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China Adopts Revised Drug Administration Law

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Food, Drugs, and Devices

On August 26, 2019, China's Standing Committee of National People's Congress ("NPC) adopted a significant revision of the Drug Administration Law ("DAL"). The newly adopted DAL ("Revised DAL") will go into effect on December 1, 2019. The Revised DAL is the first overhaul of the DAL since 2001.¹

Perhaps the most significant feature of the Revised DAL is the adoption of a nationwide marketing authorization holder ("MAH") system. This system links marketing licenses directly to the products, permitting flexibility in designing contract manufacturing and distribution arrangements. The Revised DAL addresses a number of other significant issues, including encouraging drug innovation, facilitating the drug approval process, improving drug traceability and pharmacovigilance, and amending the definition of counterfeit drugs. This client alert highlights and summarizes important takeaways of the Revised DAL.

Expansion of MAH System Nationwide

The Revised DAL officially adopts the Pilot MAH Program ("Pilot Program") that began in 10 provinces and cities in 2015 and was extended through November 2019.² The Pilot Program allows domestic research institutions, drug manufacturers, and individuals to hold licenses to market drug products without holding a manufacturing license for a facility. Previously, the facility license requirement blocked research-based companies from bringing their drugs to market without partnering with a larger company. Companies abroad that manufacture imported drugs and hold imported drug licenses could not participate in the Pilot Program.

Under the Pilot Program, qualifying individuals or entities can either contract out to one or more contract manufacturers or distributors or hold their own manufacturing and distribution licenses for certain activities.³ MAHs are permitted to sell their drugs directly to another distributor without having to apply for a drug distribution license, provided that they meet certain substantive criteria.

Although the Revised DAL largely adopts the contours of the Pilot Program, there are a few notable differences in the Revised DAL:

- Perhaps most notably, in the Revised DAL a foreign entity can now be a MAH, provided that it designates an entity in China to perform the MAH's obligations.⁴ The Revised DAL does not make it clear whether a domestic MAH may use foreign manufacturing sites, or vice versa. Under current practice, the manufacturing location dictates whether the drug product and the license holder is domestic or foreign. In other words, 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 be outside of China.
- Although the scope of potential MAH applicants in the Revised DAL includes enterprises, research institutions, and "others,"⁵ it is not clear whether "others" would still

include individual researchers, as is the case in the Pilot Program. In fact, the State Council noted in a 2018 observation report regarding the Pilot Program that individual researchers might not be able to ensure the safety and quality of the products due to their limited capabilities, and there is no precedent in any of the 10 Pilot Program provinces that an individual researcher has successfully become an MAH.⁶

The Revised DAL sets forth a more concrete, consolidated list of MAH responsibilities. Together with establishing a stronger pharmacovigilance and post-market surveillance system (discussed below), the Revised DAL makes it clear that MAHs are responsible for the safety, efficacy, and quality of their drugs during the entire "life-cycle," including non-clinical research, clinical trials, manufacture, distribution, and post-marketing surveillance.

Importantly, similar to the Pilot Program, the Revised DAL allows transfer of a product's marketing authorization, provided that the transferee has the capacity for quality control, risk management, and compensation for claims and to ensure the safety, efficacy, and quality of the product.⁷ Details on how a transferee can demonstrate sufficient capacity in this regard are not clear.

Encouragement of Innovation

The newly adopted DAL codifies certain prior reform policy measures based on a 2017 policy document (the Innovation Opinion).⁸ These include the following examples.

Priority Review

The Revised DAL adopts China's existing commitment to encourage clinical value-oriented drug innovations,⁹ stating that priority review and approval will be available for drugs for pediatric indications, urgently needed drugs for clinical use that are in short supply, new drugs for major contagious diseases, or drugs for orphan diseases.¹⁰

Conditional Approval

The Revised DAL adopts a conditional approval pathway that had already been established by prior policy documents. Drugs that treat life-threatening illnesses for which there is no effective treatment, and drugs for which there is an urgent public health need, can be approved on the condition that studies are completed post-marketing if the drug's effectiveness has been demonstrated through early-stage clinical trial data.

The MAH of a conditionally approved drug must undertake risk management measures in addition to completing required supplementary research in accordance with the conditions set forth in its marketing authorization. Failure to meet these conditions could result in the revocation of the drug license.

Clinical Trial Implicit Approval and Bioequivalence Notification Systems

The Revised DAL adopts an existing system that permits clinical trials to proceed in accordance with the submitted protocol if there is no objection from the National Medical Products Administration ("NMPA") within 60 working days of the date of filing the application. NMPA has been implementing this system for new drug trials since mid-2018. There is no limitation for "new" drug trials in the Revised DAL. Prior to this approach, NMPA's review and approval of a clinical trial application could take one year or longer. Separately, the Revised DAL also

incorporates and confirms another existing NMPA rule that bioequivalence studies for generic drugs are subject to a different notification system.

