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E-ALERT | Food & Drug

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CFDA RELEASES DRAFT REVISION OF PRIMARY DRUG APPROVAL REGULATION

The China Food and Drug Administration (CFDA) has issued a draft revision to the Drug Registration Regulation (DRR), which could bring significant changes for pharmaceutical companies operating in China. The DRR is the primary CFDA regulation for seeking approval of clinical trials and for bringing innovative and generic drugs and biologics[1] to the market in China. CFDA has authority to amend and administer this regulation pursuant to China's Drug Administration Law (DAL) and the DAL's Implementing Regulations.

CFDA made statements in the press earlier this year that it was planning to revise the DRR by the end of 2013. On November 12, 2013, CFDA released a short document proposing revisions to several key articles of the DRR, as well as a "drafting explanation" explaining CFDA's reasoning behind the change, as it is required to do pursuant to CFDA rules on administrative rulemakings. Comments on the draft revision are due on December 13, 2013.

The draft revision makes three core changes affecting foreign industry in China:

1. it creates a procedure for making certain changes to ongoing clinical trials;
2. it attempts to resolve a tension between China's Patent Law and the current DRR over the Patent Law's exemption for using patented drugs in research and development of generics; and
3. it permits sponsors with accepted clinical trial applications to proceed to product approval even if a prior applicant has obtained exclusivity pursuant to a CFDA imposed "monitoring period."

We explain each of these changes below.

CLINICAL TRIAL APPLICATION SUPPLEMENTS

In the drafting explanation to the draft revision, CFDA states that the current DRR provides sponsors with no procedure for making changes to their approved clinical trial applications (CTAs). As a result, sponsors may be required to file an entirely new CTA to accomplish changes, which can lead to delays of up to 10 months for drugs and around 18 months for biologics. Therefore, CFDA proposes to add a new article to chapter four of the DRR that would permit "supplements" to make changes to approved clinical trials. Specifically, "new article Forty Nine" would permit filing of a supplement for:

1. a change to the "applicant";
2. "a necessary adjustment to the manufacturing process, formulation, or specifications of the drug prior to a Phase III clinical trial of a drug or biological product"; and
3. a change to the "manufacturing site" prior to Phase III.

[1] Biological products (or biologics) undergo through the same application process as new drugs, regardless of whether they are pioneer or generic products.

This change will likely make clinical trials easier to conduct in China. However, the draft revision leaves a few questions unanswered. For example, the procedure for submitting supplements is unclear. The DRR already contains a procedure for supplements to make changes to approved drugs, but many of the provisions in that chapter of the DRR are context specific and apply only to licensed drugs. It is possible, therefore, that CFDA may have to draft additional rules and/or guidance on this point. Also, CFDA does not appear to be creating an expedited procedure for review and approval of the new supplements. Therefore, it is unclear whether the new ability to submit a supplement for changes will result in significant time savings over the existing procedures.

REMOVAL OF TENSIONS WITH CHINA'S PATENT LAWS

The second core change relates to the "linkage" between patent protection for drugs and the drug approval process.

Over the past six years since the last amendment to the DRR, CFDA has gradually retreated from any role in policing intellectual property during the drug approval process. The 2005 version of the DRR permitted drug patent-holders to petition CFDA to cancel a marketing authorization for products that infringed existing patents. That provision was removed, however, in 2007. As a result, the current DRR states only that applicants must certify that they are not infringing other patents claiming the pioneer drug when they submit an application to CFDA. Applicants are required to list any relevant Chinese patents on the application form. All patent disputes must now be handled solely under the Patent Law, which is interpreted and enforced by agencies other than CFDA and ultimately perhaps the courts.

At the same time, the Patent Law has been amended to include important exceptions to patent infringement related to pharmaceutical patents. For example, the current Patent Law permits the use of patented drugs in research and development. This exemption has been compared to the "Bolar Amendment" in the United States, which creates an infringement exception allowing generic manufacturers to begin research and development on generics before the end of the innovator patents. Similar exemptions exist in Canada and Europe.

The current DRR contains two provisions that are in tension with the research exemption under China's Patent Law. First, the current DRR states that if a patent dispute arises during the drug registration process it shall be handled under the relevant patent laws and regulations. As indicated in the drafting explanation, CFDA has become concerned that this provision can be read to mean that use (e.g., testing) of a proposed generic drug solely for purposes of developing an application for marketing authorization might infringe the pioneer's patents. CFDA already rejected this position in an opinion that it issued in 2006. Second, the current DRR states that generic manufacturers cannot submit generic drug applications until two years prior to the end of the patent term of any patent listed in the aforementioned certification that claims the pioneer drug. This provision is also in some tension with the Patent Law's research exemption, which contains no similar time limit.

