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Safeguarding biopharma R&D

New heights in China's human genetic resources management

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Contents

HGR regulations have reached a new height

Between 1998 and 2017, the Ministry of Science and Technology and the former Ministry of Health jointly formulated, and released multiple draft versions of the regulations of human genetic resources (HGR).

The first comprehensive set of *Regulations on the Management of Human Genetic Resources of the People's Republic of China* ("HGR Regulation" *《中华人民共和国人类遗传资源管理条例》*) was formally introduced by the Chinese State Council and became effective on July 1, 2019. The policies not only emphasized the importance of HGR regulatory compliance but also provided more transparencies on the scope of studies subject to HGR review and approval:

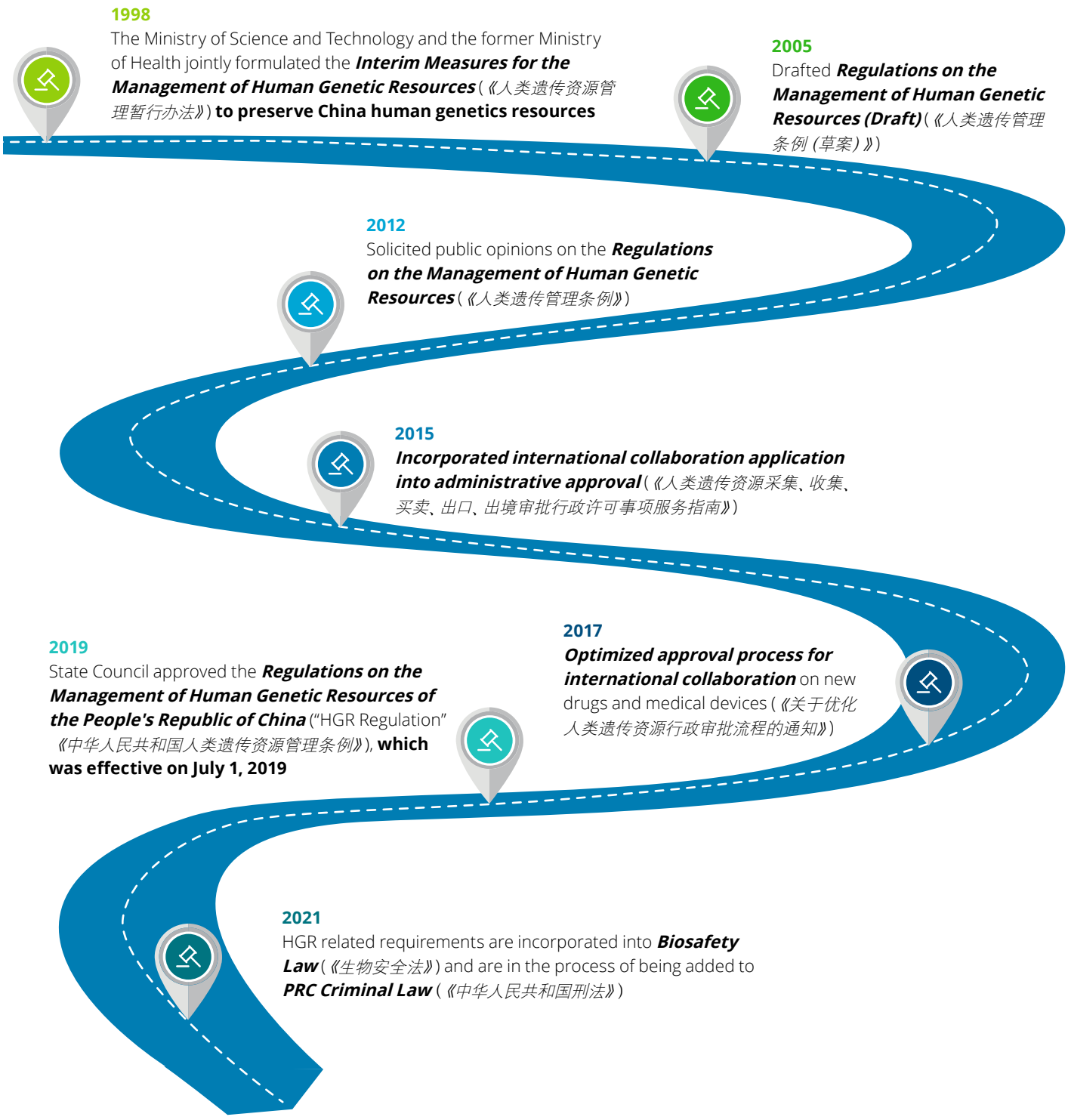
- HGR definition covers human genetic resources materials and information. Despite generally broad definition, certain materials and data, such as whole blood, tissue biopsy, and genetic sequencing data are regarded as highly sensitive, therefore most scrutinized by HGR Administrative Office (HGRAO) compared to others.
- The regulation scope applies to various types of studies, including registration researches (such as phase 1, 2 and 3 studies that involve asset-based interventions), early phase exploratory researches (such as phase 0 study of cancer epidemiology to elucidate different genetic subtypes), as well as post-market studies (such as real-world label expansion studies).

