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## **China on the Move: An Improving Regulatory Landscape with New Challenges Ahead – Genomics and National Security**

China's drug registration timeline has been long criticized as lengthy and indefinite. It was **reported** that in 2015, China had a backlog of 21,000 drug registrations pending review and approval. Consumers yearned for access to affordable, high-quality drugs, and pharmaceutical companies for a robust market for their products.

In recent years, the Chinese government has been devoted to reforming the pharmaceutical regulatory framework, which covers three interrelated segments: medicine registration, medical care, and medical insurance. Dating back to 2015, China's reform of medicine registration hinges on improving the quality and transparency of drug review and approval, resolving the backlog in drug registrations, improving the quality of generics, and encouraging the research and development of new drugs.

However, there are new structural challenges that may compromise the strategic vision for promoting pharmaceutical innovation. This GT Advisory explores the following considerations:

- Speed and predictability are the Chinese government's primary achievements in the regulatory space.

- National security considerations inevitably lead to laws regulating the collection of sensitive personal information and human genetic resources, creating new uncertainties and additional administrative processes in research and development activities in China, especially for foreign companies.
- Poor handling of human genetic resources can be a critical hurdle in the execution of companies' global development plans.
- The trigger to be required to collaborate with a Chinese partner can complicate the desired partnership model and further jeopardize the foreign companies' intellectual property protection in China.
- Revisiting the corporate partnership structure in China and the gap analysis in the current compliance program are the first steps in addressing this new challenge.

### **China's Faster and More Predictable Review and Approval Timeline Rewards the Investment in Product Launch**

The interaction of various reform policies and systems since 2015 has led to two major accomplishments in China's new drug registration regime: increased **speed** and **predictability**.

In the past, the Center for Drug Evaluation (CDE) took about 900 days to review and approve a drug registration. This procedure was shortened to about 300 days in 2019. A direct reason for the reduction is that CDE staff increased from 100 in 2015 to about 1000 in 2020. The Administrative Measures for Drug Registration (revised in 2020, "2020 Drug Registration Measures") further require that review and approval be finished in principle within 200 working days. This time limit may be reduced with fast tracks.

Similar to the U.S. Food and Drug Administration (FDA), China's National Medical Products Administration (NMPA) established certain fast tracks for the registration of drugs with significant therapeutic value: priority review and approval, breakthrough therapy designation (BTD), and conditional approval. Innovative drugs with significant clinical value may apply for the fast tracks. The time for priority review and approval may be further shortened to 130 working days or even 70 working days, if the drug has been marketed overseas. In addition, NMPA waived the requirement to conduct clinical trials in China and established an expedited six-month review period (three months for orphan drugs) for the drugs identified as "urgently needed" in China.

Biogen's Spinraza, which treats the rare disease of spinal muscular atrophy (SMA) was granted priority review and approval in September 2018; in February 2019, NMPA granted the marketing authorization of Spinraza, 794 days after FDA granted the authorization. The review and approval in China took 173 days. The swift process was also attributable to NMPA's conditional acceptance of overseas clinical trial data, since Biogen had acquired a considerable amount of clinical trial data from more than 300 patients. Other similar examples include Selexipag for pulmonary hypertension (PH), Glecaprevir-Pibrentasvir for Hepatitis C, etc., all of which were listed as innovative drugs in urgent clinical need. According to an NMPA report on drug review in 2019, 253 applications (139 in generic names) were granted priority review and approval, among which 52 applications involved pediatric drugs and orphan drugs; marketing authorizations of 143 applications (82 in generic names) were granted through priority review and approval.

NMPA's established timeline for the entire review and approval process makes the registration procedure more predictable. Under the 2020 Drug Registration Measures, an application for clinical trial is deemed approved by CDE if not objected to by the CDE within 60 working days of CDE's acceptance of such

application. In addition, the overall time limit for review and approval is in principle 200 working days, which may be reduced when fast tracks mentioned in the section above apply.

