Clinical Trials in Asia
Overcoming regulatory and IP
ROADBLOCKS

As Asia continues to attract an increasing number of clinical trials, project sponsors need to take into consideration the specific laws and regulations of each country where the trials take place. This article will highlight the different processes in place in China, Thailand and Vietnam, as well as the importance of the agreements signed between the parties from the perspective of intellectual property law and drug importation.

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Is Asia the new place to be for clinical trials? It has only been twenty years since commentators ceased describing all Asian countries as "developing nations." At present, it is recognised that most of the world's products are manufactured in Asia, and more specifically in the People's Republic of China (PRC), India, Taiwan, Thailand, and Vietnam. But these countries do not limit their activities only to manufacturing. Due to infrastructural improvement and an increasingly educated workforce, Asian countries now attract numerous clinical trials from phases 1 to 4 which previously had been primarily conducted in the United States or in Western Europe. A few reasons are usually invoked by the industry as well as governments for Asia's rise: (1) a large population ensuring availability/diversity of patients, (2) a broad range of developed and developing markets, (3) expanding markets, (4) infrastructure at standards almost identical to Western countries, (5) competitive pricing, and (6) increasing experience in conducting multinational trials.

Due to population growth and the rise of traditional and new diseases, Asia is seen as an expanding pharmaceutical market and is expected to observe a continued rise in consumption and market share with the PRC taking third place by 2013, below the US and Japan but ahead of France and Germany, according to the IMS Health study Changing Faces of Top 20 Global Pharmaceutical Markets Through 2013. ▶

In Thailand, the process by which the Thai Food and Drug Administration (TFDA) reviews a new drug application takes up to two years. However, the time frame for obtaining marketing approval for generic drugs is usually shorter—six months to one year only. This discrepancy can also be observed in other countries. Very often, the reasons for a lengthy approval process 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.

Moreover, the diseases present in Asia are not confined to infectious diseases typical of developing countries but also include diseases usually found in the richer countries, including cancer or heart diseases.

Asia is also attractive due to the competitive pricing offered to both patients and pharmaceutical companies for services offered. Singapore and Thailand are head-to-head in both promoting and attracting medical tourism. ClinicalTrials.gov, a U.S. registry of federally and privately supported clinical trials conducted worldwide, states that since 2000 at least 1,286 clinical trials have been or will be conducted in Southeast Asia, with 571 in Singapore and 572 in Thailand. In comparison, in the PRC more than 1,200 clinical trials have been listed.

However, despite Asia's appeal as a place to conduct clinical trials, there are still regulatory and intellectual property roadblocks to overcome. In order to highlight this contrast, we have targeted three countries which in our view represent three different pictures of the clinical trial industry in Asia: the PRC, recognised as a large market commonly targeted by pharmaceutical companies; Thailand, which offers infrastructure on par with Western countries; and Vietnam, which is starting to attract more companies since its WTO accession in 2007.

Regulatory process

Drug registration process

Drug registration in Asian countries is generally slow compared to the process in European countries or in the US. The length of time required for the process may be attributed to the insufficient number of regulators.

Drug registration regulations in the PRC were the subject of important changes after the 2007 recall of Chinese products such as toys, medicine, and food exported to the US. Subsequently, the PRC's New Measures for the Administration of the Registration of Pharmaceuticals have significantly curtailed individual regulator authority over drug registration and approval, clinical trials, generic pharmaceutical approval, and manufacturing. While data protection safeguards remain in place in terms of new drug application dossiers, most of the State Food and Drug Administration's (SFDA) internal procedures and requirements which before were arbitrarily and sometimes inequitably disseminated and practiced are now publicly available, the majority of them online. Nevertheless, the drug registration process has not changed and in most cases still takes a minimum of 7.5 months.

With its accession to the WTO, Vietnam has in recent years implemented new laws regulating the registration of drugs. Vietnam's registration process is deemed slower than the PRC's but faster than Thailand's. Nevertheless, even though it is a member of ASEAN, Vietnam has not yet implemented the ACTD guidelines and has been granted an extension until mid 2010. Its implementation should facilitate the registration process for foreign companies, largely due to how it harmonises the documents required.

Clinical trial approval process

Even though similarities exist in the clinical trial approval process, especially due to the fact that countries in practice follow the international guidelines such as International Conference on Harmonization of Technical Requirements for registration of pharmaceutical products for medical use (ICH) on Good Clinical Practice (GCP) guidelines and the Declaration of Helsinki, some particularities exist in each country.

Although the number of clinical trials in the PRC has been greatly increasing in recent years, companies still face difficulties in commencing them. Indeed, the clinical trial application approval process can take up to nine months, since no less than four entities have to review the application, includ-

ing multiple reviews by certain entities. The SFDA is the first agency to review the application and also reconsiders it for final approval at the conclusion of the process after being reviewed by the Center for Drug Evaluation, the Coast Institute for the Pharmaceutical & Biological Products Control, and the National Institute for the Control of Pharmaceutical & Biological Products. Since 2000, more than 1,200 clinical studies have been conducted or are planned to be conducted in China, particularly for oncology.

