

Clinical Drug Evaluation: The Regulatory Perspectives

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Abstract

Introduction: This paper presents the regulatory perspectives of the clinical drug evaluation process and the role of the newly established Centre for Drug Evaluation in Singapore in this process. It describes the major drug evaluation systems in the developed countries and their similarities and differences. **Methods:** The issues related to the benefits and risks assessments of new drugs are discussed, with examples, against the backdrop of the various drug evaluation systems and medical practices. **Results:** The implications of Singapore's Medicines (Clinical Trial) (Amendment) Regulations 1998 and the Singapore Good Clinical Practice Guidelines published by the Ministry of Health in 1998 were discussed. The future development of international harmonisation in the context of the International Conference on Harmonisation was explored. **Conclusions:** Building the capability for the evaluation of new drugs is essential as part of the regulatory infrastructure for a knowledge-based economy in Singapore. To conduct better clinical trials, investigators should develop a good understanding of the clinical drug evaluation process and an appreciation of the regulatory angle.

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Introduction

Evaluating new drugs for marketing approval is a highly specialised and knowledge-intensive activity. This is especially so if the intention is to conduct quality, safety and clinical evaluations of new drugs that have not been approved elsewhere. Such capability is available only in developed countries.

Creating a Centre for Drug Evaluation (CDE) in Singapore is an important step taken by the Singapore Government to build up this capability as part of the necessary regulatory infrastructure to support healthcare development, drug R&D and biotech industry development in Singapore. The need to build up this critical regulatory capability to evaluate new drugs has been shown by studies conducted in 1996 to 1997 by a task force comprising members from Ministry of Health (MOH), National Science & Technology Board (NSTB), Economic Development Board (EDB) and the National University of Singapore (NUS). These studies indicated clearly that such a capability is necessary for the next stage of Singapore's economic, medical and scientific development and should be established within MOH's pharmaceutical regulatory framework.

Mission

The mission is therefore to develop the capability in Singapore to evaluate new drug submissions which have

not yet been approved elsewhere. Whether this can be done at this stage of Singapore's development, and if so, how to go about it, are the crucial questions to ask. These are important considerations because this is a completely new area of scientific and medical expertise to be developed and a major extension from the existing system of drug registration. Is this mission impossible? Can we do it in Singapore?

Existing System

The existing system of drug registration relies heavily on the Free Sale Certificate (FSC) or Certificate for Pharmaceutical Products (CPP) issued by regulatory authorities in major developed countries such as the Food & Drug Administration of USA (FDA), Medicines Control Agency of UK (MCA) and Therapeutic Goods Administration of Australia (TGA). A FSC from these authorities serve as the primary assurance of the quality, safety and efficacy of the new drugs.

Under this system, sponsors, typically research-based pharmaceutical companies, are required to submit to the Ministry's Pharmaceutical Department (PD) a FSC together with a summary package which contains summaries of the product characteristics and information, as well as published papers on the new drug and their summaries. This summary package usually comprises 200 to 300 pages. This is sent

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by PD to 2 senior hospital clinicians for evaluation and their reports and recommendations are then submitted by PD to the Ministry's Medicines Advisory Committee (MAC) for advice as to whether the drug product can be approved for marketing in Singapore. This process usually takes 9 months to a year depending on the nature of the product and whether local medical practice issues are involved.

Such a system has served Singapore well for the last 12 years since Drug Registration was introduced in 1987 under the Medicines Act.¹ However, with the higher level of pharmaceutical and biotech R&D activities in Singapore, and with the national thrust to develop Singapore as a regional medical hub and a regional hub for the life sciences industry, the need to further expand and build up the pharmaceutical regulatory infrastructure in Singapore has become inexorably more urgent and crucial. It was recognised that having such a capability is critical for a country's pharmaceutical development. A case in point is the success of Switzerland as an advanced country with a high standard of medical research and service and an extensive pharmaceutical R&D and manufacturing capability. Another perhaps even more pertinent example is the success of another small country, Sweden, in these areas.

Therefore, in line with the established systems in developed countries, Singapore now has to acquire the capability to evaluate new drugs that have not been previously registered in other countries. This capability is essential to encourage high value-added economic development in the life sciences industry and to support a high standard of medical practice and service through the timely introduction and availability of new, safe and efficacious medicines in Singapore and the region. If Switzerland with a population of 5 million and Sweden with a population of 8 million can do it, perhaps Singapore with a 4 million population can emulate and follow a similar path.

