GARRIGUES

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RECENT DEVELOPMENT ON AMENDMENTS OF THE DRUG ADMINISTRATION LAW (DRAFT FOR CONSULTATION)

To deepen the reform of drug evaluation and approval system, encourage innovations in drugs, and safeguard the rights and interests of the public in regard to drug consumption, China Food and Drug Administration (the "CFDA") has published series of pharmaceutical laws and regulations recently. Among others, the most notable is the *Drug Administration Law of the People's Republic of China (draft for consultation)* (the "**Draft**") promulgated on October 23th, 2017 due to several major reforms in the area of drug registration and administration.

According to the Draft, China will fully adopt a drug Market Authorization Holder (the "**MAH**") system, the approval regime of clinical trials will be simplified, and overseas trial data will be accepted in drug registration, though an on-site check by CFDA might still be applied.

1. IMPLEMENTING THE DRUG MARKETING AUTHORIZATION HOLDER SYSTEM

As early as in 2015, the document Guo Fa [2015] No.44 (*Decision of the Standing Committee of the National People's Congress on Authorizing the State Council to Carry out the Pilot Drug Marketing License Holder System in Certain Places and Relevant Issues*) proposed to launch a pilot MAH scheme. In 2017, the State Council issued an effective notice (*the Circular of the General Office of the State Council on Promulgating the Pilot Program for the Drug Marketing Authorization Holder System (Guo Ban Fa [2016]No.41)* (the "**Pilot Program**")), dated May 26th, 2016, formally authorizing a trial plan for new drug MAH system in ten provinces: Beijing, Shanghai, Tianjin, Hebei, Jiangsu, Zhejiang, Fujian, Shandong, Guangdong, and Sichuan. Pharmaceutical research institutions and individual researchers in these provinces can submit an application for clinical trials or marketing authorization registration. Applicants obtaining marketing authorizations and approval documents can become MAHs and take legal responsibility for clinical trials, production, and marketing, which is previously not allowed.

According to the Draft, a new article is introduced as Article 5, reading "the State runs the drug marketing authorization holder system, and parties authorized to launch drugs on the market shall bear legal liability for the controllable safety, effectiveness and quality of drugs", which means that the MAH system will be rolled out nationwide soon.

(1) Qualification of Marketing Authorization Holder

Article 31 of the Draft provides that "a MAH shall be an applicant that succeed in obtaining a drug approval number", which does not clearly state the scope of subject for being an applicant.

According to the Pilot Program for the System of MAH issued in 2016, applicants include all drug research institutes in the pilot administrative region and researchers working in the pilot administrative region concerned with the nationality of the People's Republic of China. However, in accordance with the *Measures for the Administration of Drug Registration (revised version)* promulgated on the same day of the Draft, there should be a requirement that the domestic applicant for the registration of the drug shall be a pharmaceutical manufacturer or Research & Development institution (the "**R&D institution**") in China and that the overseas applicant should be foreign legal pharmaceutical manufacturers. Therefore, if the Draft is implemented simultaneously with the revised Administration of Drug Registration, natural persons may not be able to become MAH.

(2) Separation of Drug Marketing Approval and Drug Manufacturing Approval

For a long time, China has been implementing the system of binding the drug manufacturing approval and the drug marketing approval according to current Drug Administration Law[1]. Under this system, R&D institutions may obtain new drug certificates. However, if they want to put the drugs into production, they must invest a lot

[1] *Drug Administration Law (2015)* Article 31: "Production of a new drug or a drug admitted by national drug standards shall be subject to approval from the drug regulatory department under the State Council, and a drug approval number shall be issued for it."

of money into self-built factories and production lines to obtain drug manufacturing licenses, GMP certificate, in the end, applying for drug approval numbers. Due to lack of capital for R&D institutions, therefore most of them are more inclined to transfer their R&D achievements to pharmaceutical manufacturers in the form of technology transfer. For R&D institutions, the cost of self-built is too expensive, and the transfer of technology may lead to a low return rate on R&D investment. Both approaches are not the best choice.