In particular, HGR requires all studies categorized as International Collaboration to be subject to HGR compliance. They include research programs typically sponsored by a foreign entity that involve the local research institutions, such as hospitals, as collaborators. In short, all MNC pharmaceutical companies, when conducting research in China, will need to obtain the following HGR approvals, apart from the regular NMPA approval, in order to conduct human-based studies:

- Applications for international collaboration research specifying key stakeholders, project planning and purposes, intellectual property sharing plan as well as types and sizes of human genetic resources to be collected. In addition, it is also required to provide scientific explanations to rationalize the necessity of collecting a proposed amount of samples. Amendment applications are required upon changes or deviations from the original research protocol
- Applications for collection and storage of human genetic resources. This application specifically should be submitted by the Chinese collaborators
- Applications for the exportation of human genetic samples
- Data filling and backup: obtain pre-approval from HGRAO before transmitting any human genetic data to ex-China jurisdiction, including HongKong/ Macao

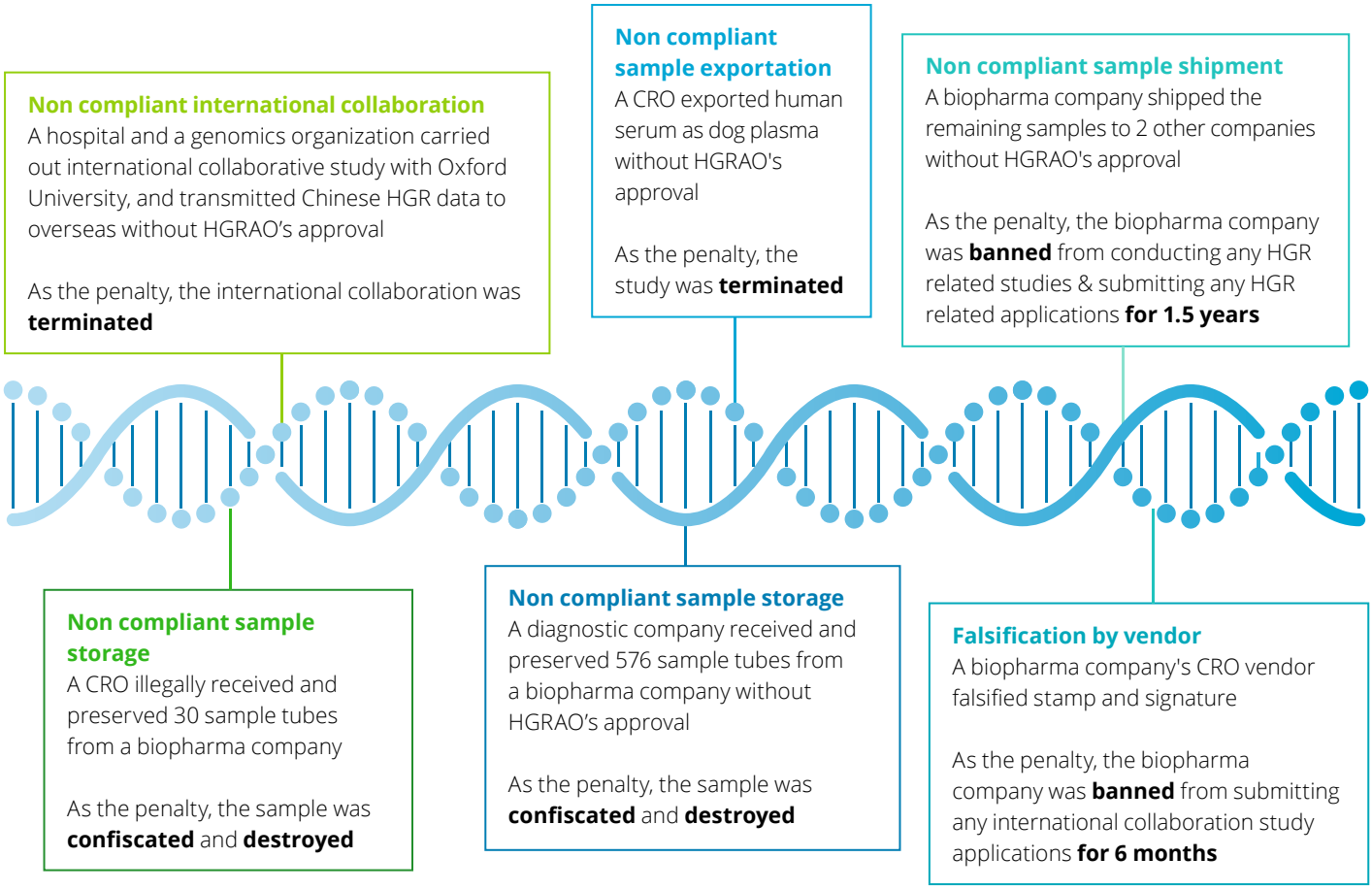
The increasingly stringent and explicit HGR regulations have also led to much strengthened enforcement. With a steadily increasing number of HGR applications over the past 5 years, the industry average approval rate has been declining, especially post the 2019 publication of the HGR regulatory framework; around the same time, more HGR violations were also disclosed as well as their penalties that have the potential to disrupt R&D programs by over up to 1.5 years.

Figure 1: Development of HGR related policies, regulations and laws from 1998 to 2021