Notification System for Clinical Trial Sites

Clinical trials can be conducted only at institutions that have been inspected and accredited by NMPA with departments that are certified for that type of clinical investigation. Under the Revised DAL, the accreditation process no longer requires pre-approval; notification is sufficient. This notification approach has been in effect since 2017 for clinical trial sites that carry out bioequivalence experiments of generic drugs.¹¹ Also, prior to the Revised DAL, the notification system had never been implemented for new drug trials of new drugs, even though several drafts containing this proposal were announced over the past two years.¹²

Simplified Definition of "Drug"

The Revised DAL simplifies the definition of "drug" and removes active pharmaceutical ingredients ("APIs") from its scope.¹³ Whereas the prior definition contained a long list of different types of medicines,¹⁴ the new definition states that a drug falls into one of three categories only: "traditional Chinese medicines, chemical drugs and biological products." Classification of a product as a "drug" continues to be based on whether it is used to prevent, treat, or diagnose human illness with a purpose of regulating human physiological functions with designated indications or primary treatment functions, a use method, and dosage.

The removal of APIs from the definition leaves unclear the applicability of other drug-related rules to APIs. A separate article of the Revised DAL states that the production of APIs must comply with Good Manufacturing Practice ("GMP") rules and applicable standards,¹⁵ but it is not clear whether other drug-related rules would apply, such as Good Supply Practice ("GSP") or other distribution rules.

The Revised DAL does not define the terms, "new drug," "innovative drug," or "generic drug."

Combined Review for API, Pharmaceutical Excipients, and Packaging

Approval of APIs, pharmaceutical excipients, and packaging materials will now be combined with the drug registration review process, instead of requiring applicants to submit separate applications.¹⁶ The Revised DAL codifies the system that has been in place since November 30, 2017, when NMPA stopped accepting separate applications for APIs, excipients, and packaging, and began reviewing them together with the corresponding drug application.¹⁷

Abolition of Separate GMP and GSP Certificates

The Revised DAL combines drug manufacturing and distribution licenses with GMP and GSP certificates. Thus, only a single process and inspection should be necessary to accredit a facility for manufacturing or distribution. Drug manufacturers and drug distributors must still comply with current GMP and GSP requirements. And, indeed, pursuant to the Revised DAL, NMPA and its provincial counterparts are directed to strengthen their surveillance of drug manufacturers and distributors, including through regular and continuous site inspections.

Online Distribution of Drugs

The Revised DAL allows MAH and licensed drug distributors to sell drugs online, except for vaccines, blood products, narcotic drugs, psychotropic drugs, toxic drugs for medical use, radioactive drugs, pharmaceutical precursor chemicals and other drugs under special state administration.¹⁸ Third-party online drug distribution platforms must complete a record filing process, and are required to check the qualifications of the distributor's license and manage the drug distribution that occurs on the platform.

Unlike current rules and prior drafts of the DAL,¹⁹ there is no prohibition on the distribution of prescription drugs. Although this apparent flexibility in the DAL is significant, it does not necessarily mean that online distribution of prescription drugs will be permitted, and the final direction will likely be determined by implementing regulations. According to senior NMPA officials, the NPC adopted an "inclusive and prudent attitude" during the revision of the DAL, and will listen to the opinions of relevant departments to further draft administration measures for online drug distribution.²⁰

Improvement of the Drug Traceability System

The DAL requires MAHs, drug manufacturers, drug distributors, and hospitals to implement a drug traceability system.²¹ The purpose of this system is to ensure the traceability of a drug's entire life-cycle—from research through production and usage²²—to eliminate counterfeit or substandard drugs, and to conduct recalls accurately.

This reform follows a number of prior efforts to improve the drug traceability system. Over the last year, NMPA has been working on a traceability system under which MAHs, drug manufacturers, drug distributors, and relevant medical institutions are required to keep records of their activities and provide traceability data to NMPA through an online platform, which will be publicly available.²³ MAHs and drug manufacturers are required to assign a unique traceability mark, generated in accordance with a uniform coding rules, to each product packaging unit.²⁴ It is not clear how the Revised DAL will affect the implementation of NMPA's system. It is likely that NMPA will release more rules to clarify each party's responsibilities and the timing for implementation.

Pharmacovigilance System

The Revised DAL increases the requirements for pharmacovigilance, including requiring MAHs to create management plans, conduct post-marketing research to continually assess a drug product's safety and effective, and institute robust adverse event monitoring practices.²⁵

Specifically, a MAH is required to proactively monitor, gather, and analyze adverse events. While MAHs are primarily responsible for this work, drug manufacturers, drug distributors, and medical institutions also must regularly consider adverse events related to the products they make, distribute, or use. If they discover a suspected adverse event, they must report it promptly to the authorities in charge of drug and health administration at local levels. The precise details of this reporting system will be addressed in implementing regulations. The Revised DAL is not clear on whether or how the seriousness of the adverse event will affect reportability.