Predictability also comes from the MAH (marketing authorization holder) system. Simply put, CDE now focuses on the review of a medicine's safety, efficacy, and quality controllability when determining if the marketing authorization will be granted. Previously, under the 2007 version of Administrative Measures for Drug Registration ("2007 Drug Registration Measures"), an applicant also was required to obtain the drug manufacturing license and GMP certificate, and also to explain the title to the patents related to the medicine and make a statement that no patent infringement existed. Because medical research institutes did not necessarily intend to manufacture medicines, the 2007 Drug Registration Measures made it impractical for the institutes to apply for drug registration, since it was difficult for them to get the manufacturing license and GMP certificate requiring heavy assets; thus, they had to transfer the new drug to a manufacturing enterprise. The MAH system enables research and development institutes to register drugs in their own names. MAHs may entrust third parties with drug manufacturing licenses to produce the drugs, though MAHs must be equipped with qualified personnel and policy to ensure quality control. MAHs are responsible for the safety, effectiveness, and quality in research and development, manufacturing, sales, and usage of the drugs. The qualification of an MAH may also be transferred with the approval of NMPA.

By contrast, the no-infringement statement under the 2007 Drug Registration Measures often led to a delay of the review and approval of a generic until the patent expired, in case of a dispute between an innovative drug and a generic. China's new Patent Law (amended in 2020) introduces the patent linkage system, which creates a patent dispute resolution mechanism between the patentees of innovative drugs already registered and generics applying for marketing approval. The interested parties may, within a prescribed period, bring a lawsuit or initiate administrative proceeding to request the determination of whether the technology solution of the generics falls within the patent of the registered innovative drugs. Before granting the market authorization for chemical generics, CDE will wait nine months, during which time the technical review will continue. Biosimilars are not restricted by such waiting period, and the marketing authorization will be granted directly, based on technical review.

### **Ongoing Development of the Scheme to Promote the National Interest of Human Genetic Resources Complicates Clinical Development in China**

In recent years, the regulation of human genetic resources (HGR) has been increasingly approached as part of countries' national security priorities; therefore, such regulation has become stricter. Foreign investments, even non-controlling ones, in enterprises maintaining or collecting genetic information, regardless of the quantity of the data, have been the focus of CFIUS review since 2019. Out of a similar concern, China's Administrative Regulations on Human Genetic Resources ("HGR Administrative Regulations") were published in May 2019. The COVID-19 pandemic further highlighted the significance of biosafety, an integral part of national security, covering prevention and control of a pandemic, safety of biologic technology research and application, HGR safety, etc. The Biosafety Law was enacted in October 2020, and together with the HGR Administrative Regulations, imposes strict compliance requirements on pharmaceutical companies and clinical research organizations (CROs) dealing with HGR.

In fact, pre-approval for the collection, export, international cooperation or other provisions abroad related to China's HGR has long been established by the Ministry of Science and Technology (MST) via its 1998 Interim Measures on Human Genetic Resources ("Interim Measures"). In the following years, the Interim Measures seemed to attract very limited attention, until in October 2018, MST surprisingly published six penalty cases of violation of the Interim Measures involving several prestigious hospitals,

pharmaceutical companies, and CROs for their unauthorized export/preservation/international cooperation.

Under the current HGR-regulation regime, collection, preservation, utilization for international cooperation and export of China's HGR is subject to MST's pre-approval. Foreign entities are prohibited from participating in the collection, preservation, and export of relevant HGR, and are only allowed to carry out international cooperation with Chinese entities in terms of utilizing China's HGR. Two types of activities involving foreign entities require information filing with MST: (1) multi-center clinical trial based on China's HGR in order to obtain marketing authorization in China; (2) supply of HGR information to foreign entities (including online transmission, provision of physical storage medium, etc.), or access (including publication of papers, books, or conference materials, information sharing, etc.) to HGR information by foreign entities.

Therefore, China's regulatory framework emphasizes the control on foreign access to China's HGR. Foreign entities and their Chinese partners should be mindful of the following issues, which reflect certain ambiguity in HGR Administrative Regulations.