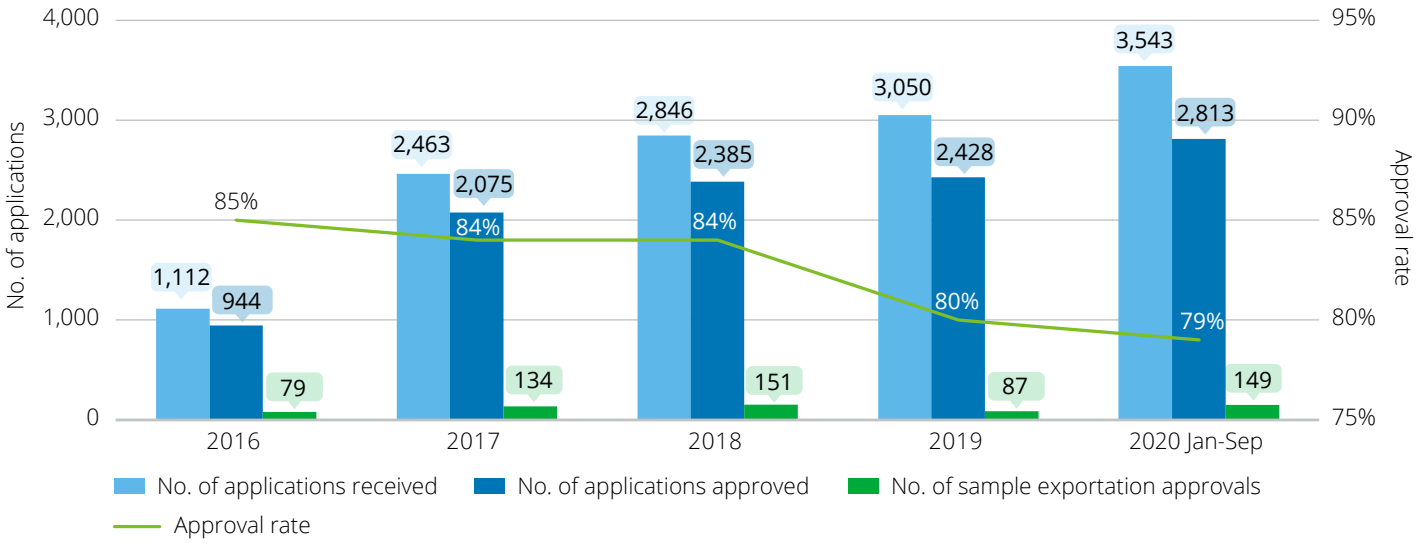
Source: DIA meeting open session presentation

Figure 2: Recent penalties in the last three years



Source: *Administrative Penalties of Human Genetic Resource Management, Ministry of Science and Technology of the People's Republic of China*

Figure 3: Historical approval rate from 2016 to 2020 September



The approval rate has been declining given increasing number of applications

Source: DIA meeting open session presentation; Deloitte analysis

The winning agenda for HGR management

We expect HGR policies continue to evolve and strengthen in the coming years to accommodate government's top priority of protecting HGR security as well as China-based innovation. Therefore, HGR management excellence has become, and will continue to gain more traction, as a key capability within the R&D organization. This not only applies to MNC pharmacos conducting China-based research, but also holds equal importance for leading domestic biopharmas with more globalized R&D operations and partnerships.

To secure study approvals and ensure compliant study executions, companies will need to not only effectively interpret current policies, but also to anticipate future policy directions so that they can adapt to changes in the regulatory requirements with more agility. With likely future policies directions in mind, we believe companies will have to focus on the following agenda for winning HGR engagement:

Effective policies interpretation

As a direction, we expect HGR regulations to keep evolving rapidly in the future to provide more clarity and flexibility. Take data-filing for example, currently there is no clear definition of "in-scope data", so any data transmitted to overseas vendors theoretically would require data back-up and data filing before an actual transfer can happen. This requirement is especially challenging to implement for highly time-sensitive data, such as patient toxicity data which will have to be analyzed almost in real-time overseas to render critical decisions regarding clinical studies. In the future, however, HGRAO might adopt a category-based approach to data back-up and data filing. For example, toxicity data may be filed retrospectively, while non time-sensitive data, such as biomarker data, will have to be filed before overseas transfer.

The likely constantly evolving regulatory requirements would imply that companies must effectively anticipate, interpret, and internalize these changes, so that implicated studies can maximize their chances of approval as well as HGR compliance during the study execution phase.

Capabilities localization

In addition to the HGR policies assessing the use of human sample and data based on scientific rationales and perceived clinical value, their exportation is increasingly scrutinized to prevent unwarranted exploitation by foreign organizations. Despite the notion that many multi-centered global clinical studies require global central labs and data vendors in a single location to maximize sample and data analysis efficiency and quality consistency, we do expect the use of localized vendors, including global vendors based in mainland as well as domestic vendors, to be more heavily encouraged by the HGR policies.

This will be especially true for vendors where perceived local capabilities are mature enough to meet global standards, such as local central labs and sequencing labs for sample testing. So it is conceivable that in the near future, except for extreme cases where no local technologies are available, there will be more limited room to negotiate sample exportation, and that most sensitive tests such as biomarker tests and tests related to gene sequencing will have to be locally performed.