The draft revision alters both of those provisions. It replaces the words "during the registration process" with "after the drug is marketed." This would remove the potential implication that testing or other use of a generic drug for purposes of developing and submitting a generic drug application can infringe pioneer patents. Additionally, the two year limit on submitting generic applications is removed altogether. As a result, generic drug manufacturers would be free to submit generic drug applications at any time, regardless of the status of pioneer patents. CFDA explained in the drafting explanation that it was concerned that this two year limit was leading to an expansion of patent protection afforded to innovative drug makers.

These changes further ensure that CFDA will have a small role in policing intellectual property. First, there will be less pressure on CFDA to look for infringing behavior during the drug registration process because infringement cannot take place until after a drug is on the market. CFDA already took this position (i.e., non-infringement prior to marketing) in an opinion that it issued in 2006, and this revision would essentially codify that position in an administrative rule, making it more formal. Second, CFDA will no longer have to police generic applications coming in to ensure that they are no more than two years prior to the end of the patent term. These changes solidify the position that all recourse for intellectual property infringement must take place under the Patent Law and other intellectual property laws. If the draft revision is adopted, CFDA will not play a role.

MODIFICATION TO THE "MONITORING PERIOD"

The draft revision also lessens the exclusivity provided by the new drug monitoring period. CFDA has the power to place drugs approved for the first time in China under a monitoring period, during which other manufacturers are excluded from receiving marketing approval for the same drug. Thus, the monitoring period serves as another type of marketing exclusivity in China.[2] The length of the monitoring period can vary depending on the type of drug, up to a maximum of five years. As it currently stands, however, the monitoring period does not apply to any manufacturers that already have an approved CTA for the same drug in China. Because of the monitoring period's exclusivity, and this exception for approved clinical trials, there is often a race between manufacturers to get their CTAs approved before the first applicant gains approval of its new drug application, in order to avoid being shut out of the market.

The draft revision would further reduce the scope of the monitoring period's exclusivity. Under the revisions to Articles 66-72 of the DRR, it would no longer be necessary to gain approval of a CTA in order to avoid the monitoring period. Instead, acceptance of the CTA for examination by CFDA would be sufficient. When a sponsor submits a CTA, CFDA does a preliminary review of the submission to ensure that the content requirements have been met and that the CTA is in the proper form. If it is, CFDA issues a notice to the applicant of the CTA's acceptance. According to the draft revision, applicants with CTAs that have been accepted for examination will be permitted to proceed through the clinical development process and, potentially, to drug approval, notwithstanding any pre-existing monitoring period.

Related to this change, after an imported drug has received approval for marketing in China for the first time, the draft revision would allow "registration applications," which includes CTAs, that CFDA has accepted for examination to proceed to approval. Under the current DRR, once imported drugs were approved for the first time in China, other pre-approved CTAs were allowed to proceed through the registration process. The draft revision proposes to lessen exclusivity in this context as well by allowing applications to continue that are accepted for examination but not yet approved. Applicants also have the opportunity to withdraw their accepted applications and re-file it as an application for a generic drug.

These changes in the monitoring period comes at the same time that CFDA is requiring all clinical trial sponsors to register their clinical trials online.[3] The two changes together could cause an influx of clinical trial applications to CFDA because competitors will be able to monitor each other's trials and submit clinical trial applications for the same drugs to avoid any possible monitoring period. It is unclear to what extent this change may affect CFDA's time frames for conducting preliminary reviews of CTAs and sending out notices of acceptance.

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[2] Drugs imported into China may be excluded by the monitoring period, but are not eligible for the protection of a monitoring period even if they represent first use of the drug in China.

[3] Click here for our client alert on CFDA requiring clinical trial sponsors to register clinical trials online.

ADDITIONAL DRAFT REVISION CHANGES

Beyond these three core changes, the draft revision also contains other changes, such changes as related to the timing of CFDA inspections of generic drug manufacturing facilities. Under the current DRR, CFDA conducts inspections of generic drug manufacturing facilities prior to approval of the generic manufacturer's CTA. The draft revision would require CFDA to conduct its inspection after completion of the clinical trial or bioequivalence study and the submission of application materials, but before CFDA finally approves the generic drug. This change is meant to improve the overall effectiveness of the process for assessing generic drugs. As CFDA's drafting explanation states, the bioequivalence study, for example, can cause changes in the formulation of the drug or the manufacturing process. A post-study facility inspection would, therefore, increase the "effectiveness and quality" of the inspection at assessing the safety of the product ultimately going on the market. Another change involves adding a requirement for certification of compliance with Good Laboratory Practices for institutions conducting non-clinical safety assessments.

These changes could potentially have a significant effect on pharmaceutical companies doing business in China. As a result, industry should continue to monitor the progress of the draft revision as it moves forward. As noted above, comments on the DRR revisions are due on December 13, 2013.

If you have any questions concerning the material discussed in this client alert, please contact the following members of our Food & Drug Practice Group:

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