The risks and opportunities for pharma under China's new rules

Sweeping regulatory changes in China will have big implications for the pharmaceutical industry, Shanghai-based Ropes & Gray lawyer ***Katherine Wang*** tells ***Neena Brizmohun***.

Pharmaceutical companies looking for insight into how the recent raft of new and proposed drug rules in China might affect them need look no further than the risks and opportunities arising from a good manufacturing practice (GMP) requirement that kicked in late last year.

As many as 65% of the established companies that make vaccines and other sterile products in China failed to meet the 31 December 2013 deadline to comply with the new GMP rule*. If they are unable to upgrade their facility to the level needed to obtain the new GMP certification, they will be forced to cease production and, in some cases, may be shut down, Katherine Wang, chief China life sciences advisor in the Shanghai office of law firm Ropes & Gray, told *Scrip Regulatory Affairs*.

This spells good news for multinational drug companies, which are likely to have the means to meet the GMP standards, according to Ms Wang. "We expect to see more asset or licence transfer discussions taking place in the future as sterile product makers unable to meet the GMP standards start selling their products to the multinational manufacturers that are able to do so." Substandard drug companies will be eliminated from the market, providing a higher likelihood of market consolidation, the lawyer predicted.

The GMP obligations were promulgated several years ago. Prior to coming into force for existing sterile product makers, they had applied to newly established drug manufacturers and newly established, reconstructed or expanded workshops of existing manufacturers since March 2011. As of 31 December 2015, they will apply to all other manufacturers in China.

The 2013 GMP deadline was one of a number of high-level regulatory changes that have taken place in China recently or are on the way. In September last year, the country's State Council outlined a master plan of healthcare industry reforms that signal the council's intention to liberalize the healthcare services industry, in which pharmaceutical companies are a major player. In particular, the government wants to upgrade China's lifesciences industry by encouraging innovative drug and medical device R&D activities. According to Ms Wang, the newly implemented and proposed rules will increase the potential for more transactions and co-developments between companies.

For example, the China Food and Drug Administration in February 2013 eased the requirements for product license transfer. Previously, product licenses were not transferrable unless they were part of an equity acquisition. Product licenses are considered to be a personal entitlement of the specific manufacturer producing the drug, Ms Wang explained. However, the CFDA – in its desire to implement the new GMP requirements and recognizing that companies unable to meet the new manufacturing standards may have to close down – now acknowledges certain scenarios in which the product license for non-biological products may be transferred in the form of an asset acquisition instead of an equity acquisition, she said. These scenarios are as follows: relocation of the manufacturing site; inter-affiliate product license transfer where both the transferor and the transferee are owned more than 50% of their equity by a non-pharmaceutical manufacturer; and where the transferor decides not to upgrade for GMP compliance. Easing the transfer of licences will "open up a lot of interesting transactional opportunities for companies that would like to acquire product licenses but don't want to invest in particular drug manufacturers as an equity investor", Ms Wang said.

In another move that promises to result in more transactions between companies, the CFDA is proposing to also ease its rules on transferring clinical trial authorizations (CTAs).

At present, if a company wants to sell or license a drug it is developing to another entity, it cannot transfer any CTA it might have received for that product. As is the case for product licenses, a CTA is considered a personal entitlement that belongs to the recipient. The entity taking on the product must go through the time-consuming process of applying to the CFDA for a brand new CTA, explained Ms Wang.

The CFDA's proposal seeks to make amendments to China's Drug Registration Rule that would make it possible for a company to transfer a CTA for a drug it is developing to another entity during any of the clinical study phases. "A biotech company that has developed a product up to Phase II, for example, would be able to transfer the asset as well as the underlying study data to a company that intends to in-license the product."

The CFDA also wants to make it easier for CTA holders to change the manufacturing process, product specification and manufacturing location in their CTA without having to apply for a completely new CTA. Instead, CTA holders would make the changes by simply filing a supplementary application to the CFDA before entering into Phase III studies.