Data localization, on the other hand, is considerably harder to realize in the near future largely due to the perceived capability gaps between local data vendors and mainstream international ones. Although the switch to domestic data vendors will take time, we do anticipate more international data vendors to consider localizing their infrastructure in mainland.

The implications to MNC biopharmas are two-fold. For sample testing, they need to seriously revisit local vendor strategy, initiate comprehensive market engagement to assess the capabilities of Chinese labs, and later develop strategic alliances with selected local labs to drive more efficiency and scale across study portfolios. For data analysis, they will have to formulate interim solutions to fulfill data backup and filing requirements at the same time, while initiating discussions with key data vendors such as EDC and Data Management CROs to potentially develop onshore servers in China. Meanwhile, local partnerships and alliances may serve to fulfill localization in specific data categories, such as genetic sequencing data.

Taking the collection and analysis of Chinese genomic sequencing data as one example, in the announced partnership between Foundation Medicine One (FMI) and Di An lab, the latter provides DNA sequencing lab services against FMI's genetic biomarkers, allowing FMI to address local data compliance requirements[1].

Robust HGRAO communication and engagement

The former CFDA used to be challenged with outdated regulatory processes and capacity constraints that resulted in long IND/NDA review times and significant launch lags as much as 7 years. To increase productivity, it adopted more developed market standards, created more open channel communications, and expanded internal capacities and specialized capabilities. NMPA successfully managed to reduce the launch lags to 3.5 years in just over 3 years of time[2].

With the backdrop that China is already becoming a global hotbed for life sciences R&D, especially for next generation therapies, such as cell and gene therapies[3], today's HGRAO also has a heavy challenge to tackle: how to most effectively protect human genetic resources without stifling China-based innovative R&D.

In the past 12 months, HGRAO has organized workshops during the DIA (Drug Information Association) annual meeting and held targeted HGR management training for industry practitioners to both provide guidance as well as seek constructive inputs from the industry. Going forward, we expect HGRAO will strengthen its connections with the industry, providing more opportunities for the industry voices to be heard, as well as for program teams to better interact with the HGRAO for study reviews. New venues such as industry forums, virtual training sessions, offline office visits, may all become more available.

As a result, companies will need to critically reevaluate their HGRAO engagement plans. It is important to develop a discussion agenda not only about the innovative nature and clinical benefits of their program portfolio, but also thoughtful suggestions on how HGRAO and pharmacos can foster a stronger partnership to jointly safeguard HGR security. Rather than one-on-one meetings, a more diversified set of venues may have to be considered for such dialogues, with the right senior leadership, even industry association representation.

1. Dian diagnostics, *Announcement on cooperation with Foundation Medicine, Inc. and Roche to promote the development of personalized cancer diagnosis and treatment in China*, 2018-04-27
2. National Medical Products Administration, *National Medical Products Administration's implementation of the State Council's notice of separating permits from the business license for drug regulatory approval*, NMPA[2018] No.46
3. The Central People's Government of the People's Republic of China, *Completion of the Essential Drug Research and Development Project*, 2021-02-02

At the program level, study teams will need to be better educated on the HGRAO requirements, and reflecting them in both administrative reviews as well as the expert reviews. Before administrative reviews, open channel consultation is strongly recommended to avoid any obvious issues, such as specific reporting requirements for raw data versus result data. For expert reviews, it may be helpful to establish a local external advisory network that can provide HGR perspectives on study application readiness, and to prepare for Q&As regarding any potential concerns & challenges by HGRAO.

The two suggestions above will not succeed without strong internal cross-functional collaborations. Multiple functions, such as government affairs, clinical development, operations, IP/legal will have to work hand in hand to achieve effective HGRAO engagement.

Proactive legal and compliance risk mitigation

With the planned formal introduction of *Biosecurity Law* later this year[4], as well as the possible incorporation of HGR into *Criminal Law*, companies & individuals will face more severe punishment for violations. The legislation signals not just strengthened enforcement against violations, but also more routine HGRAO directed inspections aimed at monitoring compliance readiness and violations.

