Clinical Therapeutics in Hong Kong

[1]Bernard M Y CHEUNG, PhD, FRCP

[2]Henry K C YAU, BSc, MBA

[1]Department of Medicine

[2]Clinical Trials Centre

The University of Hong Kong, Hong Kong

Correspondence:

Prof. Bernard MY Cheung,

University Department of Medicine,

Queen Mary Hospital,

102 Pokfulam Road, Hong Kong

Email: mycheung@hku.hk

Tel: +85222554347 Fax: +85228186474

Abstract

Hong Kong is a compact territory in Southern China enjoying a high degree of autonomy. Despite its high population density and unequal 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 part of the Pharmaceutical Inspection Co-operation 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 two well-established clinical trials centres in university hospitals that also run phase 1 and clinical pharmacology studies.

Introduction

Many people have heard of Hong Kong, but few can point it out on the map, because it is just a tiny dot in the southern part of China. Yet, its population of 7.3 million is larger than half the countries in the world. Its volume of trade ranks seventh, largely because it is a free port, 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 fifty 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 organisations, such as the World Trade Organisation or the Olympics, as a separate member. It has its own currency and own laws. It is only in diplomacy and defence where the central government in Beijing

takes full charge. Hong Kong has the advantage of not spending money on defence and not being involved in regional or international conflicts.

Nevertheless, 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 Japan. It also has one 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 subsidised. Miraculously, this is sustained with a maximum income tax of 17% and no sales tax. Health expenditure forms only around 6% of the GDP in Hong Kong, compared to around 10% in European countries.[1]

Although Hong Kong's GDP per capita based on purchasing power parity is slightly higher than that of the US,[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 healthcare 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 two medical schools are in universities that are ranked within the world's top hundred. Notable achievements included the identification of the coronavirus,[4] eradication of helicobacter[5] and non-invasive prenatal testing.[6] The two 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 centre 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 qualifications. Doctors trained outside Hong Kong are allowed to practise in Hong Kong after passing a licensing examination and serving a period of hospital internship.

Professional standards are maintained by the Hong Kong Medical Council and for the medical specialties, the respective Colleges in the Hong Kong Academy of Medicine. The Medical Council, like its counterpart elsewhere, ensures that doctors are fit to practise and holds quasi-judicial disciplinary hearings. The Colleges define specialist training requirements, hold examinations and oversee continuous medical education programmes. A self-regulating profession defining its own standards and keeping a register 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 Board before they can be marketed.[7] This is true both for western medicines and Chinese medicines, albeit that they are regulated under separate ordinances. For registration, the Drug Office focuses on the product's quality, safety and efficacy. This means that the manufacturer or importer has to 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 European Union Risk Management Plan (EU-RMP) or US Food and Drug Administration (FDA) Risk Evaluation and Mitigation Strategy (REMS), and the proposed package and insert. In most cases, there is no requirement for local clinical studies to be conducted to prove efficacy or safety. Instead, the Registration Pharmaceutical Products and Substances Committee, under the Pharmacy and Poisons Board, will look at the countries for which the drug has been registered. Usually prior registration in two countries such as USA, EU member states, Switzerland, Australia, Canada or Japan, is taken as evidence that the drug has reached an acceptable standard of efficacy and safety. Notably, prior registration in Mainland China does not mean automatic registration in Hong Kong.

Equally, prior registration in USA or EU alone does not automatically guarantee approval in Hong Kong. There are many examples where the USFDA and EMA reached different decisions on the approval of new drugs. For some cancer drugs, USFDA may give early approval based on early phase trials. The laws of Hong Kong make it difficult to order

withdrawal of a drug based on lack of efficacy and so unless the drug is harmful, a drug with little or no efficacy can remain registered. Therefore, in examining new drug applications, the drug registration committee in Hong Kong looks at the clinical trial evidence on efficacy carefully. The efficacy of the new drug only needs to be shown to be superior to placebo. It does not need to be better than existing drugs. The cost of the 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 process, but biosimilar drugs are treated like new drugs.

Prescription drugs must display the required information 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 letters standing out clearly are preferred. The Committee often asks manufacturers to enlarge the text or to use different colours on the packaging, since some manufacturers like to have a uniform look for all their products.