Both CTA revisions promise to "improve the environment for the transfer of promising early stage compounds to large pharmaceutical companies and foster more opportunities and dialogue for co-development transaction," Ms Wang said.

Trouble ahead for innovators

Two other proposed changes to the DRR, on the other hand, spell trouble for innovators. These amendments would curtail the degree of market exclusivity enjoyed by an innovative drug product and allow for more direct competition from local generics manufacturers.

The first proposal relates to generic applications, which at the moment can be filed only two years before expiration of the relevant patents of the innovative drug. The CFDA wants to allow generic applications to be submitted and reviewed at any time during the patent term of the pioneer drug, Ms Wang said. This would mean that a pioneer drug manufacturer would immediately face generic competition after the relevant patents expire despite an argument of a patent infringement by the generics manufacturer, she explained. "The only legal remedy for the pioneer drug maker would be to wait until the drug is approved by the CFDA and about to be commercialized, and only when the drug is commercialized can the pioneer drug maker sue the generic at the court."

The second proposal concerns exclusivity provided by China's new drug monitoring period. Under the current DRR, the first-to-market manufacturer of a locally produced new drug is granted a period of up to five years of administrative exclusivity – also known as the new drug monitoring period. During this monitoring period, other manufacturers of drugs comprised of the same active pharmaceutical ingredient as the new drug cannot gain approval unless they have already received approval for a CTA for – and conducted clinical studies on – the same drug in China. Under the proposed amendment, the CFDA would reduce this exclusivity by removing the need for follow-on submitters to have already conducted clinical studies. Instead, manufacturers seeking CFDA review would only have to file their investigation new drug applications before the start of the exclusivity period.

"So theoretically, this would compromise the actual length of new drug monitoring

period because the generic product – once its filing for clinical trial authorization has been accepted by the CFDA – would stay in the review process."

Companies worried about the market exclusivity proposals have until 23 March to communicate their concerns to the CFDA. Ms Wang predicts that the revised DRR could be finalized and promulgated in Q4 of this year.

Contract manufacturing is another area that is set for change. According to a recent draft regulation, the CFDA is seeking to streamline the approval process for contract manufacturing by delegating the authority to review and approve contract manufacturing to the provincial FDAs. There are also plans to raise the bar for contract manufacturing. The provincial FDAs are to conduct onsite inspections. In addition, more categories of drugs would be prohibited from contract manufacturing, Ms Wang said, adding that it is noteworthy that the draft regulation prohibits all types of biological products from being manufactured by a contract manufacturer. "This is actually not in line with the modern trend of how biologics are manufactured," she explained. "Biologic makers should be very vigilant and monitor the development of this regulation in order to decide their market entry strategy into China."

The CFDA has also tightened up its clinical trial standards for vaccine makers, which, as Ms Wang explained, follows recent scandals related to adverse events from vaccine products. Good clinical practice (GCP) for vaccines was promulgated last October and its measures are more stringent than those in the drug GCP. The requirements will increase the cost of getting a vaccine approved, Ms Wang warned, though they are unlikely to be as problematic for multinational vaccine makers as for local companies. Comparatively speaking, when it comes to multinational companies, their management and their standard of clinical study administration is at a much higher level than their local counterparts, giving them more opportunity to compete, she said.

As for another new rule concerning clinical trials, the CFDA last September made it mandatory for CTA holders to register all CFDA-approved studies (including Phase I, II, III, IV, pharmacokinetic and bioavailability/ bioequivalence studies) on the government's website. The online platform is expected to enhance study transparency and strengthen the oversight of clinical studies by the CFDA and the public.

Notably, the agency's Center for Drug Evaluation will only engage in study-related communication with CTA holders that have completed the registration. "Even though there is no immediate sanction or penalties related to the failure of non-registration of studies on this website, if you don't register your study you will deprive the sponsor of the opportunity to engage in frequent and timely communication with the CDE," Ms Wang warned. "This may have adverse effects on how fast the product can gain access to the market."