Two Models

Strong support for this initiative was received from the National Biotechnology Committee and the NSTB. Two possible models for building up this capability were considered:

- Decentralised Model
- Centralised Model

Decentralised Model

The first model was to build up this capability as a network of organisations that can provide all the necessary building blocks to meet the objective. This would involve having a New Drugs Unit under the Pharmaceutical Department to manage the new drug submission process

and to evaluate toxicological and clinical data, and a New Drugs Laboratory under the Department of Scientific Services to evaluate chemical and biotechnological data, as well as a pool of external experts from local universities and hospitals to serve as external evaluators.

Such a model is a minimalist model that relies on existing organisations and expertise to meet the needs. It is at best difficult to coordinate and develop, and at worst a non-priority project dependent on the limited resources available in the existing organisations. After careful considerations by MOH, this model was rejected.

Centralised Model

The idea of a Centre for Drug Evaluation (CDE) under MOH funded by a NSTB grant was the other model proposed. This model gained support in 1998 because of the obvious advantages that it offers. It was recognised that such a Centre will be able to focus its energy on developing a viable new capability for evaluating new drugs, and provide a new organisation structure necessary to expand the existing national drug regulatory system.

Establishment of CDE

A decision to set up CDE was taken by MOH in August 1998 and CDE was established as a new Department under the Service Regulation Division of MOH, as a sister organisation of the National Pharmaceutical Administration (NPA) (PD was renamed NPA in March 1998). A NSTB research grant of \$6 million was provided for a 3-year programme of development. The process of establishing the legal, financial and administrative framework for CDE was started immediately. By December 1998, the first 2 staff for CDE were recruited and a temporary office was set up on borrowed premises in the Singapore General Hospital. The staff grew to 5 in April 1999 when CDE moved to its temporary office in the School of Nursing, and to 8 in July 1999. At the same time, plans were drawn up to establish a permanent office at one wing of the School of Nursing near to the main road. This is targeted to be completed in November 1999.

Organisation and Procedures

From the outset, it was recognised Singapore should adopt the best practices in drug evaluation from other well-established agencies such as FDA, MCA, TGA and especially the European Medicines Evaluation Agency (EMA). It should also draw upon the guidelines and experiences of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). It was also decided that being a small country with limited resources, CDE should build up a system that makes optimal use of the expertise available in the hospitals and the university. The

main operational principles of CDE are therefore:

- build up a small but effective core group of drug evaluation experts and project managers in CDE;
- access a large panel of experts in hospitals, university and research institutes, both locally and internationally, as external evaluators;
- establish close linkages with reputable overseas and regional agencies; and
- adopt ICH guidelines as far as possible.

The Drug Evaluation Systems

While there are many different systems of drug evaluation in the world, such as US FDA, European EMEA, Australian TGA, Canadian TPP and Japanese MHW systems, there are a large number of common elements in all the systems. Some of these are already or are being harmonised by the ICH process. A special project to harmonise the drug submission format is currently being undertaken by the ICH and this is expected to lead to a Common Technical Document (CTD)² which can be adopted by most countries. As this may take some time to come about, CDE has decided to adopt the EU format as the preferred format for receiving New Drug Application (NDA) submissions. This is similar to the stance taken by TGA.

The European Union (EU) format³ represents an important attempt to rationalise the format of new drug submission dossier. It comprises 4 parts, namely:

- Part I: Administrative data, product information and expert reports
- Part II: Pharmaceutical/chemistry dossier
- Part III: Pharmacotoxicological dossier
- Part IV: Clinical dossier

Such a dossier in EU format for a NDA usually runs into 100 to 200 volumes of 500 pages each (i.e. 50,000 to 100,000 pages), while a FDA format dossier^{4,5} could be 2 to 3 times this size because of the different emphasis of the FDA system and the additional data that need to be included in the FDA submission.

Drug Evaluation Process

There are broadly three main areas of evaluation in the conduct of a drug evaluation. These are the evaluation of the quality, safety and efficacy of the drug, which in the EU dossier correspond to the evaluations of Part II, Part III and Part IV of the dossier. By the very nature of these subjects, they are normally evaluated separately by chemistry, toxicology and the clinical experts, respectively. The three evaluation reports are then consolidated into a final evaluation report. In this process, specific experts in pharmacy, pharmaceuticals, pharmacokinetics, pharmacodynamics, clinical pharmacology, biopharmaceutics,

microbiology, biotechnology, molecular biology, immunobiology and biostatistics may also need to be involved to various degrees so as to address all the pertinent issues in the submission.

