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A Legal Review of China's Life Sciences and Healthcare-No.1

—General Introduction and MAH System

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I. The Life Science and Healthcare Industries in PRC

Supported by the improvement of general life quality and strong need for high quality medical and healthcare services, recently, the life science and healthcare industries have been two of the most fast-expanding industries in China. According to the outline of the "Healthy China 2030 Plan" released by the Chinese government in October 2016, the market size of the medical and health care industry in PRC was expected to reach RMB 8 trillion by the end of 2020 and RMB 16 trillion by the end of 2030.

Although hit by the unexpected pandemic of Covid-19 at the beginning of 2020, we still witnessed a strong growth in China's healthcare market in the recent two years. According to a report released by the China Internet Association in July 2021, the overall market size of the healthcare market is likely to reach RMB 7.4 trillion at the end of 2021 and is estimated to reach RMB 17.6 trillion by 2030, making it an important market for all participants to the global healthcare related industries including drug, medical device, cosmetics, health food, and health information service.

And as a part of the Chinese government's plan to boost the healthcare market, since 2019, the Chinese government has launched a series of major legal reforms in the areas including drugs, medical devices, cosmetics and health foods which have largely changed the landscape of China's healthcare market and there is still no sign of putting an end to such a major reform.

One of the most important move of these reforms is the establishment of the Marketing Authorization Holder (MAH) system in 2019 to replace the pervious drug registration system. Like in all other countries, the drug application system has been the cornerstone of the whole drug administration system in China. Under the MAH system, the MAH should be the major party to take all responsibilities for all the safety managements for the whole lifespan of a pharmaceutical product covering the processes of development (pre-clinical research, clinical trials, post-marketing research), production, marketing (including issues of legality of distribution, efficacy labeling, etc.), monitoring, recall, risk management, and reporting to the authorities. The adoption of MAH system has brought a series of chain effects to all the participants to the drug products industry.

Therefore, we think it will be a good start point to make a review on the recent legal reforms in the healthcare industry in China. In this article and a few follows, we will first introduce the key points of the MAH system and the Good Vigilance Practice (GVP) which is one of the newly adopted important regulations.

II. Key Points of the MAH System in China

Before we go in-depth of the post-marketing safety management system and the new Good Vigilance Practice ("China GVP"), adopted on 7 May 2021 and come into effect on 1 December 2021, we would like to first start from a quick review of the MAH system to provide the readers with a general picture.

(1) Comparison of the Drug Marketing Approval Systems in China and Japan

In following table, we summarize the MAH system in China in comparison with the marketing approval system in Japan.

	China (after the 2019 amendment)	Japan
Domestic MAH	■ Companies and research institutes that have obtained approval for the sale of pharmaceutical products become MAHs. ■ Companies and research institutes that have obtained marketing approval for a drug become MAHs. Compliance with GMP, GVP, and other regulations such as Measures on the Drug Adverse Reaction Reporting and Monitoring Management is required. ■ MAHs are required to have a production license for both in-house and contract manufacturing, but the requirements are different. ■ The main obligations of other MAHs are as follows (1) Establishment of a quality assurance system (assignment of an appointed quality manager) (2) Establishment of regulations for determining the marketing and shipping of pharmaceutical products (regulations and assignment of an appointed quality authority) (3) Establishment of a traceability system for pharmaceutical products (4) Establishment of an annual reporting system (5) Post-marketing research and post-marketing risk management (6) Monitoring and reporting of adverse reactions (7) Recall response	■ A person who intends to manufacture and sell (sell as a principal) a pharmaceutical product (a manufacturer and distributor licensed to manufacture and sell) must obtain marketing approval from the government (Ministry of Health, Labour and Welfare) for each pharmaceutical product. ■ GQP and GVP compliance is required. To manufacture, a separate manufacturing license is required.
Overseas MAH	■ Companies and research institutes, etc. that have obtained marketing approval for a drug become MAHs. ■ The overseas MAH designates its own domestic agent, and the domestic agent carries out various obligations (GVP compliance, etc.) as the MAH and assumes joint and several responsibility.	■ (However, only a distributor appointed by the foreign manufacturer at the time of application for approval may market (sell) the imported drug). ■ The appointed manufacturer and distributor shall be responsible for post-marketing safety management.
Drug production company	■ Drug Manufacturing license required ■ GMP compliance required	■ Drug production license required ■ GMP compliance required
Drag sales company	■ Requires a Drug distribution license ■ Compliance with GSP is required ■ MAHs can wholesale drugs for which they have marketing authorization, but they must meet the requirements of Article 52 of the Drug Administrative law, and they must obtain a drug sales license for retail sales.	■ Requires a Drug sales license ■ Compliance with GSP is required