**a) Almost all entities with a foreign element can fall under the jurisdiction of the HGR Administrative Regulations.**

Foreign entities, as highly regulated participants, are defined as foreign organizations and those institutions established or controlled by foreign organizations or individuals. Though the wording of the HGR Administrative Regulations is not totally clear, more and more observers tend to believe that foreign entities include (i) a joint venture with foreign investment registered in China, regardless of the shareholding ratio; and (ii) an entity controlled by a foreign entity through a VIE arrangement. All "foreign entities" should keep in touch with MST and its local branches before participating in any projects involving China's HGR. After all, any entity can be a 'foreign entity' if one of its shareholders is non-Chinese, given the definition's broad nature.

**b) Pharmaceutical companies and CROs should pay attention to the HGR materials and information they utilize in the development of biologics and carefully evaluate if pre-approval/record filing is required.**

MST's administrative guidelines on the approval of international cooperation give specific examples of HGR information: demographic information, medical images such as B-scans, CTs, or X-rays, biomarker data, gene data (such as sequencing data), protein data, metabolism data, etc. Since the scope of HGR information is extensive, the requirement for pre-approval/record-filing will easily be triggered. For example, B-scans, CTs, and X-rays seem to be routine diagnostics, yet the transmission of such images to foreign entities may require record-filing with MST.

**c) A mandatory intellectual property sharing with Chinese partners can be an unintended consequence.**

Although the HGR Administrative Regulations require only the joint ownership of a patent, resulting from international cooperation utilizing China's HGR, the foregoing MST guidelines require that the distribution of patents, copyrights, data, standards, processes, software, and trademarks resulting from international cooperation be disclosed to MST; the disclosure should be "clear and concrete." Therefore, these types of intellectual property would likely be jointly owned by the parties. This inference is strengthened by the Biosafety Law provision on share of "relevant rights and interests" not being

restricted to a single type of right. A “one-party-takes-all” distribution arrangement could be turned down by MST.

More importantly, what is intellectual property “resulting from” the international cooperation utilizing China’s HGR? A realistic problem is that biologics products, such as genetically engineered immune cells, are cultivated based on patient cells, so the intellectual property underlying cell therapy products may comprise products resulting from the utilization of HGR and should be jointly owned by Chinese entities and foreign entities. Sponsors and CROs should at an early stage envisage the distribution of intellectual property and evaluate to what extent joint ownership is acceptable.

**d) Approval and record filing are continuous obligations.**

Clinical trials involving international cooperation have obtained MST approval/record-filing, with the transmission of HGR information to foreign entities (e.g., a research institute outside China, the parent company outside China, or even a foreign invested CRO registered in China) requiring additional record-filing later, as such transmission constitutes supply of HGR information to foreign entities. MST may conduct a national security review to determine if the data is sensitive, the procedure for which is unclear. That is to say, each data transmission to a foreign entity may be delayed. According to HGR Administrative Regulations, a backup of the data to be transmitted should be submitted to MST by the Chinese partner of such international cooperation.

**e) HGR information raises additional legal implications, for example, under China’s Cybersecurity Law.**

HGR information is classified and regulated as personal information under the Cybersecurity Law. Pharmaceutical companies, hospitals, and CROs are obliged to comply with the law’s obligations in respect of collection, use, processing, and transmission of personal information, which must be legitimate, justified, and necessary. Entities must obtain consent from an individual before dealing with the personal information and take necessary measures to ensure the security of personal information. Such requirements may align with the informed consent under good clinical practice for pharmaceutical studies. Critical information infrastructure operators are further required to store the personal information and important data collected in the business course within China and shall not export such information or data without security assessments. Since China has not yet adopted the draft regulations on identification of critical information infrastructure and security assessments on data exports, it is hard to predict how the compliance obligations of critical information infrastructure and data exports will impact clinical studies, and if there will be any exemption or leeway for data transmission in clinical studies. However, biotechnology industry and biological information may well be a focus of governmental regulation, judging from the draft regulations.