Clinical Evaluation

In the drug evaluation process, clinical evaluators play a key role. The clinical evaluator has the critical responsibility of ascertaining the clinical efficacy of the drug and of balancing the clinical benefits against the risks that are revealed by the various safety studies. This requires knowledge, experience, skill and an analytical mind.

In Singapore, CDE relies on a core group of experts in-house and a large pool of external evaluators to conduct the evaluation. Obviously there must be close liaison between CDE staff and the external evaluators in this process. Expertise must be built up both in-house as well as in the pool of external evaluators. This is why CDE has embarked on an extensive and regular programme of CDE seminars and workshops to address drug evaluation issues. CDE is also developing a computer-aided training package for evaluators. This will be done collaboratively with TGA.

Good Clinical Trials

Good submission dossier must of necessity depend on good clinical trials. The principles of Good Clinical Practice (GCP) have been well enunciated in the ICH Guidelines finalised in 1996 (ICH E6).⁶ These principles have been fully incorporated in the Singapore GCP Guidelines published by MOH in 1998.⁷ In Singapore, clinical trials need to be conducted with the approval of hospital Ethics Committee and MOH's Medical Clinical Research Committee (MCRC), and under clinical trial certificates issued by MOH. This is to protect trial subject and ensure proper protocols. Investigators should be familiar with the various guidelines on drug trials and development as well as those that pertain to the drug they are doing trials on. They must ensure compliance with the Medicines (Clinical Trial) (Amendment) Regulations 1998⁸ which replaced the earlier version of March 1978.⁹ The main changes in the new regulations introduced in 1998 are to clarify issues concerning the consent of trial subjects, clinical trials in emergency situations, explanations and information to trial subjects, notification of serious adverse events, record keeping time frame and GCP.

Good clinical trials should be well designed to meet the objectives of the study. The key question to ask is: what is the trial's objective? Often, this is to test a hypothesis about the drug against a placebo or against a comparator drug. Once this is clear, the trial can be designed with the appropriate protocols and endpoints and monitoring to ensure that the objective is met. This is especially important for pivotal trials in Phase III which will eventually form the

main basis for efficacy and safety in the submission of the new drug application to the regulatory authorities. It is critical that a biostatistician is involved in the design of the pivotal trials so as to adequately address the important issues of double-blinding, randomisation, control groups and data analysis. If a pivotal trial is not properly designed and executed, it will be evaluated as such during the regulatory evaluation stage, and will have little value in the evaluation of the drug and may even be discounted altogether. This would be a great waste of time and resources. One could say that even if no harm was done, conducting a trial on human subjects which does not produce useful and reliable data is in itself an ethical issue.

Therefore, to be most effective, clinical trial investigators should have a good understanding of the relevant clinical and regulatory issues and should be able to anticipate issues and questions that are likely to be raised in the eventual regulatory evaluation of the dossier. In fact, without a good understanding of the drug evaluation system, it is difficult for clinical trials to be designed and conducted at a sufficiently high standard that meets the drug approval system of developed countries. The relationship between clinical trialists and drug evaluators is therefore one that is mutually reinforcing and beneficial. A good clinical investigator makes a good drug evaluator and vice versa. In Singapore, with the setting up of the CDE, it can be expected that the standard of clinical trials will improve in tandem with the development of the drug evaluation expertise.

Pre-Submission Consultations

In view of the need for effective communications between sponsors, investigators and the regulatory authority, many countries have put in place a system of pre-submission meeting or consultation. This enables relevant issues and questions to be addressed in the course of drug development. Experience has shown this to be effective in improving the quality of the eventual drug submission dossiers and to help speed up the drug evaluation process. CDE has established such a mechanism to help drug sponsors and investigators improve their drug development plans and protocols. This would be of mutual benefit to the industry and the regulators.

