Trials and tribulations

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outline current pharmaceuticals issues

Thailand

In the last decade Thailand has seen rapid growth in the pharmaceutical and biotech industries. While the regulatory system for these industries operates independent of the IP system, interactions between the two systems are critical to development in these areas. The Thai Ministry of Public Health's (MOPH) decision to announce compulsory licences on various key patented drugs in Thailand has attracted considerable attention from around the world recently. Tension exists between IP protection afforded for pharmaceutical products and the Health Ministry's radical approach to reducing drug prices.

Compulsory licensing

Around the end of 2006 and early 2007, the MOPH, acting on behalf of a post-coup military-appointed administration, decided to issue the first set of compulsory licences on three patented drugs. The Health Minister at the time, Mongkol na Songkla, took a strong view against expensive patented drugs and believed that issuing compulsory licences was the solution to improving access to medicines for Thai patients. The three drugs that were subject to compulsory licences were Merck's antiretroviral efavirenz, Abbott Laboratories' antiretroviral lopinavir/ritonavir, and sanofi-aventis' heart disease drug clopidogrel. The legitimacy of these compulsory licences was debated extensively both at home and abroad. As a policy matter, it was widely questioned whether the actions of the MOPH would benefit Thai patients and help to improve the healthcare system and access to medicines in the long run.

From a legal perspective, the validity of the compulsory licences issued by the MOPH remains questionable. A careful reading of Section 51 of the Thai Patent Act and its reference to the procedures for issuance of compulsory licences under Section 50 would seem to suggest that the MOPH has not taken the appropriate steps required by law in seeking to impose compulsory licences on the patented drugs. This view, however, is not the prevalent view among Thai Government authorities at present.

Despite the question of the legitimacy of the compulsory licences and the efforts of the industry to work with the ministry to resolve compulsory licensing issues through collaboration and dialogue, the ministry insisted upon implementing the compulsory licences to import generic products into Thailand through the state-owned Government Pharmaceutical Organisation (GPO). In early 2008, Mongkol na Songkla signed a further announcement of compulsory licences on three cancer drugs just before the end of his term as Health Minister. The new set of compulsory licences include the breast cancer drug letrozole produced by Novartis, the breast and lung cancer drug docetaxel made by sanofi-aventis and the lung cancer drug erlotinib produced by Roche. In view of the newly-elected government and volatile political climate at present, it is yet to be seen whether the compulsory licence policy will be continued or whether the new administration will adopt less severe measures to solve problems of access to medicines while protecting drug originators' investments in the research, development, registration and launch of new medicines.

Clinical trials

In recent years Thailand has begun to see an increase in the number of clinical trials being carried out at hospitals, medical centres and research institutes throughout the country. In spite of this trend, the process for approving clinical trials has not yet been centralised. The FDA's role in this area is at most an indirect one through its responsibility to control the import of drugs into the country for research purposes. Drug developers/sponsors will need to obtain approval from an ethics committee to conduct a clinical study in humans. At present, government agencies that play a central role

with regard to clinical trial operations include the Ethical Review Committee for Research in Human Subjects of the MOPH and the Department of Medical Services.

Generics approval and data protection

Generally, drug originators face the most difficult task in registering drugs in Thailand, as each element of drug safety, efficacy and effectiveness must be demonstrated to the satisfaction of the Thai FDA.

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Generic producers, on the other hand, generally receive more lenient treatment. As is the case in many countries, an abbreviated form of approval is available in Thailand for generic drugs. The generic applicant only needs to submit bioequivalence data, as opposed to conducting rigorous trials and tests to prove safety and efficacy of the chemical entity or biological molecule.

The extent to which a generic applicant can rely on clinical test data on file with the FDA has been subject to criticism and debate for many years. In 2002 Thailand enacted the Trade Secrets Act BE 2545 in compliance with the TRIPs obligations. With respect to data or information submitted to the FDA by a drug originator in order to obtain approval to market a new drug, the Act recognises that such data may amount to a trade secret in the form of testing result or other information regarding its preparation, discovery or creation. In this case, the owner has the right to request that the FDA maintain the confidentiality of the data submitted. Upon such request, the FDA would have "the duties to maintain the trade secrets from being disclosed, deprived of or used in unfair trading activities". However, the Trade Secrets Act does not specifically define what this means and leaves it to ministerial regulations to address the point in detail.

The ministerial regulation on data protection was not issued until last year. Since the Thai Patent Act contains a Bolar provision, generic manufacturers may submit applications for regulatory approval before the expiration of the patent. The legal question one must consider is whether FDA reliance on the data submitted by the drug originator in order to assess a subsequent application constitutes unfair commercial use. While the FDA in fact refrains from disclosing the data submitted by drug originators to third parties, generic manufacturers clearly obtain a commercial benefit from the originator's confidential data.

Unfortunately, the ministerial regulation issued in 2007 completely fails to establish the breadth of data protection and/or data exclusivity under the Trade Secrets Act and hardly protects data owners against unfair commercial use as prescribed by the Act. Whereas the regulation purportedly establishes a standard for protection of data submitted to the FDA, the relevant sections merely address the physical security of the documents submitted and simply prevent unauthorised disclosure. For instance, Section 16 provides that in the case of application for drug registration, the data submitted must be stored in a securely locked cabinet, and so on. Section 18(2) merely states that government officials have the responsibility to protect/keep the trade secret information in a safe place.

No doubt these provisions leave drug originators ample cause for concern.