Since 2016, the Pharmacy and Poisons Board of Hong Kong has joined the Pharmaceutical Inspection Co-operation Scheme (PIC/S), which is an international organization consisting of pharmaceutical inspection authorities round the world.[8] This shares out the task of inspecting manufacturing facilities to ensure their compliance with Good Manufacturing Practice (GMP). Medicines manufactured in Hong Kong have to comply with this set of standards. Medicines manufactured outside Hong Kong have to provide evidence that the manufacturers comply 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 to the two medical schools in Hong Kong, largely on the recommendation of Sir John Dollery. Cyrus Kumana and David Davis were the first appointees at the University of Hong Kong and 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. Besides clinical work and teaching, they also sit on drugs and therapeutics committees, and advisory committees in the Hospital Authority and Government. Notable innovations include a set of antibiotic guidelines and Immediate Concurrent Feedback to discourage the unnecessary use of broad spectrum antibiotics, the reformulation of arsenic trioxide for acute promyelocytic leukaemia,[9] a Poisons 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 starting carbamazepine and allopurinol can now be ordered routinely.[10] The genetic basis for the high incidence of statin-induced myopathy has also been elucidated.[11]

Clinical trials centres in Hong Kong

Hong Kong is a good place to conduct clinical trials because of the advanced medical care system, computerised 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 can therefore be suitable sites for multinational clinical trials, especially if China is a potential market for the 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 have since grown to a

full-fledged organization with some sixty full-time staff members, acting as one-stop centre to facilitate all sorts of clinical trials.[12] The contract research organization and site management organisation 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. It is also a founding member of the International Clinical Trial Center Network (ICN), and has links with other top-tier clinical trials centers globally such as those at Harvard, Cambridge, Zurich and Kyoto. In the last 20 years, the Centre has handled more than 1200 trials. This is a remarkable number for a centre that is self-sustaining and receiving only nominal funding from the university.

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

With government seeding money, two phase 1 clinical trials centres were opened in the two university hospitals, each has 24 beds. Studies are on either human volunteers or patients. Currently, most of the phase 1 trials done in Hong Kong have been on oncology, hepatology and rheumatology. The two phase 1 clinical trials centres in Hong Kong are unique in that they have received accreditation from the China Food and Drug Administration (CFDA, recently renamed National Medical Products Administration (NMPA)). This means that data from trials done in these two centres may be used for drug registration purpose in China.

To encourage involvement in clinical trials, Good Clinical Practice (GCP) and the practicalities of clinical study operation are taught in training programmes. For example,

HKU-CTC's unique programme, named 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 knowledge and skills are taken to places off the radar of the large multinationals, in remote parts of China and countries like Vietnam, UAE and Egypt. HKU-CTC is also part of TRREE (Training and Resources in Research Ethics Evaluation) – an international, non-profit e-learning platform initiated from Switzerland for training and learning human research ethics and GCP.

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 re-examine their own clinical trials data. If they were not satisfied with 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 trial centres 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, CFDA required trials done in Mainland China before a new drug is registered. It could be a long and expensive process to get a novel drug registered and becoming available in Mainland China. This might be appropriate at a time when clinical trials were done primarily in the US and Europe, on Caucasian study subjects, but suffered from 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 multicentred trials now enroll patients of Chinese ethnicity, or there may be study sites in Mainland China. The need to repeat studies from phase 1 to phase 3 is much reduced nowadays. Since June 2017, China is part of the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). 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 prioritised 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 metabolising enzymes in Chinese. Hong Kong, as part of China, still has a significant role to play because it is quicker to have trial initiation, and no translation is needed for the protocol and all the other trial documents and records.

Conclusions

There is something paradoxical about Hong Kong's high population density and yet low infant mortality and long life expectancy. Free port, unfettered economy and low taxation combine to create a strong economy. The unequal wealth distribution is ameliorated to some extent by an almost free and affordable educational system and health service. The health service leans heavily towards a hospital and clinic based rather than a community-based service. It seems to be a cost-effective set-up. Standards are maintained by professional organisations 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 records in international clinical trials and robust healthcare system, where the subjects are Chinese and protocols in English do not need to be translated.

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Table 1

Comparison of drug registration and clinical trials in Hong Kong and Mainland China

	Hong Kong	Mainland China
New Drug Registration	Takes reference from USFDA and EMA approvals. Local studies not required.	Local studies sometimes required
Regulatory Review and Approval for Drug Clinical Trials	Parallel review by the Drug Office of Hong Kong Department of Health (HK DOH) and research ethics committees	Implied approval if no objection/opinion is received from the Center for Drug Evaluation (CDE) under NMPA within 60 days 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 two teaching hospitals with well-established clinical trials centres. About ten 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.

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