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Pharmaceutical Issues in Perspective

China rings the changes

Ding Jianhua outlines the major regulatory changes China has implemented over the past few months, while Susan Capie analyses the impact they may have on the international pharma industry

China's pharmaceutical industry is in a state of continuous transformation, with ongoing mergers, consolidations and new investment. A major driver for the changes is a stream of new regulations issued by the Chinese State Food and Drug Administration, affecting domestic and joint-venture manufacturers as well as foreign companies applying for import drug licences. So what are these regulatory moves and how do they affect international pharma?

In its overall drive for pharmaceutical modernisation, the Chinese Government has implemented several major changes, including the reorganisation of the former State Drug Administration (SDA); key amendments to drug regulation and good manufacturing practice (GMP); enhanced intellectual property protection and changes to import drug licensing.

In April 2003, the SDA was renamed the State Food and Drug Administration (SFDA), and all regulatory responsibilities for functional foods, dietary supplements and cosmetics were transferred from the Ministry of Public Health (MOPH) to the new body. The SFDA consolidated its responsibilities to include prescription, non-prescription, vaccines, biologicals, medical devices and drug packaging along with those formerly under the MOPH.

Since the Chinese Government's top priority is to strengthen the legal framework for drug administration, there has also been a major overhaul in drug regulation. The original 1985 drug law was revised in 1998 and 1999, and in December 2001 the new Administrative Pharmaceuticals Law was promulgated, defining new regulations on drug research, manufacturing and distribution. In addition, it discontinued the local (ie provincial) drug quality standards to ensure uniform national standards.

GMP is another area being transformed. The concept of compliance was introduced in the late 1980s, and in 1998 the SDA revised its GMP guidance for pharmaceutical products. Chinese GMP is based primarily on World Health Organisation (WHO) GMP guidelines, and extensive education and training – including courses in processes, validation and quality assurance – have been conducted for regulatory personnel and pharma manufacturers. GMP compliance is now compulsory and, in general, the deadline for obtaining a GMP certificate is June 2004. Companies unable to meet GMP regulations at that time will have their production licences revoked.

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It is estimated that US$2.5-US$3.6 million has been invested on average in Chinese factories to upgrade their facilities and ensure they are compliant. Many plants operating with chemical rather than production licences have been applying for pharmaceutical licences, whereupon they must also comply with GMP regulations. At present, some 1,870 plants have been certified, leaving around 1,000 pharma manufacturers and medical trading companies uncertified. Although the statistics seem alarming, note that these 1,870 plants serve two-thirds of the Chinese market, including all major pharma companies. In light of the substantial investment needed by smaller companies to be GMP-compliant, it is likely that these companies will be acquired by larger firms or face bankruptcy.

Patent protection enhanced

In terms of enhancing intellectual property (IP) protection, amendments to China's patent law became effective in 2001, allowing statutory damages for patent infringement to be based on either the patent owner's losses or the financial gains of the infringing party. In 2002, the Chinese Government promulgated several laws to improve IP rights. As part of WTO accession, China extended all patent coverage to 20 years. The new legislation now includes provisions for patent linkage and data protection. Notably, applicants for a new drug for clinical study for production or import must submit documentation regarding the product's patent status and a letter of guarantee confirming the product does not infringe the patent rights of others.

Import drug licences (IDLs) have seen significant changes too. Through its Department of Drug Registration (DDR), the

SFDA regulates not only domestic/foreign-invested manufacturers but also foreign manufacturers seeking to sell into China. Major changes in the requirements for dossier submission, in terms of content and Chinese translation, have been made in the past three years. The SFDA has a required format for the dossiers and, on submission, will do a preliminary review to confirm all the required content. It also aims to further streamline applications via electronic filing and by issuing a timeline for each step in the process (see Figure 1). Currently all steps from the receipt of dossiers through technical evaluation and approval are computerised. Applicants can view the status of their dossier by entering the application number on the SFDA website.

Meanwhile, in the SFDA's desire for greater harmonisation on technical requirements, 29 guidelines on chemistry and manufacturing control, pharmacology and toxicology and clinical trials are under amendment, using ICH guidelines as a reference.

There are several departments involved in the process of registration. The DDR is the registration policy-maker, and it controls drug registration functions throughout China. The Center For Drug Evaluation (CDE) is responsible for the technical evaluation of the dossiers. The National Institute for the Control of Pharmaceuticals and Biological Products is charged with validating drug specifications and preparing drug reference standards. Additionally, 12 assigned coastal drug control institutes are responsible for testing the quality of import drugs. Last year, the SFDA extended the validity of an IDL from three to five years, and confidentiality has been enhanced throughout the review process.

One major SFDA concern regarding technical evaluations is the necessity of relying on the manufacturer's dossier when evaluating quality, safety and efficacy. Currently, the SFDA neither inspects nor requires an SFDA inspection of a foreign site as part of the approval process. This has prompted the agency to require additional literature in the dossiers, and all must submit the relevant approval from the applicant's home country's regulatory authorities. Domestic manufacturers are inspected as part of the GMP application procedure.