If a marketed drug has quality or other safety issues, the MAH must cease distribution and/or manufacturing immediately and conduct a recall.²⁶ Consistent with existing practice, NMPA has the power to order a recall and stop distribution, even if the MAH does not choose to do so.²⁷

The Revised DAL also creates a risk-based system for amending marketing authorizations, depending on the impact of the change on safety, effectiveness, and quality control. Significant changes require preapproval by NMPA, while lesser changes can be notified or included in periodic reports.

Expanded Access Programs

The Revised DAL creates an expanded access pathway for investigational drugs under which a company sponsor of a clinical trial in China can apply to establish an expanded access treatment program for patients with life-threatening illnesses that otherwise cannot qualify for a clinical trial.

To quality for expanded access: (1) the drug must be used for life-threatening diseases that lack effective treatment; (2) the drug must have demonstrated its potential effectiveness based on medical observations; (3) such use is in line with ethical principles; (4) such expanded uses have been reviewed and approved (although the approval pathway not clear), and have obtained patients' informed consent; and (5) the drug must be used within the clinical trial institution and used on patients with similar conditions.²⁸ Unlike the prior draft of the DAL in April 2019, the Revised DAL does not require that expanded access patients be incorporated into the scope of the trial.

Special Importation of Unapproved Drugs

The Revised DAL grants provincial governments authority to approve the one-time importation of unregistered foreign drugs for urgent clinical use. Under the prior DAL, the authority to approve importation of unapproved drugs belonged to NMPA, but the agency has rarely invoked this authority to approve these requests. This change is similar to the measures adopted as part of a pilot program in Hainan Province in the Bo'ao Medical Tourism Zone (see our alert, <u>here</u>) under which the local affiliate of NMPA can approve special importation.

Decreased Penalties for Importation of Unapproved Drugs

The Revised DAL removes manufacturing and importation of unapproved drugs from the definition of counterfeit drugs, and it reduces or eliminates the penalty for importation of small amounts of these drugs. Under prior practice, drugs imported or manufactured without NMPA approval were deemed counterfeit drugs with stringent penalties, including fines and criminal liability.²⁹ The Revised DAL still explicitly prohibits importing unapproved drugs, but now states that authorities might reduce the penalty or impose no penalty for the importation of a small amount of a drug that has been legally marketed abroad. The relevant provision does not limit this potential mitigation to importation for personal use.³⁰ The change likely follows from significant public and media attention on efforts to import inexpensive generic drugs.

Enhanced Penalties

Consistent with the trend in food and drug regulation in China over the last several years, the Revised DAL contains increased monetary and other penalties.

Increased Monetary Penalties

The Revised DAL increases monetary penalties for prohibited acts. For example, the potential fines for manufacturing or distributing a drug without a license, and for manufacturing or distributing counterfeit drugs, have increased from 2 to 5 times the value of the goods, to 15 to 30 times the value of the goods with a minimum fine of RMB 1,500,000 (about USD 208,000). Those who seek compensation under the law for quality issues (see below) may also request punitive sums in the amounts of 10 times the purchase price or three times the loss caused.

"First-Responsible-Party" Compensation Mechanism

The Revised DAL also establishes a "first party to be responsible" compensation mechanism, meaning whichever party (MAH, manufacturer, distributor, or hospital) first receives a claim as to quality issues is responsible for compensation if the claim is determined to be valid.

Increased Liability at the Individual-Level

The Revised DAL explicitly provides that legal representatives³¹ and executives in charge may be individually liable for prohibited acts, including monetary fines and debarment sanctions. The maximum penalty is now lifetime debarment from the pharmaceutical industry in certain cases.

No Patent Linkage or Regulatory Data Protection Provisions

Earlier policy documents proposed to establish in China a patent linkage system, regulatory data protection, and patent term extension for innovative drugs.³² These initiatives, however, were not included in the Revised DAL. Patent term extension was included in the latest draft of the Patent Law, which has not been finalized. Patent linkage and regulatory data protection have been included in NMPA proposed rules to some extent, but the agency has not finalized any of these rules.

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 practice³³:

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¹ The Drug Administration Law (Standing Comm. Nat'l People's Cong., 2019), available at: http://www.nmpa.gov.cn/WS04/CL2076/357712.html. The first DAL was promulgated in 1984, and then revised comprehensively in 2001. Minor amendments were made in 2013 and 2015.

³ Notice for Issuing the Drug MAH Pilot Plan (State Council General Office No. 41, 2016), available at www.gov.cn/zhengce/content/2016-06/06/content_5079954.htm.