**Failure to Address HGR Issues in Advance Can Be Costly**

Since the promulgation of the HGR Administrative Regulations, MST published only two penalty cases. In those cases, the sponsor, BMS China, appointed ICON’s Chinese subsidiary as its CRO to conduct certain clinical trial related to an indication of BMS’s PD-1 product (Opdivo). An employee of ICON was found guilty by a Chinese court of falsifying the seal of a hospital and its ethics committee in the application documents submitted to MST, and was sentenced to two years’ imprisonment and two years’ probation. MST disqualified both BMS and ICON for six months from applying for international cooperation. ICON withdrew from the clinical trial and BMS announced that global cooperation with ICON had been terminated. Because the incident was discovered before the clinical trial started, the integrity of the BMS data and patient safety were not affected. However, time, cost, and reputational damage occurred.



Pharmaceutical companies and CROs should establish a sound and functioning compliance scheme to avoid potential HGR regulatory violations. “Under the HGR Administrative Regulations, penalties for dealing with HGR without proper MST approval/record-filing include an order to cease illegal acts, confiscation of illegal gains and relevant HGR, and a fine of RMB 500,000 to RMB 5,000,000; if the illegal gains exceed RMB 1,000,000, the fine will be five to 10 times the illegal gains. Penalties on foreign entities are more severe. MST may impose a fine of RMB 1,000,000 to RMB 10,000,000, and if the illegal gains exceed RMB 1,000,000, the fine will be five to 10 times the illegal gains. The Biosafety Law further raises the fine on foreign entities to 10 to 20 times the illegal gains if the illegal gains exceed RMB 1,000,000. Apart from monetary penalties, the responsible entities and responsible officers or employees may also be disqualified by MST from future activities involving HGR for at most five years, but in extreme cases, a permanent ban may be imposed. These severe punishments give teeth to MST and its HGR regulation.

The National People’s Congress enacted the 11th Amendment to Criminal Law in December 2020 and created a new crime of illegal collection of China’s HGR or illegal export of China’s HGR materials that harms public health or public interest. If convicted, the responsible person may be sentenced to imprisonment of at most seven years. Shortly before the enactment of the 11th Amendment, Zhang Fangliang, chairman of China-based immunotherapy development company GenScript and its affiliated company Legend Biotech, was arrested in November 2020 for the suspected crime of smuggling goods (probably HGR material) prohibited by import and export regulations.

Early in May 2021, it was widely reported by Chinese media that Shanghai customs seized 247 human cell samples smuggled into China by a biotechnology company in Shanghai. These cell samples were concealed in culture medium. Import of HGR is not regulated by the HGR Administrative Regulations but is subject to quarantine requirement under customs regulations and the Biosafety Law. The official further disclosed that such biotechnology company had repeatedly smuggled human cells since June 2020, and the anti-smuggling department is investigating this company. The disclosure of this case is another clear warning for companies conducting cross-border cooperation involving HGR to attach more importance to the cross-border flow of HGR.

### **Evolving Stringent Requirements in Data Privacy Regimes Can Further Burden Local Operation**

The draft Personal Information Protection Law (PIPL), released on 21 October 2020, is a legal framework in China equivalent to the EU’s General Data Protection Regulation (GDPR). Various data privacy requirements under previous legislations such as Measures for Administration of Population Health, Civil Code, Cybersecurity Law, and Personal Information Security Specification are incorporated into the draft PIPL.

A majority of obligations under the PIPL regulations are addressed to processors of personal information. When participating in a clinical study, a medical institution, a CRO and a pharmaceutical company will likely all be deemed a processor based on their collecting, storing, using, handling, transmitting, providing and publicizing of personal information. These parties may agree upon mutual rights and obligations in the processing of personal information but shall be jointly and severally liability to individuals. Necessary security measures shall be implemented to protect personal information from leakage, theft, tampering or deletion. A processor of personal information under PIPL may or may not simultaneously be a network operator under Cyber Security Law. Therefore, different compliance requirements related to personal information may apply to the same entity.

