average of 44%. A company needs to be equipped both financially and emotionally for the major decisions of development and growth.

A bird's eye view for Hong Kong to capture the biotechnology marketplace

Empower more scientists and scholars to become entrepreneurs

Hong Kong is a unique city; it is a hotbed of countless successful business ventures. One of the key factors that contributes to the success of Hong Kong is the people. Hong Kong people have a natural instinct for business. Many of them do not receive formal training. Often, these business skills can match or even exceed those of the best MBA students from Wharton, Harvard, or the University of Chicago. These natural instincts resemble those of the griffin. A griffin is a mythical beast with the head and wings of an eagle and the body and legs of a lion. The griffins found gold hidden in remote mountains and built their nests of solid gold. Their instincts let them know where buried treasures lay, and they zealously guarded those treasures until their rightful owners were identified. Therefore, the leaders in the biotechnology field need to empower more scientists and scholars to become entrepreneurs in this exciting industry.

Provide a blueprint for success in biotechnology

I am impressed with the speed and efficiency of Hong Kong businessmen. Their successes can be attributed to (i) personal connections, (ii) product quality, (iii) reasonable pricing, (iv) goal orientation, (v) responsiveness to the marketplace, (vi) preparation, and (vii) flexibility. Product lifespan is often short, and marketplace offerings turn over quickly. In biotechnology, development take so long that failures are prohibitively expensive. The biotechnology industry is compatible with the character of those Asian businessmen who share the vision and understanding of this industry. One essential message that needs to be learned is that there is a need for a product longevity blueprint.

In 1932, French car designer Ettore Bugatti created his masterwork: Type 55, widely rated the most beautiful, long-lasting, and exciting racing car ever made. Bugatti's successes are due to his willingness to combine the best components he could design with the best parts used by his rivals. In creating a biotechnology corporation, the founders should equip themselves with Bugatti's mentality. The founders should challenge themselves with the following questions: What products/services are we producing? How would our products excel compared to current products/services? How do we plan to compete in the next five years, next 10 years, etc.?

Differentiate significant from insignificant

The generosity and kindness of many Hong Kong people is indeed admirable. They often arm themselves with a very powerful philosophy of giving and sharing. In **Tao Te Ching**, author Lao Tzu stated, "The more he does for others, the more he has, the more he gives to others, the greater his abundance." However, biotechnology is a strange, new industry to many. Leaders need to educate the public about the potential of this technology. Many Hong Kong people are giving and tenderhearted people. These unique characteristics may be attributed to the suffering they have witnessed or experienced. The majority of successful Hong Kong people started their businesses and enterprises without much family or other support. Most philanthropists have a vision of creating and contributing something significant in life. In **Discovering the Laws of Life** (New York: Continnum, 1994, p. 165), author John Marks Templeton asserts, "To be great means to move beyond the possession of wealth or fame. It means to

create, to become more helpful than you imagined you could be. The price of this greatness is responsibility for your response to life, for the beauty of your thoughts every minute and every hour of every day, for knowing that your response is the very power that changes your life, perhaps greatly." Therefore, we need to encourage these visionaries and let them share our holistic view regarding the enormous potential of this field.

Promote and preserve core ethical values

Hong Kong is one of the engines that will move China into the competitive global marketplace of the 21st Century. Hong Kong will play an essential leadership role in promoting and preserving the core values. One of the major focuses of the biotechnology industry is to save lives, cure disease, and relieve human suffering. However, life is not merely the external and physical process of being but also a social, emotional and spiritual process. The philosopher Masood Ghaznav emphasized that "Intellectual exercise alone cannot know the truth. A spiritual element must be there. There has to be faith. Wisdom has to be seeking something of value, which promotes a good life, and justice." (**The Philadelphia Inquirer**, March 23, 1997, p. H6). The core values of the inner process of being are expressed as credibility and integrity in the global arena. If the organization is guided only by profit and neglects the core values, the institution usually stumbles.

Embrace a collaborative approach

I was brought up in Hong Kong, which was entirely different from my later experience in the U.S. While I was growing up, there were limited opportunities for high school students to pursue higher learning, and a lack of initiatives to promote and guide students. However, limited resources always stimulate new thinking, from which emerge new possibilities and opportunities. Instead of trying to claim every territory in our vicinity, a key strength is to team up with leading figures. Collaborating with experts with different insights and expertise will often perfect our approach in dealing with specific problems. With the advent of rapid information flow, the Internet would be one powerful vehicle with which to enhance this type of work. Furthermore, one can promote collaboration in achieving the goal through workshops, conferences and specific taskforces.

To summarize, here is a roadmap Hong Kong authorities can use to capture the biotechnology marketplace in the new millennium.

1. Educate high school, college and postgraduate students and the public regarding the opportunities, problems and promises in biotechnology. Invite successful entrepreneurs to show them how to take an idea all the way to the marketplace.

2. Establish a foundation to oversee the vision and goals, assign research and development grants, and monitor and report progress. The foundation should have a clear picture and thorough and systematic plan for advancing the various projects.

3. Encourage more philanthropists to participate in the vision and mission of the foundation, hence more new products will be able to reach the marketplace with abundant capital.

4. Identify the needs and wants in the various fields, from agriculture to medicine.

5. Empower and promote partnerships between research institutions and companies.

6. Encourage entrepreneurs to take their ideas to the marketplace.

7. Emphasize the core values system in life in addition to developing the best product.

About the Publisher

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141-07 20th Ave., Suite 604,
Whitestone, NY 11357, U.S.A.
Tel: (718) 357-8836 Fax: (718) 357-8552
Email: kitchanlaw@aol.com

About the Editor

Albert Wai-Kit Chan, Ph.D., J.D., is a partner at Cooper & Dunham LLP, an intellectual property law firm in New York City. Chan handles all areas of intellectual property law (including patents, trademarks, copyrights, and trade secrets), and his specialty is biotechnology patents. He is well-versed in all aspects of prosecution and litigation and is experienced in licensing, technology transfer and the evaluation of intellectual property portfolios.

Chan is founder of United States-China Intellectual Property Institute and adjunct professor of law at The City University of New York Law School at Queens College, both in Flushing, New York. He teaches classes on intellectual property law, patent law and technology transfer.

Born and raised in Hong Kong, Chan graduated from The Chinese University of Hong Kong with a B.Sc. degree in biology. He was awarded his Ph.D. in virology by Baylor College of Medicine in Houston, Texas, and completed his postdoctoral training at Cold Spring Harbor Laboratory in New York as an American Cancer Society postdoctoral fellow. Chan received his J.D. degree from Columbia University School of Law in New York.

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