(2) Before and Now

In China, before the establishment of MAH system, only those drug production companies who are holding drug manufacturing permit and have meet the good manufacturing practice (GMP) are eligible to make new drug application (NDA) and hold the drug registration license. Such a system is established based on the fact that for quite a long time in the history, most of the drug companies in China only focused on manufacturing generic drugs. Therefore, the regulation system has put its emphasis

on the "manufacturing" of the drugs and left the drug development institutions without much choices but to "sell" their research fruits to drug production companies.

However, with the growth of the drug development industry in China, the previous system was criticized for not being supportive to the drug development institutions. Because eventually the development institutions have to transfer their research fruits to manufacturing companies, they would rather focus on short-term interests than the continuing development and research. As a response to such problem, in 2016 the Chinese government decided to launch the trial of MAH system in a few areas including Beijing and Shanghai.

After a two-year trial, by the amendment of the Drug Administration Law in 2019, the MAH system is officially adopted nationwide. Companies and institutions whose primary business is research and development without manufacturing functions are now eligible to apply for and obtain marketing approval of medicinal products and separately outsourcing the manufacturing and sales to other qualified entities.

According to the Measures for the Supervision over and Administration of Drug Production, if a MAH chooses to outsource the manufacturing of the drug products to a third party manufacturer, then such MAH shall also meet the following requirements.

(a) has the drug technicians, process technicians and other relevant technicians, legal representatives, company managers, manager in charge of production, manager in charge of quality control, qualified person, and other related personnel who meet the requirements of the Drug Administration Law;
(b) has mechanisms and personnel capable of conducting quality control and quality inspection of the drug products to be produced;
(c) has a drug quality regulation system and meet GMP requirements; and
(d) has a production license for contract manufacturing and imposes requirements such as owning the necessary equipment).

(3) Domestic Agent System for Overseas MAHs

According to the Drug Administration Law amended in 2019, if the MAH is a company outside of China, the MAH shall designate one company in China (the "Domestic Agent"), have the Domestic Agent perform the duties of the MAH. The domestic agent shall be jointly and severally liable with the MAH (Article 38 of the Drug Administration Law).

In the case of Japan, when a foreign manufacturer applies for an NDA and obtains a marketing authorization directly, the foreign manufacturer shall appoint a Japanese marketing authorization holder with a marketing authorization in Japan at the time of application. Only the designated marketing authorization holder shall be allowed to sell (ex-sales) the imported drug product. The appointed marketing authorization holder shall be responsible for the safety management of the product after its sale in Japan.

On the other hand, when applying for an NDA, foreign companies need to delegate their application to the representative office of such company in China or a third party contractor in China (often an affiliated company or CRO will serve this role). Still, its role is mainly to serve as a contact point for responding to the NMPA, which is different from the roles and responsibilities of the Domestic Agent under the Domestic Agent system. For this reason, before the 2019 amendment, there were concerns that MAHs who located overseas do not have sufficient means to ensure, manage, and hold accountable for the performance of post-marketing safety management tasks which required to be performed by overseas MAHs. As a response, the amendment adopted the Domestic Agent system. However, at the time of this article, the regulation with respect to the Domestic Agent, namely Provisional Rules for Managing Domestic Agents of Overseas MAHs was released by NMPA but still in the process of gathering public comments.

In some cases, overseas drug companies have their own manufacturing or distribution companies in China to manufacture or sell their products in the Chinese market. Under such a case, as those entities belong to a same group, the overseas drug company can impose a more effective monitoring over the manufacturing and distribution companies in China. But for those overseas drug companies who have no associated entities in China or such entities in China are not being able to manufacture or sell such drug product in China, then the overseas drug companies must outsource the manufacturing and sales of the drugs to third party companies in China.

And especially in the case of drug distribution, although all companies engaged in drug distribution must obtain a drug distribution license and comply with the GSP, many of them are small to medium in size and do not have an

organization and personnel structure sufficient for post-marketing quality control of drug products. Furthermore, because of the massive geographic scope of the Chinese market, those drug distribution companies need to further engage second-tier distribution companies which would make the situation more complicated. Therefore, it is of vital importance for the MAH to select an appropriate Domestic Agent and implement effective measures to ensure a strict compliance with all relevant regulations including the China GVP.

In next article, we will present an outline of the China GVP.

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