Now, the Draft has made a major improvement of this system. In accordance with Article 31 of the Draft "Where a drug marketing authorization holder manufactures drugs on its own, it shall have obtained a drug manufacturing certificate; where it distributes drugs itself, it shall meet the requirements on drug distribution as stipulated in this Law; where it entrusts a drug manufacturing or distributing enterprise with the required qualifications to manufacture or distribute its drugs, it shall enter into an entrustment agreement with the entrusted enterprise to clarify the rights, obligations and duties of each party, in order to ensure that the manufacturing or distribution activities of the entrusted enterprise comply with the requirements set out in this Law", this article formally separates the listing of drugs from the manufacture approval, which encourages R&D institutions, in the meantime it is also a good news for those without research and development capabilities' pharmaceutical factories.

(3) Change of MAHs

All along, there are no laws and regulations on the issue whether the MAHs can be changed or transferred, which urgently needs a solution due to the actual needs for transfer, inheritance, M&A and dissolution in practice.

In the Draft, it officially said that "Changing the drug MAH requires the satisfaction of the requirements set forth in this Law and shall be subject to the approval of the drug regulatory department under the State Council", which means changing or transferring the MAH is legally feasible in the future.

This improvement has brought us in line with international standards, establishes the long-term development trend of the MAH system, and promotes the development of Chinese medical science.

(4) Obligation of Re-evaluate of MAH

The current Drug Administration Law stipulates that the drug regulatory department under the State Council shall re-evaluate the drugs that have been approved for manufacturing and marketing[2]. However, the Draft attributed the drug re-evaluation obligations in Article 34[3] to the MAHs and has further stipulated in the same article that "Where a drug MAH fails to perform its obligations of re-evaluating drugs as required, the drug regulatory department under the State Council shall order it to carry out such re-evaluation. The said department may directly organize the reevaluation of drugs in question when necessary".

Although the Draft does not directly impose strict legal liabilities on the MAH for not performing the drug re-evaluation obligations, but MAH should give attention to.

(5) Legal Liabilities of MAH

The Draft sets clear legal liability for the MAH. Article 94 of the Draft stipulates that "any MAH that violates the provisions of Article 32 in this Law shall be fined more than CNY100, 000; where the case is serious, it shall be ordered to suspend production or business operation for rectification, with its drug approval document withdrawn as the worst measure taken; where a crime is constituted, its criminal liability shall be investigated."

[2] *Drug Administration Law (2015)* Article 33: "The drug regulatory department under the State Council shall organize experts in pharmaceutical, medical and other fields to evaluate new drugs and re-evaluate the drugs having already been approved for production."

[3] *Drug Administration Law (2017 draft version)* Article 34: "Under any of the following circumstances, a drug MAH shall re-evaluate the drug voluntarily:

1. Where the safety and effectiveness of drugs are understood differently, according to the latest development of scientific research;

2. Where additional potential risks are found or the risks change;

3. Where it is found by monitoring the adverse effects of drugs and other adverse reactions in connection with the use of these drugs and evaluating the risks of these drugs that the risks of these drugs outweigh their benefits."

In addition to the aforementioned legal liability clause of Article 94, the Draft also adds corresponding liabilities in the relevant legal obligations and liabilities provisions of the MAH, e.g. Article 71[4], 72[5], 80[6]. At the same time change the "drug manufacturer" to the "MAH" in the relevant provisions, e.g. Article 90[7], 91[8], 93[9].

It is noteworthy that, although the changes are reasonable in the relevant clauses mentioned above, but the manufacturing factories which are only authorized of production are likely to evade the relevant legal liability on this ground.

