Health care roadblocks need to be addressed

Thailand's attempt to become a regional medical hub is being held back by pro-generic policies and burdensome regulatory approval processes. **Alan Adcock** and **Clemence Gautier** of **Tilleke & Gibbins** examine three obstacles to the country's aim

Thailand is endeavouring to become a regional medical hub in an effort to attract drug innovators. However, Thailand's pro-generic policies – for instance, the government's 2007 liberal granting of compulsory licences – and burdensome regulatory approval processes deter pharmaceutical developers from establishing a presence in Thailand. This article looks at three issues of particular relevance, which some consider roadblocks to the medical hub Thailand hopes to become.

Conducting clinical trials in Thailand

Since 2000, more than 568 clinical trials have been conducted or are in the process of being conducted in Thailand according to clinicaltrials.gov, the largest clinical trials database in the world run by the United States National Library of Medicine at the National Institutes of Health. Most human trials in phases 1 and 2 have involved HIV and other infectious-disease-related drugs, and in phases 3 and 4, cancer and heart disease drugs appear heavily. Thailand is the Southeast Asian country conducting the highest number of trials at hospitals, medical centres and research institutes nationwide, ahead even of Singapore, which proudly claims itself to be a medical hub. One of the probable reasons for Thailand's dominance is the absence of formal regulations on how to conduct a trial. A bill on Research on Human Trials is under review by the Council of State and should be passed; the bill is expected to cover the establishment of a national ethics committee on human research and a national guideline for clinical trials. In the meantime, in the absence of clear regulations, the Thai Food and Drug Administration (TFDA) recommends following the guidelines of the International Conference on Harmonisation of Technical Requirements (ICH) for registration of pharmaceutical products for medical use (ICH) on Good Clinical Practice (GCP) and the Declaration of Helsinki.

The lack of clear and direct regulations enabling the TFDA to provide clinical trial oversight may also explain some of the particularities regarding the approval process for trials. The TFDA has only a secondary role in Thailand in the obtaining of a clinical trial approval, since the TFDA is only responsible for granting the import licence of the investigational drugs as well as, of course, having responsibility for product registration.

Trial authorisation is obtained from the relevant authorised government agencies which play a central role in regard to clinical trials, namely the Ethical Review Committee for Research in Human Subject of the MoPH (ERC) and the Department of Medical Services. In January 2009, the TFDA issued a list of 10 TFDA-approved ethics committees whose approval can be used to apply for the TFDA import licence. Most of the major (public) institutions in Thailand are on the TFDA list, which also includes the Ministry of Public Health Ethics Committee. None of the ethics committees listed is a private entity. Many public universities (medical schools) and research institutions are now being restructured; therefore, some of the TFDA-approved ethics committees may no longer be considered government bodies (in the strict sense) or may not remain so in the near future.

To launch a clinical trial in Thailand, a drug developer/sponsor needs to obtain approval from an ethics committee overseeing human research projects undertaken in an implementing institution prior to launching the trial. Approval must be obtained from the ERC and also from the ethics committee of the research institute or university that will conduct the trial. A protocol for the conduct of the clinical trial must be established and approved at the outset before approval can be obtained. The proposed protocol is sent to the Department of Medical Services within the Ministry of Public Health for review and consultation. Once a drug developer/sponsor receives approval from an ethics committee to conduct a study in humans, the develop-

er/sponsor may proceed to request a licence from the TFDA to import drugs into Thailand for research purposes.

Getting the authorisation for conducting a clinical trial in Thailand is only a first step. The involved parties also have to draft agreements, such as the Investigator Agreement between the developer/sponsor and the investigator, and the Informed Consent Agreement between the investigator and the participant. There may be a whole suite of ancillary agreements related to the site or to third parties subcontracted to provide related services/materials integral to the trial. A main concern regarding informed consents is the use of the personal data of the participants.

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Personal data protection

One of a clinical trial's objectives is to gather information on how the drug in question works on a particular participant. Investigators thus need to obtain certain personal information from participants that can eventually be used for reports transmitted to third parties, such as the developer/sponsor, and sometimes submitted to the local FDA. Some of these data may be confidential (such as the name or other personal information regarding the subject). The question of exactly what and how much of the information can be provided to third parties is often raised.

