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China on the Move: Fine-Tuning the Life Sciences Regulatory and Compliance Landscape

In China, recent technological advances and legislative and regulatory developments that attempt to balance risk mitigation and innovation continue to reshape the life sciences sector in terms of cross-border partnerships and domestic business operations.

This GT Advisory explores the following topics:

- New drug development activities are robust notwithstanding a temporary industry slowdown.
- The national drug regulatory authority has tightened regulation and oversight over the contract manufacturing activities of the marketing authorization holders (MAHs) in China. Local provincial-level authorities must conduct onsite inspections to determine whether the MAHs are qualified to outsource the drug manufacturing.
- Updating regulatory documents regarding human genetic resources (HGR) to clarify operational issues related to international collaborative research and the scope of regulated HGR samples.

New Drug Development Activities

The latest annual statistics for registered clinical trials in China show a consistent increase in the number of registered clinical trials for new drugs from 2019, reaching a record high of 3,410 in 2022. The growth rate slightly decelerated in 2022 due to environmental factors and increased investor caution. That said,

the general upward trajectory of new drug development activities underscores the robust local innovation environment in China and the importance of investment from multinational pharmaceutical companies. While fundamental challenges with reimbursement and commercialization remain, the regulatory environment in China is improving.

On average, innovative drug applications (from the date of first clinical trial approval to the date of marketing authorization) in 2022 took **7.6 years**. Biological products had the shortest approval time, averaging **4.6 years**, followed by chemical drugs at **6.9 years**. Traditional Chinese medicine (TCM) took the longest, averaging **15 years**. Of the innovative drugs approved in 2022, 10 products received marketing authorization within five years, accounting for 47.6% of the total. Four of these products were anti-tumor drugs, representing 19% of the total.

Clinical trials in China were primarily initiated by domestic sponsors. In 2022, domestic sponsors initiated 88.5% of clinical trials. The number of clinical trials overseas sponsors initiated increased from 2019 to 2021 but declined in 2022. Despite this, domestic sponsors still accounted for most clinical trials, and their proportion continues to grow significantly. Thus, China's clinical trials were predominantly domestic projects, accounting for 91.1% (3,105 trials). On the other hand, multi-regional clinical trials made up only 8.6% of the total, including a 14.8% share (292 trials) for new drugs.

Among the therapeutic areas of new drug clinical development activities, oncology remained the primary indication for new drug clinical trials for both chemical drugs and biological products, accounting for 36.7% and 48.1%, respectively. In 2022, 46 clinical trials were registered for cell and gene therapy products. Nearly 26% of these trials were related to mesenchymal stem cells (MSCs), while only two trials were for gene therapy. Oncology continued to be the primary indication for these trials.

Enhanced Oversight of Contract Manufacturing

On Oct. 23, 2023, China's National Medical Products Administration (NMPA) issued the *Notice of Enhancing the Supervision of Drug Marketing Authorization Holders That Outsource Manufacture* (《国家药监局关于加强药品上市许可持有人委托生产监督管理工作的公告》, the Notice). The Notice, which took effect immediately, responds to rising challenges associated with the research and development (R&D) institutions or companies obtaining drug marketing authorizations via the MAH mechanism and subsequently outsourcing drug manufacturing to contract manufacturing organizations (CMOs).

While the MAH mechanism has boosted the growth of clinical development activities in China, it has also raised drug regulatory authority concerns. For instance, R&D institutions which are MAHs may lack sufficient experience managing the quality of drug production and monitoring pharmacovigilance. These concerns arose after CMOs' non-compliance with the good manufacturing practice (GMP) were found during onsite inspections. In one case, a provincial NMPA authority conducted an onsite inspection of a CMO entrusted with the production of a liquid tonic and found the CMO employee had mistakenly added the preservative potassium sorbate used in other drugs to the liquid tonic, resulting in administrative punishment of the product's MAH. Notably, however, CMOs with plants across China have brought challenges to NMPA's interprovincial supervision.

The Notice aims to address emerging compliance concerns related to contract manufacturing practices by strengthening the outsourcing authorization process and by stipulating MAHs' quality management obligations in relation to outsourcing manufacturing activities.

