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Three Major Changes in the *Drug Registration Measure*

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Drug registration is an important part of drug administration and supervision. With the development of drug administration and supervision system in China, regulations on drug registration are improving step by step as well, developed from *Provisions for New Drug Approvals* (新药审批办法) (1999) , *Drug Registration Measures* (*Trial*) (药品注册管理办法(试行))2002 to *Drug Registration Measures* (药品注册管理办法) 2005. After a major revision in 2007, the Drug *Registration Measures* has been revised again this year, with the new *Drug Registration Measures* being implemented on July 1, 2020.

The revision of the *Drug Registration Measures* this year has implemented the new Marketing License Holders system (hereinafter referred to as "MAH") introduced in the *Drug Administration Law* revised in 2019, and made amendments corresponding to the revision of the *Drug Administration Law*. Furthermore, the revision has also responded to some hot topics including drug and vaccine safety, accelerated registration procedure, transparency of administrative and etc.

This article will focus on three major changes in this recently revised *Drug Registration Measures*.

1. Accelerated Registration Procedure of New Drugs

The new drug approval system in China has always been a precedent but less efficient process. Due to the lack of efficiency, many innovative drugs, orphan drugs, drugs in urgent clinical need sold in other countries are facing difficulties to be launched in China. To deal with this problem, a brand new chapter "Accelerated Drug Marketing Registration Procedure" has been added to the new *Drug Registration Measure*. This chapter has been released for public consultation in the early draft version in September 2019. After the global outbreak of COVID-19 which brings urgent needs for new drugs and vaccines, the implementation of accelerated registration procedure at this time encourages the public and the pharmaceutical companies to develop innovative drugs.

The current regulations only allow for special application procedure that applies to innovative drugs and new drugs treatment of serious diseases.[1] The revised *Drug Registration Measure* not only implements the Breakthrough Therapy Designation ("**BTD**") procedure for new drugs to treat serious or life threatening diseases, it also includes the conditional approval, priority review and approval procedures.

a) Procedures for BTD Drugs

BTD Drugs refers to innovative drugs or modified new drugs to be used during drug clinical trials for the prevention and treatment of diseases that seriously endanger lives or seriously affect the quality of lives, for which there is no effective measure for prevention and treatment or, compared with existing measures of treatment, there is certain sufficient evidence proving obvious clinical advantages. In relation to BTD drugs, applicants may apply to communicate with CDE personnel during the clinical trial, or ask for comments by the CDE personnel. When applying for marketing registration, BTD drugs can apply for conditional approval and priority review and approval to further accelerate the marketing.

It is noted that the *Drug Administration Law* revised in 2019 introduced expanded use if BTD drugs at the clinical trial phase, that is compassionate use, which refers to the use of BTD drugs mentioned above, upon approval and in line with ethical principles, to other patients with the same disease condition in the institution where such clinical trials are carried out. This expanded use progress provides to pharmaceutical companies more clinical data from patients outside the clinical trial, and it provides a chance to these patients that cannot be enrolled or fails to participate in a clinical trial a chance to save lives.

b) Conditional Approval Procedure

Conditional approval procedure applies to (i) BTD drugs, (ii) the drugs that are urgently needed for public health, (ii) vaccines that are urgently needed to deal with major public health emergencies or other vaccines which the National Health Commission deems to be urgently needed. The drugs

[1] Section 45, *Drug Registration Measures* 2007.

under (i) and (ii) may only apply for conditional approval if data generated from clinical trials can prove its efficacy and forecast its clinical value. The vaccines that are urgently needed may apply for conditional approval as long as the benefits brought by the vaccine outweigh the risks associated with them. The latest *Drug Administration Law*[2] and *Vaccine Administration Law*[3] have also included the conditional approval procedure. For example, the drug GV-971 for Alzheimer's disease has been registered with conditional approval. This revision implements the conditional approval following the practice under the *Drug Administration Law*, and further clarifies the application of the conditional approval procedures.

After accessing the potential risks, possible efficacy of the treatment, and the instant value raised from registration, the drug that is in urgent clinical need, and for the diseases without other effective treatments can be registered before the completion of all researches, but the registration certificate shall indicate the validity period of the conditional approval registration certificate, the researches to be completed after marketing and the time limit for completion, and other relevant matters.[4] If MAH fails to complete the researches or fails to prove the benefits outweigh the risks, the National Medical Products Administration ("NMPA") may take actions, including revocation of the drug registration certificate. [5]

c) Special Approval Procedure

Special approval procedure applies to situation when threatening or actual public health emergency exists. Once the NMPA decides to adopt a special approval procedure, it will accelerate and perform in parallel acceptance, review, verification and inspection of drug registration procedures. The special approval procedure was initially put forward in the *Drug Special Approval Procedure* released by the CFDA, and this revised *Drug Administration Measures* has finally included such procedure in a formal ministerial measure.