The requirements for an informed consent agreement according to the ICH GCP and the Declaration of Helsinki include voluntary confirmation from the participant to contribute and complete information on all aspects of the trial that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form. According to the ICH GCP, the form should be in the language of the participant and, of course, the participant must be legally capable of giving consent. Local laws also have to be taken into consideration since certain rules can differ from one to another, such as over what is understood as personal data.

In Thailand, no personal data protection legislation has yet been implemented. However, a Personal Data Protection Bill is under consideration and is designed to protect the personal data of individuals and private sector entities and prevent the misuse of that data. This bill will deeply affect the understanding of personal data in Thailand since it would provide guidelines on the meaning and use of such data.

Section 35 of the 2007 Constitution of Thailand provides the current determination of what type of protection a subject is granted. Its brief reference to data privacy and data protection states that "it is prohibited to spread or publicise news or images by any means to the general public, which violates or infringes a person's rights ... including disclosure of personal information without the owner's consent, except in the public interest". In other words, consent is mandatory if an investigator intends to disclose certain personal information, for example in a publication. However, the legislation has yet to clearly define what falls within the scope of personal data.

After obtaining all the required approvals, the clinical trial can start. After completion of phase 3 of a clinical trial in which the safety and efficacy of the drug is assessed, drug registration with the TFDA can be sought.

Drug registration process

Before considering filing a drug application with the TFDA, pharmaceutical companies have to apply for a licence to produce, sell and/or import pharmaceuticals in the country. However, Thailand does not yet have any active pharmaceutical ingredients (API) production facilities, and thus few licences to produce have been granted to date. The TFDA is organising training to ensure that these manufacturing companies follow the ICH Good Manufacturing Practice guidelines to facilitate development of API production sites in the near term.

Pharmaceutical companies have to register their products for actual sales and submit an application for marketing approval. Usually, the procedure for applying for marketing approval for drugs will depend on whether the applicant is the drug originator or a generic producer, with varying requirements accordingly.

New drug registration process

A full marketing approval application must be compiled to accompany samples of the new drug. All the required documents such as the relevant application form, the proposed labels and leaflets, the human and animal pharmacological study data and animal toxicology studies, the data generated from the safety and efficacy studies including clinical trial results dossiers and the full chemical (or biological) details of the new drug have to be submitted to the Drug Control Division of the TFDA. Drug originators have to prove the safety, effi-

cacy and effectiveness of the drug in order to get the approval from the Drug Control Division of the TFDA. In Thailand, the process by which the TFDA reviews a new drug application takes up to two years. Very often, the cited reasons for these lengthy approval times include a lack of staff competent to review the applications, as well as the increasing list of documents required for submitting not only new drug applications, but clinical studies as well. However, in a desire to harmonise with the most efficient regulatory practices worldwide and thus accelerate the approval process, ASEAN countries have implemented the ASEAN Common Technical Requirements and Dossier (ACTD) on Quality, Safety and Efficacy, which provides guidelines on analytical and process validation, stability studies, and bioavailability/bioequivalence. Thailand was an early proponent.

Generic process approval

Generic producers receive more lenient treatment before the TFDA. The timeframe for obtaining marketing approval for generic drugs is usually shorter – six months to one year only. The generic applicant has only to submit bioequivalence data as opposed to conducting rigorous trials and tests to prove the safety and efficacy of the chemical entity or biological molecule. Reproductions of clinical trials or pre-clinical tests are not required. This practice is partially due to the government's health care policy, which seeks to improve access to medicines and make drugs affordable and thus available for everyone – a practice that many would term pro-generic.

Level the playing field

If Thailand hopes to attract pharmaceutical developers, there must be a shift in the government's preference for generics to one in favour of innovators (or at least a levelling of the playing field). The establishment of a stronger regime of personal data protection and a more streamlined regulatory approval process are important first steps in the right direction. These measures would help to draw more drug developers to Thailand thereby facilitating the country's desired reputation as a medical hub.

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