At present, Shanghai, Fujian and other pilot cities have issued specific guidelines and material requirements for applying for the MAH. Once the Draft is implemented, the system of the MAH will greatly enhance the innovation initiative of drug R&D institutions, reduce the cost of R&D investment, release the production capacity and promote the innovation and development of pharmaceuticals.

2. CANCELLING CERTIFICATES OF GMP AND GSP

Article 10 of the Draft has cancelled the requirement that drug manufacturing enterprises shall acquire the certificate of GMP and modifies to "Drug manufacturers shall comply with the Good Manufacturing Practice for Drugs formulated by the drug regulatory department under the State Council based on this Law, establish and improve their own quality management system, and ensure compliance at all times during production processes".

Meanwhile, Article 16 of the Draft has cancelled the requirement that drug supply enterprise shall acquire the certificate of GSP, while it changes to "Drug distributors must deal in drugs in accordance with the Good Distribution Practice for Drugs formulated by the drug regulatory department under the State Council based on this Law".

The cancellation of GMP and GSP certification actually reflects the changes in regulatory thinking of drug regulatory authorities from "certificate-oriented" to "regulatory-oriented". The simplification of administrative examination and approval has reduced administrative procedures and saved administrative resources. However, the legal liabilities of pharmaceutical manufacturers and distributors have not been lightened by the simplification. In accordance with the Article 79 of the Draft, "any drug manufacturer, drug distributor, institution for non-clinical safety study, institution for drug clinical trial or contractual research institution that does not implement the Good Manufacturing Practice for Drugs, the Good Distribution Practice for Drugs, good practices of non-clinical drug research or good practices of clinical drug trials as required shall be given a warning and ordered to make corrections within a time limit. If it fails to do so within the time limit, it shall be ordered to suspend production or business operation for rectification and shall concurrently be fined not less than CNY5,000 but not more than CNY20,000. If the circumstances are serious, the Drug Manufacturing Certificate or Drug Distribution Certificate shall be revoked, and the institution for non-clinical safety study, institution for drug clinical trial, or contractual research institution concerned shall be

[4] *Drug Administration Law (2017 draft version)* Article 71: "The State applies a system of report on adverse drug reaction. The **MAH**, drug manufacturers, drug distributors and medical institutions shall make constant investigations into quality, therapeutic efficacy and reactions of the drugs produced…"

[5] *Drug Administration Law (2017 draft version)* Article 72: "Drug testing institutions of the **MAH**, drug manufacturers, drug distributors and medical institutions or their staff members shall accept technical instructions given by drug testing institutions set up by the local drug regulatory departments."

[6] *Drug Administration Law (2017 draft version)* Article 80: "Any **MAH**, drug manufacturer, drug distributor or medical institution that, in violation of the provisions of Article 34 of the Law, purchases drugs from the enterprises without a Drug Manufacturing Certificate or Drug Distribution Certificate shall be ordered to make corrections, and have the drugs illegally purchased confiscated, and shall concurrently be fined not less than two times but not more than five times the value of the drugs illegally purchased; the illegal gains, if any, shall be confiscated. If the circumstances are serious, the Drug Manufacturing Certificate, Drug Distribution Certificate, or the practice license for the medical institution shall be revoked."

[7] *Drug Administration Law (2017 draft version)* Article 90: "**The MAH**, drug distributors or medical institutions that offer or accept, in private, the rake-offs or other benefits in the course of purchasing and selling drugs or **the MAH**, drug distributors or their agents that offer money or things of value or other benefits to leading members, drug purchasers, physicians, or other related persons of the medical institutions where their drugs are used shall be fined not less than CNY10,000 but not more than CNY200,000 by the administrative departments for industry and commerce, and the illegal gains therefrom, if any, shall be confiscated. If the circumstances are serious, the administrative departments for industry and commerce shall revoke the business licenses of **the MAH** or drug distributors and inform the drug regulatory departments of the matter, which shall revoke their Drug Manufacturing Certificate, or Drug Distribution Certificate. If a crime is constituted, criminal liabilities shall be prosecuted in accordance with the law."

