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Commentary

Clinical Therapeutics in Hong Kong

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ABSTRACT

Hong Kong is a compact territory in Southern China that enjoys a high degree of autonomy. Despite its dense population and uneven wealth distribution, infant mortality is low and life expectancy is long. The health service is more hospital and clinic based than community based. This seems cost-effective while professional standards are high and rigorously maintained. Drug registration follows American and European requirements. Hong Kong is a part of the Pharmaceutical Inspection Cooperation Scheme, which brings a high standard of drug regulation. Hong Kong is a good choice for clinical trials because the subjects are Chinese and protocols in English do not need to be translated. There are also 2 well-established clinical trials centers in university hospitals that also run Phase I and clinical pharmacology studies. (*Clin Ther*. 2019;41:592–597)

Keywords: Clinical trials, Hong Kong, Pharmaceutical inspection cooperation scheme, Therapeutics.

INTRODUCTION

Many people have heard of Hong Kong, but few can point it out on a map, because it is just a tiny dot in the southern part of China. Yet, its population of 7.3 million is larger than those of half the countries in the world. Its volume of trade ranks seventh, largely because it is a free trade zone, with virtually no restrictions on the flow of goods and capital, no customs duties, and no sales tax.

Most of the population are Chinese, but there are sizeable American, Australian, British, Canadian, French, German, Japanese and other Asian communities, as evidenced by international schools for each of these communities. Most Hong Kong Chinese speak Cantonese, while English is also an official language and is the language of business and higher education.

RELATIONSHIP WITH MAINLAND CHINA

Hong Kong was ceded to Britain in 1841 after the "opium wars," which China sees as shameful. After a decade of negotiations, Hong Kong went back to Chinese sovereignty in 1997, with the guarantee that the economic system and the freedoms enjoyed by Hong Kong people would not be altered for 50 years.

The "one country, two systems" concept, invented by the former Chinese leader Deng Xiaoping, requires some explanation. Hong Kong is not a country but a "special administrative region." However, it is allowed to join international organizations, such as the World Trade Organization or the Olympics, as a separate member. It has its own currency and its own laws. It is only in diplomacy and defense where the central government in Beijing takes full charge. Hong Kong has the advantage of not spending money on defense and not being involved in regional or international conflicts.

Nonetheless, there are strains in the relationship between Hong Kong and mainland China. For instance, some citizens in Hong Kong want prompt electoral reform, while the central government wants it to be gradual. The dilemma Hong Kong faces is the same faced by the international community. China has a powerful economy and a large market; closer trade ties are inevitable.

THE HEALTH SYSTEM IN HONG KONG

Hong Kong now enjoys the longest life expectancy in the world, surpassing that of Japan. It also has one

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of the lowest infant mortality rates. For an urbanized population living in high density, this is somewhat surprising. Some credit must go to the health system. While primary care is mostly carried out by private practitioners, most public hospitals are run by the Hong Kong Hospital Authority and are highly subsidized. Remarkably, this is sustained with a maximum income tax of 17% and no sales tax. Health expenditure forms only around 6% of the gross domestic product in Hong Kong, compared to around 10% in European countries.[1]

Although Hong Kong's gross domestic product per capita based on purchasing power parity is slightly higher than that of the United States,[2] the wealth is not evenly distributed. While 1 in 7 of the population is a millionaire (US $), 0.3 million are on social welfare.[3] Only a small section of the population can afford private health care and the high-priced treatments, so the majority of patients flock to the public hospitals.

PROFESSIONAL STANDARDS IN HONG KONG

The standards of the medical profession in Hong Kong are high. The 2 medical schools are in universities that are ranked within the world's top hundred. Notable achievements have included the identification of the coronaviruses,[4] eradication of *Helicobacter*,[5] and noninvasive prenatal testing.[6] The 2 medical schools expect applicants to be in the top 1% in the Hong Kong Diploma of Secondary Education, International Baccalaureate, and the British General Certificate of Education Advanced Levels. This stands in great contrast to mainland China, where the most academically gifted students do not usually choose medicine as a profession. While the admissions policies of the Hong Kong medical schools are debatable, there is no doubt that many of the brightest in Hong Kong are in the medical profession.