After the global outbreak of COVID-19, the conditional approval procedure and special approval procedure accelerates the development and approval of new drugs and vaccines. By April 27, 2020, 625 clinical trials for the therapies of COVID-19 have been registered in the Chinese Clinical Trial Registry.[6] Although some of these clinical trials have been rescinded, or are unable to pass the early experimental phase, fast and effective approval procedure ensures that research institutions, pharmaceutical companies can keep trying and find out the effective therapy as soon as possible.

d) Priority Review and Approval Procedure

Priority review and approval procedure applies to (i) drugs in short supply in urgent clinical need, innovative drugs and modified new drugs for the prevention and treatment of serious infectious

[2] Section 78, *Drug Administration Law.*
[3] Section 20, *Vaccine Administration Law.*
[4] Section 64, *Drug Administration Measures* 2020.
[5] Section 67, *Drug Administration Measures* 2020.
[6] http://www.chictr.org.cn/index.aspx

diseases, rare diseases and other diseases; (ii) pediatric drugs of new varieties, dosage forms and specifications that meet the physiological characteristics of children; (iii) vaccines urgently needed for disease prevention and control and innovative vaccines; (iv) drugs included in the procedures for BTD drugs; (v) drugs meeting the conditions for conditional approval; and (vi) other circumstances for priority review and approval stipulated by the NMPA.

Applicants for the drug registration that has been included in the priority review and approval procedure are allowed to communicate with the CDE before submitting an application. Additionally, priority review and approval is subject to a shorter review period. Generally speaking, a review of drug registration takes more than 200 days, but the review under the priority review and approval procedure takes no more than 130 days or 70 days with respect to orphan drugs in urgent clinical need which have been marketed overseas but not yet marketed in China.

It is worth noting that the priority review and approval, conditional approval and BTD procedures can be used simultaneously. If several accelerating registration procedures apply at the same time, the approval procedure will be accelerated greatly and the drug can reach the market within the shortest time.

2. Promoting development of Generic Drugs

Within the context of encouraging the development of innovative drugs, the revised *Drug Registration Measure* also supports the development of high quality generic drugs. Increasing the quality of generic drugs and replacing certain branded drugs with qualified generic drugs can make treatment more affordable and meet different needs in the society. The revision of *Drug Registration Measure* applies to generic drugs an approval procedure which is materially similar to that applied to innovative drugs.

The new drug registration application system under the existing *Drug Registration Measure* is divided into the system for innovative drug applications and for generic drug applications, where different application procedures and different standards apply. For the generic drugs, it is only required to have the same active ingredient, administration, dosage, specification and therapeutic effect as the original drug.

With the development of generic drugs during recent years, it has been found that even generic drugs have the same active ingredient, administration, dosage, specification and are able to have the same "therapeutic effect", their quality still cannot compete with their branded counterparts. Furthermore, there was no requirement that the "original" drugs (with which generic drugs are supposed to compare) must be branded drugs. The original drugs of certain generic drugs are themselves generic. The generic drugs are developed based on another generic drugs, and the disparities in the quality and efficacy between the generic drugs and the branded drug become larger.

After the revision, innovative drugs and generic drugs will not be subject to two separate registration systems. The drug registration system is now classified by the type of drugs, including traditional Chinese

medicine, chemical drugs (including innovative drugs, modified new drugs and generic drugs) and biological products. Branded drugs and generic drugs are now subject to the same standard, and the simple requirement of the same "active ingredients, route of administration, dosage form, specifications" has been abandoned. Generic drug is now required to "be consistent with the quality and efficacy of the reference-listed-drugs ("RLD")." [7]It not only sets a higher standard for the quality of generic drugs, but also requires that generic drugs must be equivalent to the qualified RLD, rather than any original drugs.

This revisions to the approval standard for generic drugs is not started from scratch. The *Chemical Drugs Registration Classification Reform Work Plan* and *New Chemical Drugs Registration Classification and Declaration Documents Requirements* published in 2016 have already proposed that sufficient test data and documentation must be provided to prove that generic drugs have the quality and efficacy equivalent to those of the branded products. Since the *Opinions on Carrying out the Consistency Evaluation of the Quality and Efficacy of Generic Drugs* and related procedures for the quality and efficacy consistency evaluation of generic drugs were released, the standard for the selection of RLD has become higher and requirement for the consistency of generic drugs and branded drugs has become stricter.

In this revised *Drug Registration Measures*, generic drugs are required to be consistent with branded drugs at the drug registration procedure. The standard for generic drugs will be increased in the future, and the generic drug manufacturers and developers are under the pressure to meet this higher standard.

This revised *Drug Registration Measures* also exempt generis drugs from bioequivalence trials in the consistency evaluation so that qualified generic drugs can apply for marketing authorizations without the bioequivalence trials. The standard for exempt from bioequivalence trials has not published yet and reference can be made to the *Guidelines for the Exemption from Bioequivalence Trials in Human Bodies* for consistency evaluation.

