COVINGTON

China Promulgates Revised Drug Registration Regulation

April 29, 2020

Food, Drugs, and Devices

On March 30, 2020, the State Administration of Market Regulation of China, the parent agency of the National Medical Products Administration (NMPA), released a revised Drug Registration Regulation (Revised DRR). The Revised DRR implements a significantly revised Drug Administration Law (DAL) adopted by China's Standing Committee of National People's Congress and effective in 2019 (see our previous client alert on the revised DAL here).

The Revised DRR is arguably the most critical implementing regulation of the DAL. It is the regulation that governs research and development of innovative and follow-on medicines, their pre-market inspection and registration for marketing, and their license amendments and renewals. The Revised DRR goes into effect on July 1, 2020. It is the first major revision of the DRR since 2007.[1]

Drug Registration Categories

The requirements to develop and register a medicinal product in China depend on its type, i.e., small molecule drug, biological product, or Chinese medicine. Each type is then divided into registration categories, which determine the materials that the applicant must provide as part of its registration application (i.e., clinical trial application (CTA), marketing application, supplemental marketing application, renewal application). China began to reduce the number of registration categories in 2016, reducing the categories for small molecule drugs from six (some with six subcategories) to five broad categories.

The Revised DRR provides three registration categories for each type of medicine. For chemical drugs, registration categories include innovative drugs, improved new drugs, and generics. For biologics, registration categories include innovative biological products, improved new biological products, and marketed biological products (including biosimilars)—a marked reduction from the 15 categories that existed previously.[2] The meaning of the third category of biologics is unclear; it is not further defined in the Revised DRR.

Consistent with earlier drafts of the DRR released in 2019 and the DAL, the Revised DRR does not include separate sections for "imported drugs" nor any registration category for "drugs

[1] NMPA has released several implementing rules for the DAL, including new manufacturing regulations (here) and a good manufacturing practice revision (here), as well as new good clinical practice regulations (here).

[2] Revised DRR, Art. 4. None of the terms "innovative drug," "new drug," or "generic drug" is defined in the DRR itself. Other regulations and policies have contained definitions, but it is not clear if China will maintain them once the Revised DRR goes into effect.

marketed overseas but not marketed in China." It is unclear what this omission means and how drugs made and approved abroad integrate into the Revised DRR's broad registration categories.

In the 2007 version of the DRR, much of the information about registration categories was included in the appendices. The Revised DRR does not include appendices. Instead, the Revised DRR states that detailed classifications and corresponding requirements for application materials, including for drugs manufactured outside of China, will be formulated by NMPA according to product characteristics, innovation level, and review management needs of the medicines.[3] Neither NMPA nor its Center for Drug Evaluation (CDE) has issued these detailed implementing guidelines.

Applicant Requirements for Marketing Application Holders

Consistent with the DAL,[4] the Revised DRR sets forth criteria for being a marketing authorization holder (MAH) and the responsibilities of the MAH. The scope of potential MAH applicants in the Revised DRR includes both domestic and overseas entities or research institutions that can assume corresponding legal responsibilities.[5] If a foreign entity is to be the MAH, it must designate an entity in China to perform the MAH's obligations. Both are required to have quality personnel and a quality system necessary to supervise manufacturing. MAHs are responsible for the safety, quality, and effectiveness of the product and have a variety of post-market obligations under the DAL, including development, registration, and various pharmacovigilance requirements.

The Revised DRR also requires that, at the time of the application, the MAH and the drug manufacturer have obtained a drug manufacturing license.[6] A drug manufacturing license is issued to an entity by provincial drug administrations. Based on the Revised DRR and the drug manufacturing regulations released simultaneously, it is possible for a MAH to obtain a drug manufacturing license without facilities or equipment if it uses a contract manufacturing organization, provided it meets other qualifications required for a manufacturing license (e.g., qualified personnel and system).[7]

Neither the DAL or the Revised DRR makes clear whether a domestic MAH may use foreign manufacturing sites, or vice versa. Currently if the manufacturing location is in China, the license holder must be in China, and if the manufacturing location is outside of China, the license holder must also be outside of China.