1. Interactive Outsourcing Approach Involving Provincial NMPA Authorities

Measures for the Supervision and Administration of Drug Production (《药品生产监督管理办法》, the Drug Production Measures) require MAHs planning to outsource their product manufacturing to a CMO to:

a. Employ qualified key personnel, including pharmaceutical technicians, engineering technicians, and corresponding technical workers, as well as a legal representative, a responsible person for enterprise, a responsible person for production, a responsible person for quality, and a qualified person;

b. Establish an organization with personnel capable of conducting quality management and quality inspection of the medicinal products manufactured; and

c. Institute internal rules and procedures that comply with GMP requirements and assure quality of the manufactured products.

MAHs must apply for a "Category B" drug manufacturing license. The application must also include the executed manufacturing and quality agreement between the MAH and the CMO, among other required documents, and must be submitted to the provincial NMPA.

In the application process, a provincial NMPA authority will communicate with the MAHs in advance to help them complete critical steps before the official application submission, including:

a. Completing chemistry, manufacturing, and controls (CMC) study, pharmacological and toxicological studies, and clinical trials;

b. Confirming quality standards;

c. Validating the manufacturing process for commercialized productions; and

d. Preparing for drug testing and inspection for drug registration.

Notably, during the application for the Category B license, the MAH should disclose any previous "bad records" of the CMO to the local NMPA authority, including:

a. Two batches of products failed to pass the sampling inspection in the past year;

b. The CMO failed to meet GMP requirements under NMPA supervision and inspection in the past three years; or

c. The CMO or the CMO's key personnel have seriously violated drug regulatory laws and regulations in the past five years.

Provincial NMPA authorities will closely review the MAH's contract manufacturing application and conduct onsite inspections of the MAH's qualifications with an emphasis on:

a. Key Personnel: the inspection will assess whether key individuals are permanent (rather than part-time) employees. There are additional requirements for the manufacturing of sterile drugs, TCM injections, and multi-component biochemical drugs:

- Sterile drugs: the MAH's responsible person for manufacturing, responsible person for quality, and qualified person must have a minimum of five years of specific experience in managing drug manufacturing and quality and at least three years with specific experience related to sterile drugs.
- TCM injections and multi-component biochemical drugs: the MAH's responsible person for production, responsible person for quality, and qualified person must have at least three years of experience managing the production and quality of the same type of drug products. Furthermore, the outsourced products must have a record of consecutive sales in the last five consecutive years, without any records of severe adverse reactions or failed inspections. The CMO must have records of manufacturing the same type of products continuously for the past three years.

b. Establishment and operation of the Quality Management System (QMS);

c. Management of outsourcing affairs.

The CMO, entrusted by the MAH, will also undergo an onsite GMP inspection by the CMO's local provincial NMPA authority. If the CMO passes the GMP inspection, the local NMPA authority will issue a GMP compliance notice, a prerequisite for obtaining the Category B license.

If any such "bad records" exist, the MAH should submit an onsite audit report to verify the CMO's compliance with the GMP, an evaluation report on the CMO's capabilities of product inspection, and an evaluation report on the CMO's rectification for the provincial NMPA authority's evaluation. The provincial NMPA will then decide whether to issue the Category B license.

2. Emphasis on Quality Management

Quality management is a major concentration of the Drug Production Measures. The MAH should enhance the quality management of the outsourced manufacturing activities by taking the following measures:

a. Evaluate and approve material suppliers (including suppliers of active pharmaceutical ingredients, excipients, packaging, etc.) and conduct onsite audits of the quality management systems of major material suppliers on a regular basis;

b. Conduct regular review and analysis of the quality management and manufacturing management of the contracted manufacturer, including risk assessment, at least once every quarter.

In principle, the MAH or CMO are required to conduct the quality testing themselves. Nevertheless, if a third party performs such role for specific projects, where the testing equipment is expensive or rarely used, the MAH should assess the qualification of such third party, execute the agreement, and keep the local NMPA informed. For products sharing the same production lines, the MAH and CMO should jointly formulate feasible control measures to monitor and examine the cross-contamination risk.

3. Additional Practices Related to Contract Manufacturing of Biological Products, TCM Injections, and Multi-Component Biochemical Products

MAHs who outsource the production of biological products, TCM injections, and multi-component biochemical products will bear additional obligations, including:

a. Establishing a comprehensive QMS covering the entire manufacturing process, which includes the raw materials used (*e.g.*, biological materials, TCM raw material, TCM decoction pieces, TCM extracts, raw materials of animal origin, etc.);

b. Conducting annual onsite inspection of the suppliers of the main ingredients for the drug products to ensure consistency of the origin, source, and supplier of ingredients across different manufacturing sites;

c. Appointing a qualified and experienced supervisor who should be familiar with the manufacturing process and quality control with the responsibilities stipulated in the manufacturing and quality agreement;

d. Performing regular sample testing of materials and finished dosage forms.