Although the degree of severity may vary, the following are some example violations that companies must strive to avoid at all times:

- As a foreign organization, collecting and storing human genetic resources within China
- Carrying out studies without proper HGRAO approval
- Shipping, mailing or carrying Chinese human genetic resources out of the country without proper HGRAO approval and customs clearance
- Providing sensitive Chinese patient data to overseas organizations, individuals and institutions without HGRAO approval
- Oversized sample and data compared to original study protocols
- Changing of study protocols without informing the HGRAO
- Biosecurity data breach due to cyber-attacks / firewall loopholes
- Any HGR misconduct by the vendors or collaborators, e.g. human samples being stored beyond the allowed time duration

In order to navigate the post-legislation environment, companies must adopt a more proactive approach to prevent, detect and mitigate non-compliant and legal risks at both corporate level and individual level. This may include a set of standard processes, SOPs, guidance documentation and training programs to ensure compliant study execution in the first place, regular internal audits as well as external audits of vendors and collaborators to detect issues early, as well as an efficient decision-making model for issue resolution and escalation. Key enablers, such as IT solutions to track study submission status, analyze causes for rejections, and catalog best practices will be very much in need to ensure data-driven oversight.

4. The National People's Congress of the People's Republic of China (2020). "*Biosecurity Law of the People's Republic of China (No. 56)*" Chapter 6

Organizing for HGR management excellence

There are a few reasons why HGRAO regulations are faced with practical implementation challenges by the global biopharmas. First of all, the large R&D organizational complexity makes it extremely difficult to consistently apply HGRAO in daily work. Many global and local R&D departments are impacted by HGRAO, which requires a clear and consistent understanding of the policy requirements and implications to different functions; secondly, most of the China-based studies are part of global programs, as such, many program design and planning activities were already completed with focuses on the FDA and EMA registrations, with insufficient considerations for China HGRAO requirements; thirdly, because these companies have well-established internal processes for running R&D projects, it will be more difficult to make any significant changes without disrupting the current businesses.

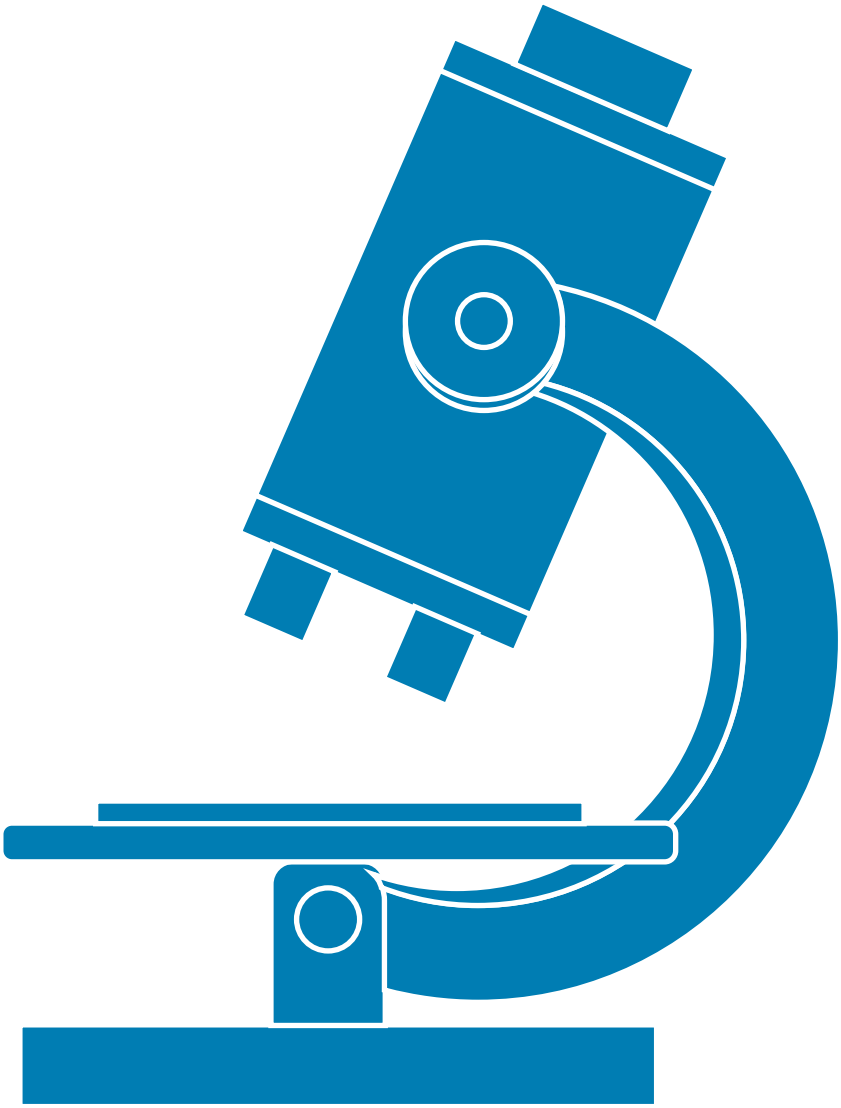
The following principles may help companies overcome these operational challenges and ensure that HGR capabilities can be fully embedded into the R&D organization.