Research and Development Process

The Revised DRR builds on earlier reforms to the research and development process for drug products. It also ties China's system closer to the guidelines of the International Conference on the Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). For

[3] Revised DRR, Art. 4.
[4] DAL, Art. 38.
[5] Revised DRR, Art. 9.
[6] Revised DRR, Art. 50.
[7] Measures for the Supervision and Administration of Drug Production, Art. 6-7. It is not clear from the Revised DRR how the drug manufacturing license will be issued to foreign MAHs or foreign manufacturers.

example, NMPA and CDE have begun accepting applications and safety reports during clinical trials in the format provided for in ICH guidelines.

Clinical Trial Application Process

China generally requires clinical data to support approval of medicines. The default requirement has generally been a clinical trial conducted in China, although NMPA has made strides in accepting foreign data and finalizing guidance on real world evidence. The Revised DRR defines clinical trials as studies to support registration applications for marketing; this appears to exclude investigator-initiated trials. The Revised DRR permits clinical trials to proceed in accordance with the submitted protocol if there is no objection from NMPA within 60 working days of the date of filing the application.[8]

The Revised DRR also clarifies that after receiving the initial clinical trial approval, the applicant does not need to apply to NMPA for additional clinical trial approval for subsequent phases of trials. Instead, the sponsor of the clinical trial only needs to obtain approval from the ethics committee and file the relevant protocol and supporting documents with CDE.[9]

Clinical Trial Inspections

The Revised DRR provides that CDE will make a risk-based assessment as to whether to conduct an inspection of a clinical trial. CDE will make that assessment according to the level of drug innovation and the past verification history of the clinical trial site.[10]

The Revised DRR also adopts a regular safety monitoring mechanism that requires the trial sponsor to submit a safety report to CDE every year (i.e., a Development Safety Update Report). Failure to submit such a report could lead to the suspension or termination of the trial by NMPA.[11] The Revised DRR also provides for a mandatory pre-registration inspection of manufacturing sites for all innovative and improved small molecule drugs and biologics.[12] Separate registration testing of samples is required prior to marketing registration.[13]

Amendments to Clinical Trial Applications

The Revised DRR allows sponsors to make amendments to the clinical trial plan and sets forth different requirements depending on the impact of the change on trial subjects' safety. If a sponsor determines that the subjects' safety will not be affected, it may implement the change and record such change in the Development Safety Update Report. In the case of a change that could potentially affect subject safety, the sponsor must submit a supplementary application, which is deemed to be approved if CDE does not object in 60 working days.[14]

Transfer of Clinical Trial Applications

The Revised DRR, makes clear that it is possible to change the sponsor of an approved CTA. The Revised DRR requires that the new sponsor assume the relevant responsibilities and

---

[8] Revised DRR, Art. 23.
[9] Revised DRR, Art. 26.
[10] Revised DRR, Art. 46.
[11] Revised DRR, Art. 28.
[12] Revised DRR, Art. 47. NMPA may also require site inspections prior to generic drug registration.
[13] Revised DRR, Art. 51-58.
[14] Revised DRR, Art. 29.

obligations for the trial.[15] It is not clear whether there are other requirements associated with this sponsor change process.

Expanded Access

Earlier drafts of the DRR had included a provision on an expanded access program for investigational products. The Revised DRR, however, no longer includes this provision. The DAL includes an authorization for expanded access programs.[16]

Priority Review and Approval Categories

The Revised DRR formally adopts various procedural programs to accelerate the review and approval of certain marketing applications based on, among other things, the severity or rare nature of the illness and the clinical need for the drug. NMPA has implemented various expedited approval programs since 2009 and expanded those programs beginning in 2015. The programs in the Revised DRR include a breakthrough program, a conditional approval program, a priority review program, and a special approval program.[17]