[8] *Drug Administration Law (2017 draft version)* Article 91: "Any leading members, purchasers or other related persons of **the MAH** or drug distributors that, in the course of drug purchasing or selling, accept money or things of value or other benefits offered by **the MAH**, distributors or their agents shall be given sanctions in accordance with the law, and the illegal gains therefrom, if any, shall be confiscated. If a crime is constituted, criminal liabilities shall be prosecuted in accordance with the law.

Leading members, drug purchasers, physicians or other related persons of medical institutions who accept money or things of value or other benefits offered by the MAH, drug distributors or their agents shall be given sanctions by the administrative departments for health or the institutions to which they belong, and the illegal gains therefrom, in any, shall be confiscated. With regard to licensed physicians who seriously violate the law, the administrative departments for health shall revoke their licenses for medical practice. If a crime is constituted, criminal liabilities shall be prosecuted in accordance with the law."

[9] *Drug Administration Law (2017 draft version)* Article 93: "**The MAH**, drug distributors or medical institutions that violate the provisions of the Law and thus cause harm to users of drugs shall bear the liability for compensation in accordance with the law."

prohibited from carrying out non-clinical safety studies of drugs or clinical trials of drugs for five years. Where a crime is constituted, criminal liability shall be investigated". It can be concluded that, in fact, it puts a higher and more stringent requirements to the pharmaceutical manufacturers and distributors.

3. SIMPLIFICATION OF THE ADMINISTRATIVE APPROVAL OF CLINICAL TRIALS

(1) Admittance to Drug Clinical Trail Institutions from Qualification to Record-filing

Another important reform in the Draft is reflected in Article 29 with respect to clinical trial of drug, which states that "Clinical trials shall be carried out in clinical trial institutions with necessary infrastructure. Clinical trial institutions shall be subject to administration by record-filing, and specific measures for this purpose will be formulated by the drug regulatory department under the State Council and the health administration under the State Council together". According to the current *Drug Administration Law* and *the Criterions for the Quality Control of Clinical Trial of Drugs*, drug clinical trial agencies shall be qualified and accredited by the relevant authority.

With respect to legal liability, Article 79 of the Draft states that clinical trial institutions do not conform to the Good Clinical Practice ("GCP") will be served a warning and ordered to correct within the prescribed time limit, as well as "where an institution for drug clinical trial fails to file a record as required under Article 29 of this Law or a bioequivalence test is conducted without filing a record as required under Article 29 of this Law, the party concerned shall be ordered to make corrections and be warned, and may also be fined less than CNY100,000".

The draft for comment version of specific regulation *Administrative Provisions on Drug Clinical Trial Institutions* has been published by CFDA on 26th October, 2017.

For this reform, CFDA officially said that record-filing is not to lower the access standards, on the contrary, this measure has actually raised the standard. Each filled clinical trial institution will receive a record-filing number, and the relevant authority will conduct routine supervision on these institutions.

(2) Changes of Clinical Trial Approval from Express Permission to Implied Consent

The Draft stipulates the approval of clinical trial in Article 29 that "the drug regulatory department under the State Council shall decide whether to agree on the clinical trials or not within 60 working days from the date on which an application for proceeding to clinical trials has been accepted; the applicant may carry out clinical trials if the said department fails to issue a notification within the required time limits". The reform posed new challenges to the ethics committee, under which the ethics committee becomes a prerequisite for approval of clinical trials according to Article 29[10].