4. Prudent Approach to Cross-Border Contract Manufacturing Scenarios

Currently, the Notice is based on the assumption that both the MAH and CMO are located within the territory of China. Historically, cross-border contract manufacturing (i.e., a domestic MAH outsourcing product production to an overseas CMO, or vice versa) is not explicitly prohibited under Chinese law, although the NMPA has been holding the bifurcation of approval pathway. We have not found relevant implementation rules and procedures established at least for commercial supply yet.

Notably, the NMPA took its first step in June 2022 to allow the MAHs in Hong Kong and Macau to outsource the manufacturing of Chinese patented drugs and chemical drugs (which should be registered within mainland China) to the qualified CMOs located within nine cities in the Guangdong Province. While this move may not explicitly demonstrate the NMPA's intent to address cross-border contract manufacturing due to the special status of Hong Kong and Macau, the approach might still signal a modest move to start addressing cross-border contract manufacturing in the commercial supply setting.

Oversight Approach Over HGR Revisited, with Clearer Guidance for International Collaboration

On Sept. 8, 2023, the China National Center for Biotechnology Development (CNCBD), a public institution under the direct charge of China's Ministry of Science and Technology (MOST), released the *Notice on Issuing Answers for Frequently Asked Questions on Human Genetic Resource Administration* (New HGR FAQs). Following the *Implementing Rules of the Administrative Regulations on Human Genetic Resources* (HGR Implementing Rules) effective from July 1 and MOST's updated guidelines released July 14, the New HGR FAQs further elaborate the latest standards and the authorities' intentions regarding the HGR regulation.

Multinational companies should consider the following points:

1. Indicate No Separate Approval for International Collaboration with Collection of HGR: International collaboration involving HGR collection may satisfy the relevant rules simply by applying for approval of international collaboration scientific research or, as the case may be, filing for international collaboration clinical trials (collectively, the "International Collaboration Approvals/Filings") (Section I, Question 2).

2. Relax the Requirement for Electronic Data Capture System (EDC) Supplier as the Sole Foreign Party: No International Collaboration Approvals/Filings will be required where the EDC supplier is the only foreign party in clinical trials (Section II, Question 2).

3. Clarify the Definition of Non-Substantial Involvement: Where the foreign party is not substantially involved in the scientific research (*i.e.* the foreign party will not obtain relevant data or information and will not own or share the research outcome), no International Collaboration Approvals/Filings will be needed. For instance, a foreign-invested pharmaceutical company simply provides drugs or partial financial support for clinical research and will not be informed of the research outcome (Section II, Question 5).

4. Tighten the Scope of "Other Participating Parties" in International Collaboration: Other participating parties here refer to the entities that have access to the HGR materials or information with substantial involvement, excluding sponsors, leading entities, CROs, third-party laboratories, and participating medical institutions (Section II, Question 8). With respect to international collaboration, relevant parties that are not CROs, third-party labs, trial sites, and sponsors will now also be defined as "other participating parties" if they gain access to HGR information and materials.

5. Request Agreements to be Submitted for International Collaboration Approval/Filing: In the case of applications for approval, collaboration agreements among sponsors, leading entities, CROs, and third-party laboratories must be submitted, while in the case of applications for a filing, collaboration agreements among all collaborators (including sponsors, leading entities, CROs, third-party laboratories, and other participating parties) must be submitted. In both cases, the Chinese version of the relevant agreements must be provided, signed, and stamped (Section II, Question 10).

6. Remove the Urine, Feces, Serum, and Plasma From Regulatory Scope: Biological samples such as urine, feces, serum, and plasma are no longer within the regulatory scope of HGR materials and the outbound transfer of such samples will not be subject to approval (Section III, Question 1, 2). Nevertheless, the whole blood used for production of serum and plasma can still be regulated as HGR material, and medical institutions (which must also conduct testing on genes, genomes, transcriptomes, epigenomes, and nucleic acid biomarkers) or the testing institution processing the whole blood into serum or plasma may be regulated as a third-party laboratory (Section III, Question 3). Furthermore, data generated from tests using materials like urine, feces, serum, and plasma for the purpose of scientific research on genes, genomes, transcriptomes, epigenomes, and nucleic acid biomarkers, etc. are still regulated as HGR information, but the regulatory requirements are only applicable when involving international collaborations and external provision or access of such HGR information (Section III, Question 4).

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