The medical graduates in Hong Kong also have a very international outlook from the outset. The medical curriculum is taught in English, and during the undergraduate years, students often go on overseas electives. During postgraduate specialist training, trainees receive full pay to spend several months at an overseas center of excellence. Most specialists in Hong Kong are members or fellows of British, Australian, or Canadian colleges, or have American board certification, in addition to their Hong Kong–based qualifications. Doctors trained outside of Hong Kong are allowed to practice in Hong Kong after passing a licensing examination and serving a period of hospital internship.

Professional standards are maintained by the Medical Council of Hong Kong, and for medical specialties, the respective colleges in the Hong Kong Academy of Medicine. The Medical Council, like its counterparts elsewhere, ensures that physicians are fit to practice and holds quasijudicial disciplinary hearings. The colleges define specialist training requirements, hold examinations, and oversee continuing medical education programs. A self-regulated profession that defines its own standards and keeps a registry of its members is the norm in most developed countries, but in mainland China, such systems are not yet in place.

DRUG REGISTRATION IN HONG KONG

In Hong Kong, medicines have to be registered with the Pharmacy and Poisons (Registration of Pharmaceutical Products and Substances: Certification of Clinical Trial/Medicinal Test) Committee before they can be marketed.[7] This is true both for Western medicines and traditional Chinese medicines, albeit that they are regulated under separate ordinances. For registration, the Department of Health Drug Office focuses on the quality, tolerability, and efficacy of a product, which means that the manufacturer or importer must provide a comprehensive dossier on the formulation, specification, laboratory analysis, and manufacturing infrastructure. In addition, the application would also include an evaluation report signed by an independent expert, any applicable EU Risk Management Plan or US Food and Drug Administration (FDA) Risk Evaluation and Mitigation Strategy, and the proposed packaging and insert. In most cases, there is no requirement for local clinical studies to be conducted to prove efficacy or tolerability. Instead, the Registration of Pharmaceutical Products and Substances Committee, under the Pharmacy and Poisons Committee, will look at information from the countries in which the drug has been registered. Usually prior registration in 2 countries, such as the United States, EU member states, Switzerland, Australia, Canada, or Japan, is taken as evidence that the drug has reached acceptable standards of efficacy and tolerability. Notably, prior registration in mainland China does not mean automatic registration in Hong Kong.

Equally, prior registration in the United States or the EU alone does not automatically guarantee approval in Hong Kong. There are many examples in which the US FDA and EMA reached different decisions on the approval of new drugs. For some cancer drugs, the US FDA may give accelerated approval based on the findings from early-phase trials. The laws of Hong Kong make it difficult to order the withdrawal of a drug from the market based on a lack of efficacy, and so unless considered harmful, a drug with little or no efficacy can remain registered. Therefore, in examining new drug applications, the Registration of Pharmaceutical Products and Substances Committee in Hong Kong looks carefully at the clinical trial evidence on efficacy. A new drug needs to be shown as more efficacious than placebo only; it does not need to be more efficacious than existing drugs. The cost of a new drug, however expensive, or its cost-effectiveness is never a consideration in the approval process. Applications for new sources of generic drugs go through a quicker approval process, but biosimilar drugs are treated as new drugs.

The proposed prescribing information and package inserts of prescription drugs must be in English; the presence of other languages, including Chinese, is optional. The committee scrutinizes the sample products carefully to ensure that key information, such as the drug name, dose, and expiry date, is clearly shown, and that there is sufficient differentiation between products to avoid dispensing errors. In general, large lettering that stands out clearly is preferred. The committee often asks manufacturers to enlarge the text or to use different colors on the packaging, since some manufacturers like to have a uniform look for all of their products.