In additional, which requires special attention recently is that CFDA released a decision on *Adjusting Relevant Matters Concerning the Administration of Imported Drug Registration* (the "**Decision**"). According to the Decision, in the case of a drug subject to an international multi-center clinical trial ("IMCCT") of drugs to be conducted in China, the phase I clinical trial of the drug is allowed simultaneously, and the requirement on the drug subject to the clinical trial to have been registered overseas or have entered a phase II or III clinical trial shall be cancelled, except for biological products for prevention. Upon the completion of the IMCCT of a drug in China, an applicant may directly file a registration application for marketing. For a new chemical drug or innovative therapeutic biological drug that is applied for clinical trial and marketing as an imported drug, the requirement on the drug to have obtained a marketing license issued by the country or region where the drug's overseas pharmaceutical manufacturer is located shall be removed. This improvement has greatly accelerated the progress of the registration of imported drugs as well as to facilitate Chinese parties' early participation in IMCCT.

[10] *Drug Administration Law (2017 draft version)* Article 29: "after the research and development of a new drug has been examined and approved by the ethics committee, the dossier on the research and development of the new drug, including the research and development methodology, quality indicators and results of pharmacological and toxicological tests, and samples thereof shall, in accordance with the provisions of the drug regulatory department under the State Council, be truthfully submitted to the said department for approval before clinical trials are conducted."

These are major moves by the CFDA to come more close to international standards since officially joining the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)[11] in 2017.

4. DEFINITUDE AND CONCRETIZATION OF LEGAL LIABILITIES

Comparing the current Drug Administration Law, the Draft adds legal liabilities of CRO according to Article 79 in order to comply with the good practices of non-clinical drug research or good practices of clinical drug trials as required.

The Draft emphasizes the legal responsibility of non-clinical safety evaluation research institutes, drug clinical trial institutes and contract research organizations in case of data infringement in Article 95[12], as well as the directly imposition against chief directly in-charge and other personnel directly held liable Article 96[13].

5. CONCLUSION

There is no doubt that this modification is a significant improvement in the reform of drug regulatory regime in China and it is in line with international standards, but also it faces numerous challenges. Overall, the drug R&D institutions, distributers and manufacturers will be greatly benefited from this reform and optimizes a variety of resource allocation.

[11] The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) is a project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of pharmaceutical product registration.

The purpose of ICH is to reduce or eliminate the need to duplicate the testing carried out during the research and development of new medicines by recommending ways to achieve greater harmonisation in the interpretation and application of technical guidelines and requirements for product registration. Harmonisation would lead to a more economical use of human, non-human animal and material resources, and the elimination of unnecessary delay in the global development and availability of new medicines while maintaining safeguards on quality, safety, and efficacy, and regulatory obligations to protect public health.

ICH guidelines have been adopted as law in several countries, but are only used as guidance for the U.S. Food and Drug Administration.

The CFDA has finally succeeded in joining ICH in 2017 as its eighth global regulator.

[12] *Drug Administration Law (2017 draft version)* Article 95: "where an institution for non-clinical safety study, institution for drug clinical trial, contractual research institution, drug marketing license holder, drug manufacturer, drug distributor, or medical institution is found to have violated laws by falsifying materials or data, or its license is revoked due to its violations, its chief directly in-charge and other personnel directly held liable shall be prohibited from being engaged in the research, development, production, distribution, import, export, and use of drugs for ten years. Any individual who has been sentenced to fixed-term imprisonment or more serious punishment as a result of drug safety offenses shall be prohibited for life from being engaged in the research, development, production, distribution, import, export, and use of drugs".

[13] *Drug Administration Law (2017 draft version)* Article 96: "where an institution for non-clinical safety study, institution for drug clinical trial, contractual research institution, drug marketing license holder, drug manufacturer, drug distributor, or medical institution is found to have violated any provisions in this law, the entity shall be punished according to the aforesaid provisions in this chapter, and its chief directly in-charge and other personnel directly held liable shall also be imposed a fine that is more than 30% of his or her income obtained from the entity in the preceding year and less than 100% of this income, if the case falls under any the following circumstances:

1. Where it intentionally violates the law or is guilty of culpable negligence;
2. Where the violation is serious and bad in nature; or
3. Where the violation results in bad consequences or causes other seriously negative impacts on the public."

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