Applicants should apply for the breakthrough and conditional approval programs during the clinical trial stage, while the priority review program should be applied for during the marketing authorization stage.[18]

- The **breakthrough program** applies to innovative drugs or improved new drugs that are used for the prevention and treatment of diseases that seriously endanger life or seriously affect the quality of life, for which there is no effective measure of prevention and treatment or, compared with existing measures of treatment, there is sufficient evidence proving the obvious clinical advantages. If selected, applicants may request communication with CDE, and CDE reviewers will provide comments on the applicant's development strategy.
- The **conditional approval program** is for: (i) drugs that treat life-threatening injuries with no effective treatment, and early trial data indicates efficacy and potential clinical value; (ii) urgently needed drugs for the public health with clinical trial data that indicates efficacy and potential clinical value; or (iii) urgently needed vaccines for major public health emergencies, or that are deemed by the National Health Commission as urgently needed, for which the benefits outweigh the risks. NMPA will place post-marketing conditions on drugs under this program and a timeline for completion.
- The Revised DRR sets forth three types of **priority review program** for drugs: (i) urgently needed drugs in short supply, and innovative drugs and improved new drugs for the prevention and treatment of serious infectious and orphan diseases; (ii) new varieties of pediatric drugs, dosage forms, and specifications that meet the physiological characteristics of children; (iii) urgently needed and innovative vaccines; and (iv) drugs

[15] *Id.*
[16] DAL, Art. 23. The DAL provides that expanded access programs, in which patients who are not subjects in a trial are allowed to receive the investigational drug, are possible for serious and life-threatening diseases for which there is no effective treatment, provided the program is reviewed and the patients give informed consent.
[17] Revised DRR, Art. 13.
[18] Revised DRR, Art. 59, 63 and 68.

approved under the breakthrough or conditional approval programs.[19] CDE evaluates priority review drugs for marketing approval on an expedited timeframe and priority review drugs receive priority for other procedures, i.e., inspection, registration testing, and approval of nonproprietary names.

- The **special approval program** applies when there is a pending or actual public health emergency, during which NMPA may legally decide to implement special approvals of drugs needed for the prevention and control of such public health emergency. For example, medicines to prevent or treat COVID-19 may use the special approval program to obtain expedited review and approval from NMPA during the pandemic.

Timelines

The Revised DRR provides clearer timelines for reviewing and approving the various types of registration applications described above, and for conducting registration inspections and registration testing. Notably, certain times—e.g., the time required to conduct an overseas inspection, organize expert consultation meetings, and delay by an applicant to supplement materials—will not be included in the relevant work time limit.[20]

Intellectual Property

The Revised DRR is silent on intellectual property. The Revised DRR removes the current DRR's provisions that require an applicant to submit a declaration that its application does not infringe existing patents of others and that prohibit NMPA from accepting follow-on applications until two years prior to patent expiry of the relevant patent on an originator drug. There is no mention of patent linkage or other measures to facilitate early resolution of patent disputes before infringing products are approved and marketed, nor regulatory data protection (RDP) for innovative products. Patent linkage and RDP were promised in the Opinions on Deepening Reform of the Review and Approval System to Encourage Innovations of Drugs and Medical Devices (Document No. 42, 2017) and were included in the US-China Phase One Trade Agreement.

According to an explanation on the latest draft of DRR in 2019, the long-standing limited patent enforcement mechanisms were removed because the "relevant principles" of a patent linkage system need to be established in "high level" laws and regulations. China has not yet released any such proposals.

If you have any questions concerning the material discussed in this client alert, please contact the following China-focused members of our Food, Drugs, and Devices practice:

John Balzano	+1 212 841 1094	jbalzano@cov.com
Julia Post	+1 202 662 5249	jpost@cov.com
Aaron Gu	+86 21 6036 2607	agu@cov.com
Muyun Hu	+86 21 6036 2519	mhu@cov.com

[19] Revised DRR, Art. 68.
[20] Revised DRR, Art. 103.