Since 2016, the Pharmacy and Poisons Committee of Hong Kong has been a part of the Pharmaceutical Inspection Cooperation Scheme (PIC/S), an international organization consisting of pharmaceutical inspection authorities around the world.[8] The PIC/S shares out the task of inspecting manufacturing facilities to ensure their compliance with Good Manufacturing Practices (GMPs). Medicines manufactured in Hong Kong have to comply with this set of standards. The developers of medicines manufactured outside of Hong Kong must provide evidence of compliance with PIC/S GMP standards. Otherwise, registration or renewal of registration will not be approved.

HISTORY OF CLINICAL PHARMACOLOGY IN HONG KONG

The discipline of clinical pharmacology was first introduced into the 2 medical schools in Hong Kong large on the recommendation of the eminent British clinical pharmacologist, Sir John Dollery. Cyrus Kumana and David Davis were the first appointees in clinical pharmacology at the University of Hong Kong and the Chinese University of Hong Kong, respectively. Later, other clinical pharmacologists joined. The clinical pharmacologists in Hong Kong are medically qualified and work as hospital physicians. In addition to clinical work and teaching, they also sit on drugs and therapeutics committees, and advisory committees in the Hospital Authority and Hong Kong Special Administrative Region Government. Notable innovations include a set of guidelines on antibiotics and "immediate concurrent feedback" to discourage the unnecessary use of broad-spectrum antibiotics, the reformulation of arsenic trioxide for acute promyelocytic leukemia,[9] a Poison Treatment Centre, and a Centre for Food and Drug Safety. Because most of the population are ethnic Chinese, pharmacogenetic testing is feasible. Genetic testing before the initiation of treatment with carbamazepine and allopurinol can now be ordered routinely.[10] The genetic basis for the high prevalence of statin-induced myopathy has also been elucidated.[11]

CLINICAL TRIALS CENTERS IN HONG KONG

Hong Kong is a good place to conduct clinical trials because of the advanced medical care system, computerized medical records, a pool of investigators with international reputations, and the use of English in all medical documents. High-quality clinical trials can be conducted without protocol translation. Hospitals in Hong Kong are therefore suitable sites for multinational clinical trials, especially if China is a potential market for a drug.

The Clinical Trials Centre at the University of Hong Kong (HKU-CTC) was established in 1998, initially to offer administrative support for clinical trials, but has since grown to a full-fledged organization with some 60 full-time staff members, acting as 1-stop center to facilitate all sorts of clinical trials.[12] The contract research–organization and site management–organization services offered include protocol development, budgeting, contract

management, ethical submission, project management, trial monitoring, drug management, biological specimen management, data management, and statistical analysis. The business development team can liaise with industrial sponsors. The HKU-CTC is also a founding member of the International Clinical Trial Center Network, and has links with other top-tier clinical trials centers globally, such as those at Harvard University, Cambridge University, the University of Zurich, and Kyoto University. In the past 20 years, the HKU-CTC has handled >1200 trials. This is a remarkable number for a center that is self-sustaining and receives only nominal funding from the university.

The Chinese University of Hong Kong has a Clinical Research Management Office, which has a strong record of conducting randomized controlled trials, as well as bioavailability and bioequivalence studies.

With government seed money, 2 Phase I clinical trials centers, each with 24 beds, were opened in the 2 university hospitals. Studies enroll either healthy

Table. Comparison of drug registration and clinical trials in Hong Kong and mainland China.

	Hong Kong	Mainland China
New drug registration	Takes reference from US FDA and EMA approvals. Local studies not required.	Local studies sometimes required
Regulatory review and approval for drug clinical trials	Parallel review by the HK DOH and research ethics committees	Implied approval if no objection/opinion is received from the CDE under NMPA within 60 d from the day of receipt of an application. Research ethics committees usually start research ethics review after approval by CDE.
Regulation for collection of human genetic materials/data in clinical trials	Not applicable	Review and approval by Human Genetic Resources Administration is required
Trial documents	Protocols and trial documents in English (except only for informed consent documents and subject-administered documents)	Protocols and trial documents in Chinese
Clinical trial institutions	Drug clinical trials mostly conducted in the 2 teaching hospitals with well-established clinical trials centers. About 10 other large public hospitals and a few private hospitals and private clinics also participate in clinical trials.	Over 700 drug clinical trial institutions registered with NMPA. Standards of study sites vary.