The DDR has been striving to improve its regulations, efficiency and transparency in a number of ways. For example, the SFDA website posts drafts of upcoming regulations for comments and takes part in many overseas conferences, including ICH, WTO, the International Conference of Drug Regulatory Authorities (ICDRA) and, most recently, the 4th Asian Regulatory Conference. IDL applicants are encouraged to contact the DDR with questions on applications, or for clarification on regulations regarding a product dossier. The SFDA also publishes annual Import Drug lists and Domestic New Drug lists, but its website (www.sfda.gov) is still only in Chinese. Another goal is to unify the approval/requirements for both domestic and imported drugs.

There are further wide-ranging changes planned for this year, with 14 new regulations due to be implemented, including methods of recording customs clearance reports; drug trading services on the internet; and medical device clinical trials. In addition, 16 existing regulations are scheduled for revision.

Pfizer China is just one pharma company encouraged by the increasing harmonisation of registration regulations, as well as the strengthened IP protection for new drug development. As the first company to obtain GMP certification for its Dalian plant, Pfizer now has a US$500 million investment in China. Speaking from Pfizer's Shanghai office, Wang Xunbiao comments that the company plans to launch 15 new products in China over the next five years.

Meanwhile, Christopher Shaw, president of Eli Lilly China, says the Chinese Government should be commended for the progress made regarding transparency in the IDL process. Lilly has regular dialogues with the SFDA, and Dan Brindle, Lilly's director of corporate and government affairs for Asia, notes that Chinese officials are very willing to engage in discussions. He also says the IDL process is currently about two years, whereas in the early 1990s it took four years.

Impact on the industry

The SFDA regulations are just part of a broader set of changes impacting the transformation of the Chinese pharma industry but the goal is a comprehensive improvement of both quality and continual supervision of production, distribution, sales, advertising and promotion.

Foreign companies often view China as a future competitor – articles frequently refer to the 'rising influence' of both China and India in the international marketplace. What is often underestimated is the growing consumption of the Chinese pharmaceutical market because of rising GDP and disposable income. In 2002, this market grew by 10%, with the total sales of US$14.7 billion, according to the US department of commerce. From January to September 2003, the total value of bulk imports into China was US$1.2 billion, with imports of finished dosage at US$843 million, according to China's Customs Administration. Meanwhile, the dietary supplement market doubled from US$3 billion in 1998 to US$6 billion in 2001, with high quality imported nutritional products accounting for only 10% of total sales.

But while the market is large, a series of moves on pricing have been detrimental. Continued decreases have squeezed margins for imported, joint-venture and domestic products. In the years prior to 1997, retail prices grew at about 10% per year, but by 1999 pricing increased only 1% on average. The end of 2003 saw price ceilings set for all drugs on the Basic Medical Insurance Drug list, and the average reduction was 15-20%. So although demand is growing, there are limits on profits.

Evaluation and approval timelines

Type of evaluation/approval	No of days
Provincial DA primary evaluation	30
Provincial QC lab tests	60
–for bioproducts	90
SFDA dossier reception office	5
CDE technical evaluation for CTA	120
–fast track	100
CDE technical evaluation for new drug production application	120
–fast track	100
CDE technical evaluation for generics	80
CDE technical evaluation for variations	80
SFDA marketing approval	40
–fast track	20

Figure 1: All steps in the registration process, from receipt of dossiers to approval, are computerised. The Center for Drug Evaluation takes on the key role of technical evaluation.

Chinese marketing approvals			
	2001	2002	2003
Pharmaceuticals	796	640	1,936
Traditional Chinese medicines	166	106	311
Bioproducts	115	52	104
Imported drugs	657	718	832
Totals	**1,734**	**1,516**	**3,183**

Raising the bar on quality

There are already close to 1,800 Sino-foreign joint ventures in China (with a total investment of approximately US$2 billion), while 20 of the top 25 multinational companies are in the region. The lure of the large Chinese market, together with greater transparency/harmonisation in IDL regulations and reduced import tariffs, means that more foreign companies will be encouraged to sell to China. In addition, with continued foreign investment and deregulation of investment in state-owned enterprises (SOE), enhanced competition between Chinese domestic producers and imports will continue to 'raise the bar' on quality.

Equally, the enforcement of GMP compliance and the consequent need for continual training by factories will lead to an overall improvement in quality of product. The closure of non-compliant plants, coupled with continued industry consolidation overall, will greatly reduce the redundancy of products. Factories are already focusing increasingly on new products and making larger investments into R&D.

One challenge is that most domestic manufacturers lack the capital required to make large investments in R&D, and to address this, the State Economic and Trade Commission (SETC) has announced plans to establish 12 top pharma firms. These companies will be given priority for technical renovation and support for R&D. The commission also offers tax incentives to foreign companies who set up R&D collaborations with domestic research institutes, and this will further increase the consolidation and efforts into new product development.

Finally, in terms of enhanced patent protection, China's new IP regulations have been welcomed by the West, although major complaints remain on enforcement, counterfeiting and time restrictions for IP protection.

It seems, then, that with the country's entrance into the WTO, its improved regulatory environment and its overall consolidation of the industry, China will surely become an increasingly important player in the international pharma industry. SM

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