Outcome

The eventual outcome of a drug evaluation is a benefit/risk assessment that can be used to decide whether the new drug should be approved for sale. Normally, this final decision is made by the licensing authority based on the advice of the evaluators and/or an advisory committee. This is clearly not an easy task and must rely to a great extent on experience, knowledge and good judgement. This is especially so because by the very nature of new drug

development, only a limited number of patients can be included in the clinical trials (which could range from several hundred to several thousand). Even though certain adverse reactions can be anticipated and investigated based on current understanding of various classes of drugs and their effects, unexpected and rare adverse drug reactions may not be detected until the drug is released for wider use in the community and the whole population is exposed to it. Some of these may be serious or fatal, or may only affect a specific population group, or in association with specific diseases or concomitant therapy. The fact that a number of new drugs are withdrawn from the market every year highlights the risk inherent in such a process.

Benefits and Risks

There have been a number of highly publicised cases of serious adverse drug reactions after the drugs have been approved by FDA or the European authorities. Some of these have led to the withdrawal of the drugs and some have led to stronger labelling requirements and warnings. The case of Viagra (sildenafil) is instructive in understanding the fine balance of benefits and risks, especially the special risks for patients with heart diseases or on certain medications. In spite of the warnings and cautionary labelling and special guidelines on the use of the drug, 128 patients have died in circumstances associated with the use of Viagra and complications of heart disease. This includes 1 case in Singapore which occurred in June 1999. The subsequent coroner's inquiry returned an open verdict as it was not absolutely certain of the cause of the fatal heart attack. As Viagra was detected in the urine of the deceased, the coroner did not exclude the possibility that Viagra could have quickened his death. Following this finding, MOH has again advised the public against the indiscriminate use of Viagra without proper medical consultation.¹⁰

In another well-known case in Australia, Tasmar (tolcapone) was approved for the treatment of Parkinson's disease after an evaluation by TGA. Following marketing and wider use, adverse reaction of liver toxicity was reported for 18 cases with 3 deaths. Based on the usage by 100,000 patients, the risk is calculated to be 1/30,000. This was despite the drug having been trialed over 3 years in Australia with 600 patients before approval and was widely accepted as effective and safe by neurologists. What concerned TGA most about this drug was that close monitoring did not prevent the adverse reaction and that it was not possible to identify the subset of patients who would benefit from the drug. This was the unpredictability issue that weighed heavily on the balance of benefits and risks. Following careful consideration, TGA, with the support of its Advisory Committee, decided to cancel the registration of the drug. This was a very unpopular decision which was not accepted by many neurologists and patients

in Australia especially because no alternative drug was available at that time. TGA therefore took the decision to fast track the approval of an alternative drug, entacopone. When this alternative drug was eventually approved and made available, there was general acceptance of the approach taken by TGA. This case also illustrated the different approaches and responses from different authorities in different countries to a specific drug. For tolcapone, Europe suspended it, Canada suspended it but allowed it for compassionate use, US FDA and Singapore restricted its use, while Australia cancelled its registration.

Other new drugs that experienced problems recently included dexfenfluramine (in Redux and Fen-Phen), trovafloxacin (Trovan), mibefradil (Posicor), bromfenac (Duract), troglitazone (Rezulin), astemizole (Hismanal) and terfenadine (Seldane). Again there were different responses from different authorities, as they took actions according to their own benefit/risk assessments and their own regulatory framework and medical practice.

Gatekeeper Role

Therefore, drug evaluation agencies have a gatekeeper role in the approval of new drugs. Due diligence and care must be exercised to ensure that adequate data are provided in the drug submissions and that all available and relevant data are properly evaluated for an accurate benefit/risk assessment to be made. Where there are indications of potential safety issues, proper systems must be developed and put in place to monitor the drug. In any case, because not all adverse drug reactions can be detected in the clinical trials (no matter how well designed and executed they are), a well-established post-marketing surveillance programme is essential for the pharmaceutical regulatory system in any country. This enables the authority to take prompt and appropriate actions in response to reports of serious adverse drug reactions after the drugs have been approved for sale.

New Drug Approvals and Withdrawals

In a recent study by FDA, over the period of 1994 to 1998, the safety-based withdrawal rate for new molecular entities drugs has been found to be 1.2%.¹¹ The previous 5-year period's rate was 1.6% and the rate before that was

3.5%. One must accept that this rate can never fall to zero although effort can be made to minimise it. It is really a risk management issue^{12,13} and there will always be unexpected adverse drug reactions that make the benefit/risk ratio unacceptable for a new drug and necessitates its withdrawal. However, this does not and should not deter new drugs to be developed. It is clear that useful new drugs have made great contributions to the improvement of healthcare and the quality of life all over the world, and have been a great benefactor of human progress.

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