- **A sufficiently optimized HGR governance can help instill a cohesive approach to HGR oversight.** Just like other markets with local specific regulations for human samples, such as those enforced by the Human Tissue Authority (HTA) in the UK, HGR is a local regulation in China that, in principle, should be dealt with locally first and foremost. R&D organizations should think about strengthening their local HGR governance in order to provide strong oversight and decisions-making on critical issues, such as HGRAO engagement, study submission, training, and resolution of HGR compliance matters. This will also help to reduce too many unnecessary escalations into the global governance.
- **A fit-for-purpose HGR operating model should be established.** Similar to regulatory affairs, who serves as both the internal regulatory subject matter expert as well as the point person for regulatory submission and inspection activities, HGR management may also benefit from having a dedicated internal team of champions. Such a team can externally interface with the HGRAO for effective policy interpretation, internally provide HGR related training programs, as well as serve as the point person to coordinate overall study submission activities.

  There are HGR issues that require highly specialized functional expertise, such as legal risks, procurement for vendor localization and HGR related oversight, data management for data backup and filing, just to name a few. Hence, a mechanism will have to be established to enable strong cross-functional involvement in HGR management.
- **Be explicit about the HGR-related KPIs in your organization.** For any organization, the success of HGR management should be measured by a clear set of goals and metrics with the right ownerships. These metrics can fall into different categories, such as productivity (study approval rate), competency (HGR awareness), compliance (inspection readiness), reputation (perceived HGR excellence by regulators and industry peers), and should be closely monitored, analyzed, and adjusted to reflect the organizational HGR maturity.

- **One cannot emphasize enough the importance of data-driven.** Similar to existing regulatory filings and data management practices that are well supported by IT systems, companies must resort to a more data-driven approach in order to meaningfully track and improve HGR productivity and compliance. There are at least four aspects of HGR management requiring IT support: study application & submission management, sample flow and usage tracking, HGR-inspection required source file curation, and training deployment. All these IT solutions can significantly drive continued improvement of best practices while ensuring that the impacts of HGR excellence to business can be clearly measured with the clear set of goals and metrics discussed above.

In summary, China's HGR regulations are presenting additional compliance barriers for foreign-involved, China-based R&D programs. Effectively navigating these regulations will require companies to establish a proactive mindset, a fungible operating model, as well as the right data-driven solutions to conduct issue resolution and track outcomes. HGR management excellence is a core competency that R&D organizations must consider building now in order to win tomorrow.



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