After revision of the *Drug Registration Measures*, the R&D costs for generic drugs will increase correspondently. However, the volume-based purchasing scheme has showed its strong support to generic drugs passing the consistency evaluation and, consequently, the market share of high quality generic drugs will grow eventually.

3. Improving Full Lifecycle Administration for Drugs

The Relevant Policies on Encouraging the Innovation of Drugs and Medical Devices and Implementing Full Lifecycle Administration of Drugs and Medical Devices published by CFDA in 2017 brought forth the concept of lifecycle administration of drugs for the first time. The revised *Drug Registration Measures* further refines and implements the full life cycle management of drugs.

[7] Section 35, *Drug Administration Measures* 2020.

a) Implementation of MAH system

The MAH system anticipated by the industry has been launched in the *Drug Administration Law*. Drug registration plays an important role in quality administration and supervision of drugs. The revision of the *Drug Registration Measures* has fully integrated the MAH system into the drug registration process.

Under the existing *Drug Registration Measures*, all applicants applying for new drug registrations and generic drug registrations must hold a drug production license. In practice, R&D institutions are seldom qualified for drug production and have to partner with another manufacturer to apply for marketing authorizations. Under the new MAH system, MAH may not be drug manufacturers. Applicants are no longer required to hold a production license. MAH can be any enterprise or drug development institution that can bear relevant legal responsibilities and overseas applicants must designate a Chinese legal entity to handle relevant drug registration matters. The new drug registration system allows R&D institutions that have no production capacity to obtain the drug marketing authorization in their own names, which encourages R&D institutions to develop more drugs.

Together with the new *Drug Administration Law* and the MAH system, once an applicant obtains a drug marketing authorization, it becomes a MAH and must be responsible for the full lifecycle of the drug. Beyond the legal responsibilities borne by different subjects for the drugs in development, production and distributions, MAHs bear the responsibilities for the safety, effectiveness, and quality controllability of drugs during the entire process of drug development, production, operation, and use under the new system. The new system helps to improve the traceability and accountability of drug management.[8] However, at the same time, it also raises a stricter requirement for MAH's c management.

b) Bundled Review and Approval

Under the existing drug registration process, API, pharmaceutical excipients, and packaging materials must be reviewed and approved separately. Although separate revision and approval can ensure the quality of each material, problems may exist during the combination of different materials. The newly launched "bundled review and approval method" in the revision, a review of the API, pharmaceutical excipients, packaging materials and containers used in direct contact with pharmaceutical preparations is required to be performed in the registration application. Only when the materials are combined reasonably and the researches are conducted over the combination as a whole, the quality of the final compound can be assured.

Furthermore, the bundled review and approval process also allows the applicants to choose materials from a larger range. Applicants are allowed to use registered materials or unregistered

[8] Section 6, *Drug Administration Law.*

materials. For unregistered chemical API, pharmaceutical excipients, packaging materials and containers that directly contact drugs, the applicant must submit the relevant researches for these materials during applications for registrations.

c) Strengthening the Supervision over the Clinical Trial Institutions

Data generated from clinical trials are the foundation of drug registration reviews and approvals. Fraud in data will seriously affect the quality and safety of marketed drugs. If clinical trials are unethical, fail to comply with the operation requirements, or bear safety risks, interests of trial subjects or of general public will be adversely affected. The existing *Drug Registration Measures* only supervises the applicants, and not the clinical trial institutions.

In response to the problems in clinical trials, the revised measure strengthened the supervision over clinical trial institutions (including non-clinical safety evaluation research institutions). Drug administration at provincial level have vires to conduct routine supervisions and inspections over clinical trial institutions, and to establish drug safety credit archive, to record and publicize (1) issuance of licenses, (2) results from routine supervisions and inspections, and (3) sanctions of illegal acts. These methods impose a greater responsibility on clinical trial institutions, urging them to conduct clinical trials with greater cautions. Pharmaceutical companies can, through public information, avoid cooperating with clinical trial institutions that have repeatedly violated regulations, so as to avoid penalties and adverse impact on the clinical trials.

4. Conclusion and Forecasting

Following the revision of the *Drug Administration Law* and *Vaccine Administration Law*, the *Drug Registration Measures* has been revised as expected. The revision of the *Drug Registration Measures* reflects the new developments in the administration of drug registration in China.

China's drug supervision has shifted from a manufacturer-oriented system to a product-oriented system, paying attentions on the entire drug eco-system, covering R&D, clinical trials, production and marketing, and capturing all-round and overall supervisions over API, pharmaceutical excipients, packaging and finished drugs. The new system avoids the loopholes in separated supervision by different participants, and also requires the MAH to take overall responsibility for drugs. It increases MAH's responsibilities, but also grants MAHs with leading positions in the whole lifecycle of the drugs.

At the same time, the reformation of China's drug registration system encourages R&D in the pharmaceutical industry, and facilitates the registrations of those clinically-needed and valuable drugs with a more efficient review and approval process, so as to encourage companies to invest in new drugs development. It is foreseeable that more small and medium-sized technology-oriented pharmaceutical companies will develop better in near future.

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