Thailand is seen as a more attractive location for clinical trials than the PRC due to the lack of stipulated regulations. While a bill governing human clinical trials is still under consideration, the TFDA currently recommends following the ICH GCP guidelines. Contrary to other countries, the duty of review is not centralised with the TFDA, which only reviews and approves the license to import clinical samples. The lack of regulations may explain the numerous clinical trials conducted in Thailand, estimated at 572 clinical studies since 2000. Most clinical 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.

Further to its WTO accession, Vietnam's objective is to attract as many companies as possible in order to become a medical hub like Thailand or Singapore. The Pharmaceutical Law of June 2005 and the Regulations on Clinical Trials of 2007 have centralised the duties to review and control clinical trials in the hands of the Department of Science & Training of the Ministry of Health. Compared to PRC, the process is quite straightforward and should take at minimum two months after receipt of the application. But it must be noted that clinical trials in Vietnam are still in their early days, with an estimated number of 49 trials since 2000.

IP roadblocks

When conducting a clinical trial, not only does the study have to be approved by the relevant authorities, but the agreements between the parties involved have to be clearly described as well. Key issues in such agreements are those relating to intellectual property rights, such as ownership rights, control of such rights, limitations on publication, and the level of confidentiality. These issues are usually addressed in an Investigator Agreement.

Publication rights

As in other jurisdictions, investigators or their teams normally request the rights to publish information about the study they are conducting in academic ▶

journals. However, the investigator must be made to understand that a publication can defeat the required novelty criteria of a patent application for the tested drug. Thus, in practice, the sponsor will request no publication or publication under their supervision in order to avoid any obstacles to their patent application. Another important point regarding publication is the timeline for filing a patent application, which usually occurs at the beginning of phase 3. Nevertheless, in case of a more in-depth publication which is not controlled by the sponsor, many laws (such as those in Thailand or Vietnam) authorise a six-month period during which the applicant, usually the sponsor, can file the application. It is also notable that if the publication occurs in the US, for example, it can still defeat novelty for a patent application in Thailand. Thus, when deciding whether to file a patent, the sponsor should consider the information disclosed in the publication as well as the expected timeline for filing patents, which could differ from one country to another.

Data protection

Data protection or data exclusivity is normally established in many jurisdictions or in bilateral trade agreements as a period of five years for pharmaceutical products and three years for new clinical information. This protection is referred to as "TRIPS-plus," since it is not mandatory for the signatories of TRIPS to implement this protection. Data exclusivity is aimed at safeguarding with the FDAs the registration files for pharmaceutical products that are deemed to contain trade secrets. These data, especially clinical studies, are important for generic companies because when filing an FDA application, these companies will claim bioequivalence to the original drug, arguing that their pharmaceutical products are clinically interchangeable in terms of efficacy and safety and that they meet the requirements regarding quality standards. By implementing a data protection system, the FDAs cannot rely on data that is TRIPS-plus protected when registering a generic product. Due to this protection, generic companies have two options: either conduct clinical trials or wait until the expiration of the data protection. In Asia, data exclusivity is not always guaranteed, as the guidelines across the region are often unclear. However, almost every ASEAN country has set up a data protection/exclusivity system.

Some particularities in these systems are apparent. In China, protection of undisclosed data is provided for a period of six years, but anecdotal evidence suggests that domestic generics can still indirectly get access to these data through regulatory loopholes. In Thailand, although data protection lasts for five years from the date of recordation, the protection available is limited to physical protection. In Vietnam, data protection is not automatic and has to be requested to be enjoyed. Interestingly, data protection does not apply to new chemical entities in Vietnam.

Confidentiality

Confidentiality constitutes a request to use the information solely for the agreed purpose and not to disclose the information to any person other than as permitted. The essential element is the definition of confidential information. By including a confidentiality provision, the parties will clearly define what has to be kept secret, that is to say not disclosed to any third parties or competitors. Moreover, such provision will avoid any disclosure of relevant information prior to filing a patent application, which could defeat the novelty criteria.

Conclusion

Pharmaceutical companies should remember that directly contacting regulatory agencies when an issue arises may facilitate the acceptance of the application. In the meantime, using the language of the regulatory agency, such as Thai in Thailand, also permits better understanding and cooperation by the examiners. When a foreign company decides to conduct a clinical trial for the first time in Asia, they sometimes forget a basic rule, which is to conduct due diligence on their partners regarding issues such as their experience in clinical trials and the quality of the infrastructure, especially if a GMP-qualified site is required. Finally, a sponsor should always keep in mind that while an agreement can limit any breach of confidentiality or intellectual property and provides grounds in case of litigation, it does not prevent such risks. Thus, information should be provided only when required and sometimes only sparingly. ■

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