⁴ Supra note 1, Article 38. The PRC entity should be jointly and severally liable with the foreign MAH.

⁵ Supra note 1, Article 30.

⁶ Report on the Implementation of "Decision on Authorizing the State Council to Implement the Drug MAH Pilot Program in Certain Areas" (State Council, 2018), available at: http://www.sohu.com/a/273285261_803087.

⁷ Supra note 1, Article 40.

⁸ The Opinions on Deepening Reform of the Review and Approval System to Encourage Innovations of Drugs and Medical Devices (CPC Central Committee General Office and State Council General Office 2017), available at http://www.gov.cn/zhengce/2017-10/08/content_5230105.htm.

⁹ Under NMPA's current policy, priority review is available for certain drugs that treat serious or life-threatening conditions, including new drugs for the treatment of HIV, cancer or orphan diseases, and new drugs that treat unmet medical needs. NMPA's new priority categories over the past two years include drugs that treat diseases prevalent among children and elderly people, drugs that are on national scientific research plans, foreign innovative drugs that transfer manufacturing to China, and drugs that are being developed simultaneously in the United States and Europe.

¹⁰ Supra note 1, Article 16 and 96.

¹¹ Notice on Several Issues Related to the Evaluation on the Consistency of Generic Drugs Quality and Efficacy (NMPA No. 100, 2017), available at: http://samr.cfda.gov.cn/WS01/CL1757/176734.html.

¹² Regulation on the Administration of Drug Clinical Trial Institutions (Draft for Comments) (NMPA, 2017), available at:

http://www.nmpa.gov.cn/WS04/CL2095/229367.html.

¹³ Drug Administration Law of the People's Republic of China, Article 2 (Standing Comm. Nat'l People's Cong., 2019), available at: http://www.npc.gov.cn/npc/c30834/201908/26a6b28dd83546d79d17f90c62e59461.shtml.

¹⁴ The prior DAL stated including this list: traditional Chinese herbal medicines, prepared slices of traditional Chinese medicines, traditional Chinese patent medicine, active chemical pharmaceutical ingredients and their preparations, antibiotics, biochemical drugs, radiopharmaceuticals, serum, vaccines, blood products and diagnostic drugs."

¹⁵ Supra note 1, at Art. 45.

¹⁶ Supra note 1, Article 25.

¹⁷ Notice on Adjusting the Review and Approval Process of API, Pharmaceutical Excipients and Packages (NMPA No. 146, 2017), available at: http://samr.cfda.gov.cn/WS01/CL0087/217747.html.

¹⁸ Supra note 1, Article 61.

¹⁹ Market Entry Negative List (NDRC and MOFCOM, 2018), available at: http://tgs.ndrc.gov.cn/fmqd/qdxz/201812/P020181225324125390049.pdf.

²⁰ See http://www.gov.cn/zhengce/2019-08/26/content_5424729.htm.

²¹ Supra note 1, Article 36 and Chapter 7.

²² Supra note 1, Article 7.

²³ The Guidance on the Construction of Drug Information Traceability System (NMPA No. 35, 2018), available at:

http://www.nmpa.gov.cn/WS04/CL2196/331501.html; and Basic Technical Requirements for Drug Traceability System, (NMPA No. 67, 2019), available at: http://www.nmpa.gov.cn/WS04/CL2138/357732.html.

24 Supra note 30.

²⁵ Supra note 1, Article 12.

²⁶ Supra note 1, Article 82.

²⁷ Supra note 1, Article 81 and 82.

²⁸ Supra note 1, Article 23.

²⁹ Drug Administration Law of the People's Republic of China, Article 48 (Standing Comm. Nat'l People's Cong., 2015), available at:

http://www.npc.gov.cn/wxzl/gongbao/2015-07/06/content_1942838.htm.

³⁰ Supra note 1, Article 124.

³¹ The "legal representative" refers to the person listed on the corporate registration documents in accordance with the law or the articles of association

of a legal entity, who acts on behalf of a legal entity in performing civil activities, not the lawyer.

³² Supra note 8.

³³ Meng Pu, Runze Li and Kexin Yang also contributed to the research and writing of this alert.

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² Decision on Authorizing the State Council to Implement the Drug MAH Pilot Program in Certain Areas (Standing Comm. Nat'l People's Cong., 2015), available at: http://www.gov.cn/xinwen/2015-11/04/content_5004817.htm; Decision of the Standing Committee of the National People's Congress on Extending the Period of Authorizing the State Council to Carry out the Pilot Program of Drug Marketing Licenses Holders System in Certain Areas (Standing Comm. Nat'l People's Cong., 2018), available at: http://www.gov.cn/xinwen/2018-10/27/content_5334906.htm