Vietnam

With a population of around 86 million and with last year's pharmaceutical sector valued at around $1 billion, industry experts estimate Vietnam's pharmaceutical market to be increasing by about 12% to 15% annually. These figures explain why legislative changes in this field are sensitive to foreign pharmaceutical companies. Imported drugs account for over 60% of all pharmaceuticals in Vietnam.

Drug registration procedure

Under the Pharmaceutical Law adopted in 2005, the timeframe for examination of a drug registration dossier was reduced by half and is now six months. When compared to other countries in the region, this approval process is notably quick.

As of January 1 2009, Vietnam, together with nine other ASEAN countries (except Myanmar) will apply the ASEAN Common Technical Dossiers (ACTD) for drug registration in order to enhance mutual recognition of drug registration in the region. The objective is to allow regional marketing authorisation of a drug registered in any of these ASEAN states. This would reduce the cost and time of bringing a drug to the regional market and, more broadly, facilitate the regional trade of pharmaceutical products.

Test data protection

Test data protection is regulated in the Regulations on Data Protection Applied to Drug Registration Dossiers. This protection is not automatically provided. Instead, manufacturers must request data protection upon applying for registration of their drugs. This makes Vietnam an exceptional country, in that no system of automatic data protection is available. Manufacturers and organisations are lobbying for the removal of this requirement.

To qualify for protection under the regulations, data must be undisclosed information that requires considerable efforts to produce, can be used in business, was created by (or lawfully assigned to) the person requesting the data protection and for whose confidentiality necessary security measures were applied. In theory, these efforts must be significant in economic terms or from a technical point of view. In practice, the authority would accept a listing of the applicant's financial investment in the creation of this data.

A request for data protection is examined within six months. If approved, any drug registration application filed within the following five years using essentially the same data would be refused. Data protection is applied to new drugs that utilise new chemical entities or new combinations of known entities only. Protection is not available for new indications, new modes of administration, new preparation forms and new dosages of an original preparation. These provisions are considered reasonable under the current technological and economic conditions of Vietnam. Pharmaceutical manufacturers are concerned, however, about the extent to which data is considered undisclosed and thus qualified for protection. The regulations on examination of data protection applications are being drafted and it is essential that they address this issue.

Generics approval

Despite its rapid development in recent years, Vietnam is characterised as a country with a "pure generic" domestic industry. Likewise, generic drugs make up a large proportion of registered drugs (approximately 96%). The remaining 4% are new drugs that do not always contain new chemical entities (NCEs) as, under the law, new drugs may contain a new combination of old and/or existing active ingredients.

The existing requirements for registration of generic drugs are basically the same as those in the ACTD. This regulation, however, does not contain specific and detailed stipulations, such as guidelines on stability studies, bioavailability/bioequivalence studies, process validations and analytical method validations contained in the ACTD. These guidelines, if available, would facilitate drug applicants in preparation of drug dossiers and help minimise inconsistencies in the drug evaluation process.

Unlike some other ASEAN countries (such as Malaysia, Indonesia or Singapore), Vietnam does not require BA/BE studies data when applying for marketing authorisation for generic drugs. The main reasons for this are the underdevelopment of domestic generic

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companies and the absence of BA/BE study centres. It is expected that this will be introduced soon. Given the current development of the domestic industry, the list of active ingredients with BA/BE data requirement would not be long and would focus on products that are most likely having problems with BA/BE.

Clinical trials

Similar to most ASEAN countries, Vietnam considers the first registration in the country as one of the key criteria in defining a new drug. The Pharmaceutical Law applies clinical trials as one of the requirements for marketing authorisation of a new drug. After a new drug is approved, there is no requirement to submit pre-clinical and clinical data to support safety and efficacy when applying for registration of a generic drug containing the same NCE, as this is considered to be well established by the previously approved innovator product using the "reference mechanism."

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The reference mechanism has raised concerns among multinational companies because most of the new drugs registered in Vietnam come from these companies. This issue has become especially contentious when a new regulation on drug registration is being drafted. The process favoured by multinational drug companies would be that if an NCE they developed is under patent protection, other applicants, when registering a generic product containing the same NCE, will have to submit clinical data to independently prove its safety and efficacy. In terms of the large investment in R&D (around 10-15 years and $800 million) necessary to develop a new pharmaceutical product, this requirement seems justifiable. However, from a public health perspective, the repetition of these clinical trials, including tests on humans, would be a waste of time and resources. More importantly, it would slow down public access to generic drugs whose prices are considerably less than the innovative ones.

Following the issuance of the Regulations on Drug Clinical Trials in accordance with Decision 01/2007/QD-BYT of January 11 2007, the Ministry of Health is drafting regulations on clinical trial standards for drug registration. These regulations are likely to extend the number of cases where the clinical trial requirement is waived for new drugs. They are also likely to establish specific criteria, based on which the drug approval committee will decide whether bridging studies are needed for drugs subject to certain clinical trial stages, such as drugs that have been placed on the market of the country of origin for less than five years. The aim is to bridge the gap between Vietnam and other countries for clinical trial requirements and, above all, to ensure and improve access to new drugs.

Thailand and Vietnam offer promising current and future markets for pharmaceutical researchers and manufacturers, both in their own countries and regionally. As both nations introduce additional legislative and regulatory parameters under which the industry will grow, it is important to understand how changes will affect participants. Projections of the direction such advancements may take need to be made within a context of an understanding of both nations' goal of encouraging more foreign and domestic participation in the field while living up to public commitments of access and price considerations.