Under the draft PIPL, cross-border transfers of personal data are only permissible under three circumstances: (1) for critical information infrastructure operators and processors handling information of a significant amount, such transfer must have passed a security review conducted by governmental authorities, (2) the processor has been certified for personal information protection by a qualified institution (not defined in the draft PIPL); and (3) the processor and the foreign recipient shall have entered into a standard contract formulated by Chinese government (comparable to the Standard Contractual Clauses under GDPR). The term “critical information infrastructure” is still undefined. Besides, individuals shall be separately informed of the details of the cross-border transfer and shall have separately consented to the transfer. This leads to uncertainties for life sciences companies that typically own sensitive data, such as personal biometrics and medical information. Any personal data transfer in the life sciences business space will also be required to undergo internal risk assessments prior to the cross-border transfer.

Notably, under the draft PIPL, failure to comply with the necessary requirements may be subject to a fine between RMB 1 million and RMB 50 million or 5% of the company’s annual turnover for the previous financial year. In addition, its business operations can be suspended, or the business license revoked.

### **“Decoupling” Can Be Inevitable If the Business Model Does Not Get It Correct Initially**

The breakthrough of life sciences business development in China is partially attributable to China’s success in leveraging foreign resources, including know-how, talent, and capital. Life sciences companies’ utilization of China’s huge patient population in global development, involvement of overseas Chinese talents in life sciences businesses in China, and increasingly common partnerships between Chinese and non-Chinese companies are the norm of Chinese market.

While reimbursement and the supply chain environment may remain the top concerns in the life sciences business community in China, national security concerns can be a wild card regarding life sciences companies’ operations, especially in their research and development activities from data privacy and biosecurity perspectives. Companies are advised to ask at least two questions before taking concrete steps in their business:

- Will my contemplated partnership structure be obscured at some point?

Overseas Chinese talents nowadays have spearheaded collaboration between foreign entities and many local Chinese companies. Given the expansive jurisdiction of HGR-focused Chinese laws, life sciences companies that normally would not be considered foreign corporations may, under the HGR laws, be deemed qualified foreign entities that are required to engage a local party to comply with applicable requirements. The burdensome record filing and uncertain approval may also favor the need to find the right local party while being prepared for any business disruption. Foreign companies must incorporate the associated risk and cost in selection of such local partner in its business activities in China, as well as revisit the need of the activities involving HGR in China in the actual partnership structure. If such need exists, the companies must carefully form a global structure to ensure utilization of the genomic data is maximized across the globe, considering the necessary approvals for data exports.

Foreign companies looking to leverage Chinese patient data must consider HGR laws, which easily come into play when the data will also be part of a global dossier. If the foreign companies use a local partner or foreign company’s local affiliate in China, the foreign companies must frame a partnership model that will not leave its local partner or itself over-exposed to the complex arena of genetic materials.

Separately, some U.S. policy makers, such as Senators Marco Rubio and Chuck Grassley, have expressed concerns and requested the U.S. Department of Health and Human Services' acting inspector general to perform oversight of potential payments made to genomics firms with ties to the Chinese government. Amid this regulatory activity and increasing scrutiny by the United States of genome companies with ties to the Chinese government, non-Chinese companies must be aware of any potential issues in engaging the local Chinese partner due to heightened attention from the United States and regulators in other jurisdictions.

- Should I put in place a compliance program to oversee my development and commercial activities in China?

The Chinese government's recent move declares sovereignty over HGR, and it wants to enhance its administration and supervision over HGR's collection, preservation, use, and outbound transmission. Recently, China's National People's Congress Standing Committee also approved an Export Control Law, a move seen as countering U.S. control over technology exports to China due to its own national security concerns. While national security has been the primary trigger of a series of promulgated regulations, there are in fact various and numerous requirements in place.

Companies should take advantage of this timing to conduct a gap analysis in their current risk exposure, and to place essential policies and standard operating procedures quickly and effectively. Enhancement of the compliance program can complement the dealmaking efforts, especially when the handling of HGR is an essential element of the companies' China strategy, which will require proper risk mitigation. In many cases, a thorough compliance program can be leveraged to negotiate with regulators in order to mitigate the potential negative consequences of a violation.

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