CDE = Center for Drug Evaluation; EMA = European Medicines Agency; FDA = Food and Drug Administration; HK DOH = Drug Office of Hong Kong Department of Health; NMPA = National Medical Products Administration (formerly, China Food and Drug Administration [CFDA]).

subjects or patients. Most Phase I trials done in Hong Kong have been in oncology, hepatology, and rheumatology. The 2 Phase I clinical trials centers in Hong Kong are unique in that they have received accreditation from the National Medical Products Administration (formerly, the China Food and Drug Administration [CFDA]), meaning that data from trials done in these 2 centers may be used for drug registration purposes in China.

To encourage involvement in clinical trials, the principles of Good Clinical Practice and the practicalities of clinical study operation are taught in training programs. For example, HKU-CTC's unique program, PRACTISE (Professional Research Accreditation for Clinical Trials Investigative Site Executives), runs not only locally but also in mainland China and internationally. It is particularly noteworthy that these skills and knowledge are taken to places "off the radar" of the large multinationals, in remote parts of China, or in countries like Vietnam, the United Arab Emirates, and Egypt. HKU-CTC is also a part of TREEE (the Training and Resources in Research Ethics Evaluation program)—an international, nonprofit e-learning platform initiated in Switzerland for training and learning ethics in human research and Good Clinical Practice principles.

DRUG REGISTRATION IN MAINLAND CHINA

There have been rapid and enormous changes in the regulation of drug registration in mainland China in recent years. Prior to 2015, some of the data submitted for drug registration were suspect. In 2015, the then-CFDA issued a notice requiring all companies that had submitted drug marketing approval applications to reexamine their own clinical trials data. If they were not satisfied with the accuracy of all their data, they were allowed to withdraw their applications. This created a big storm, and 65% of submitted applications were withdrawn by June 2017. People are now looking for clinical trials centers that can conduct high-quality clinical trials and deliver reliable data.

There have been profound changes in the rules in China regarding drug registration. Previously, the CFDA required trials be conducted in mainland China before a new drug was registered. It could be a long and expensive process to get a novel drug registered and made available in mainland China. This might have been appropriate at a time when clinical trials were done primarily in the United States and Europe, in white study subjects, but had the disadvantage of delaying the introduction of new drugs for several years. When there are many new life-prolonging cancer drugs being introduced, this kind of delay is unsatisfactory. Moreover, many multicenter trials now enroll patients of Chinese ethnicity, or there may be study sites in mainland China. The need to repeat studies from Phases I to III is much reduced nowadays. Since June 2017, China has been a part of the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. New regulations are being introduced and now overseas-trials data are acceptable for registration purposes in mainland China. For example, a new measure was announced in May 2018 to accelerate the registration of drugs for life-threatening diseases through a prioritized evaluation scheme.[13] The scope of local studies is now reduced, although bridging studies, usually on pharmacokinetics, remain necessary because of known differences in body size and composition, and drug-metabolizing enzymes in the Chinese population. Hong Kong, as a part of China, still has a significant role because trial initiation is quicker, and no translation is needed for the protocol or the other trial documents and records (Table).

CONCLUSIONS

There is something paradoxical about Hong Kong's dense population and yet low infant mortality and long life expectancy. Its free trade zone, unfettered economy, and low taxation combine to create a strong economy. The uneven wealth distribution is ameliorated to some extent by an almost free and affordable education system and health service. The health service leans heavily toward a hospital- and clinic-based rather than a community-based service. It seems to be a cost-effective setup. Standards are maintained by professional organizations, and professionals qualified overseas usually have to go through a licensing examination. Hong Kong is a good choice for clinical trials because of its solid track record in international clinical trials and its robust health care system, where the subjects are Chinese and protocols in English do not need to be translated.

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CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest with regard to the content of this article. Both authors contributed equally to the writing of this manuscript.

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