The CDE is also attempting to make its drug review process more transparent and consistent. The Draft Guidelines for Clinical Evaluation of New Drug Applications/Biologic License Applications (draft technical review guidelines) were issued last October. The guidelines are expected to lay the foundation of good review practices and standardize the CDE's approach for new drug technical reviews. "They set forth a structure that new drug makers should follow to ensure that they can anticipate – and address in their registration submission – all the questions the CDE is likely to ask," Ms Wang said. "That would definitely save a lot of time in the product registration process."

There are also plans to clarify the requirements relating to post-market studies. The CDE issued for comments last October China's first post-market study guidelines. "The guidelines specify types of post-market studies that would be considered an eligible format for a Phase IV study," Ms Wang said. "Most importantly, even though these guidelines mainly apply to those products that are required by the CDE to be subject to a post-market study, they also suggest that there are opportunities for a manufacturer to voluntarily or spontaneously conduct a scientific post-market study in order to better assess the safety and efficacy of a product in a larger patient population."

Making reference to a recent government investigation in which large-scale post-market studies organized by multinational companies were suspected to be a form of disguised commercial bribery, Ms Wang is hopeful that the new guidelines will provide companies with a legitimate basis on which to organize and conduct post-market studies on their products.

Another trend to note is that the CFDA is ramping up its overseas GMP inspections. The agency piloted seven overseas GMP inspections of foreign pharmaceutical manufacturers in 2011. It completed 10 inspections in 2012, 15 in 2013, and it expects to complete 25 in 2014, Ms Wang said. "Companies that are not located in China, especially the multinationals, should be mindful of the potential for overseas inspections ... and they should make sure that their manufacturing facility meets not just, for example, the US GMP requirements, but also the Chinese GMP requirements".

While it is not clear how the CFDA decides on the locations of inspections, Ms Wang observed that the CFDA appears to focus more on high-risk products. "So things like injectables or biologics would probably be a potential priority for inspections."

Cracking down on corruption

Finally, industry can expect to see much tougher anti-bribery rules. Under a reinforced blacklisting regulation that was due to come into force on 1 March, public or state-funded hospitals will be prohibited from purchasing from a company that is blacklisted by the health authority in the same province for two years. Public or state-funded hospitals in other provinces will be entitled to reduce these companies' bidding scores during centralized tenders for two years. In addition, companies that are blacklisted twice in any five-year period will be prevented from supplying public and state-funded hospitals nationwide for two years.

Regarding the risks involved for companies acquiring another company that gets blacklisted, Ms Wang does not believe that the parent holding company would also be implicated. "For now, the regulation distinguishes companies by their legal entity status, so a subsidiary is considered independent from the parent holding company, for example. So if the holding company itself is not found of in breach of commercial bribery rules, if one of its subsidiaries has an issue it will most likely not implicate the parent company. And vice versa."

In December last year, the National Health and Family Planning Commission issued nine prohibitions for disciplining healthcare professionals (HCPs) who engage in activities such as connecting their remuneration with their prescription of drugs or medical exams.

The good news for multinational companies, Ms Wang observes, is that the principles highlighted in both the nine prohibitions and the new blacklisting rules are unlikely to be very different from the guiding principles that are generally available in multinationals corporate policies. "The risk remains in the degree of implementation... ie how companies set up an internal compliance mechanism and management system to ensure that their SOPs and policies are very well and thoroughly implemented at all levels is going to be important," she said. "Companies can also expect to see a variation of enforcement realities at the provincial level, which of course represents risks for multinationals operating in China."

* *According to the latest figures from the China FDA, only 35% of sterile product manufacturers met the 31 December 2013 good manufacturing practice deadline.*

Neena Brizmohun is the deputy editor of *Scrip Regulatory Affairs.*