Key Takeaways of the New HGR Guidelines

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On July 14, 2023, the Ministry of Science and Technology of the PRC ("**MOST**") issued the *Notice on Updating the Guidelines on Administrative Approval Items and the Scope and Procedures for Filing and Prior Reporting of Human Genetic Resources*, which unveiled six documents, including the administrative guidelines on collection approval, biobanking approval, exportation approval and international collaboration approval of human genetic resources ("**HGRs**"), as well as the scope and procedures for international collaboration filing and data sharing reporting of HGRs (collectively "***New Administrative Guidelines***"). The *New Administrative Guidelines* have been officially implemented on July 1, 2023 and serve as the supporting documents for the *Regulations on the Administration of Human Genetic Resources* ("***HGR Regulations***") and the *Implementation Rules for the Regulation of Human Genetic Resources Administration* ("***Implementation Rules***"), which have attracted due attention from the industry since its release by the MOST on June 1, 2023 (for reference, please refer to *Highlights on HGR Regulation Implementation Rules* and its Chinese version *汉坤 • 观点 | 重磅首发：《人类遗传资源管理条例实施细则》要点解读*). The *New Administrative Guidelines* have further clarified and refined the regulatory requirements of *HGR Regulations* and *Implementation Rules* and have provided convenience and guidance for related parties to fulfill compliance obligations and go through the administrative approval, filing and reporting procedures.

The *Biosecurity Law*, the *HGR Regulations* and the newly implemented *Implementation Rules* have jointly formed the current regulatory framework for HGRs in China. Among them, the *Implementation Rules* have optimized and refined the regulatory provisions including some key definitions and scopes and obligations to be fulfilled by related parties when carrying out activities such as collection, biobanking, exportation, external provision and access opening of HGRs, as well as administrative supervision and penalties. To adapt to the changes in the regulations, the previous administrative approval/filing guidelines have also been updated accordingly by the MOST. Meanwhile, the MOST has also provided responses in the *New Administrative Guidelines* to some of the concerns and doubts on the rules and approval/filing procedures from the industry. It is also worth noting that at the end of June, the MOST launched a new version of declaration system (Human Genetic Resource Management System: https://apply.hgrg.net/), which will facilitate companies in conducting relevant regulatory procedures for HGR-related activities.

This article will analyze and summarize the key provisions of the *New Administrative Guidelines* in terms

of the scope of HGRs, the definition of foreign parties, data sharing reporting and national security review and regulatory requirements in exportation approval and international collaboration approval and filing procedures.

The scope of HGR materials and HGR information

The *New Administrative Guidelines* have clarified the scope of HGR materials and HGR information.

I. The scope of HGR materials

Regarding the HGR materials, the *HGR Regulations* have defined them as "the organs, tissues, cells and other genetic materials containing human genome, genes and other genetic substances". The *Implementation Rules* do not further limit or explain the scope of HGR materials, while the *New Administrative Guidelines* specifically list the types of HGR materials, which include "all types of cells, whole blood, tissues/tissue sections, semen, cerebrospinal fluid, thoracic/abdominal effusion, blood/bone marrow smears, hair (with follicles), etc.". Moreover, the *New Administrative Guidelines* have also provided certain limitations, indicating that "human secretions, body fluids, swabs, etc. without cells" are excluded from the scope of HGR materials.

We understand that practically, some human secretions, without certain treatments, may still include human cells, thus containing "human genome, genes and other genetic substances". Therefore, even if the *New Administrative Guidelines* have provided the aforementioned limitation, based on past practices, it is still possible for certain untreated human secretions to be deemed as HGR materials. Further observation is needed for future practices on this issue. Nevertheless, if the human secretions are confirmed that they do not contain any human cells, they will no longer be subject to HGR-related regulation.

II. The scope of HGR information

Regarding the *HGR information*, the *Implementation Rules* have narrowed the scope of it by only explicitly including human genes and genome data generated by using HGR materials while excluding clinical data, imaging data, protein data, and metabolic data. The *New Administrative Guidelines* further list some examples of HGR information, providing that HGR information includes "data information such as genes, genomes, transcriptomes, epigenomes and nucleic acid biomarkers such as ctDNA, as well as the related information such as the relevant diseases and ethnic origins". The regulatory requirements will not apply to data where human genes and genome data are not involved.

The *New Administrative Guidelines* have responded to the widely concerned question of whether certain types of data (such as biomarkers) will constitute HGR information. From the clarification that data including transcriptome data are HGR information, we understand that HGR information will not only include typical data containing DNA base sequences. The results of research on DNA methylation and the messenger RNA (mRNA) information obtained from Chinese human cells may also constitute HGR information. Moreover, regarding biomarkers, we understand that nucleic acid biomarkers such as ctDNA are clearly within the scope of HGR information, while other biomarkers that do not contain human genes and genome data are no longer subject to regulation.

The definition of foreign parties

The *Implementation Rules* have narrowed the scope of "foreign parties" by only including entities where foreign investors have more than 50% of shares, voting rights or other similar interests, and entities where foreign investors can dominate or have significant impacts on corporate decision-making and internal management. After the release of the *Implementation Rules*, the industry is very concerned about how the MOST would determine whether the foreign investors are sufficient to "dominate or have significant impacts". However, in the *New Administrative Guidelines*, the MOST does not provide further specific explanations for this issue.

According to our understanding of regulatory practices, the MOST holds the view that the companies are in the best position to make their own assessment regarding whether their foreign investors can "dominate or have significant impacts" on corporate decision-making and internal management, and the companies themselves shall be responsible for such determination. We understand that when making such determination, important factors to be considered usually include the companies' voting mechanisms at shareholders' meetings or board meetings, the methods for appointing board members, and the composition of board seats, etc. At the same time, when a company declares itself as a Chinese party, it shall provide corresponding materials as supporting documents (such as the analysis from its internal or external legal counsels) and submit a commitment letter to the MOST promising that it does not constitute a foreign party. The companies shall be responsible for the authenticity of the submitted materials. The MOST will conduct a formal review of such materials and register such companies as Chinese/foreign parties accordingly.

The *Implementation Rules* have also stipulated that companies located in Hong Kong or Macao that are controlled by domestic investments can be deemed as Chinese parties. In the *New Administrative Guidelines*, the MOST does not provide further explanations on the definition of "be controlled by domestic investments". As a result, questions such as whether companies indirectly controlled by domestic investments (such as the Hong Kong companies under the "Red Chip(红筹)" structures) can be deemed as Chinese parties, and whether the subsidiaries of such Hong Kong and Macao companies can also be regarded as Chinese parties, will still need further observation in future practice.

Data sharing reporting and national security review

According to the *HGR Regulations*, before the external provision or access opening of HGR information to foreign parties, the data sharing reporting and backup procedure must be completed. The *New Administrative Guidelines*, aligning with the *Implementation Rules*, further provide that, in an ongoing international collaboration that has already been approved or filed, the data exchange between the " collaborating parties" will be exempted from the data sharing reporting and backup procedures as long as such data exchange arrangements are stipulated in the international collaboration agreements.

Nevertheless, according to current regulatory practices, we understand that the sponsors, the leading sites, the contract research organizations ("**CROs**") and the third-party laboratories that are listed and approved/filed as the "collaborating partners" are all interpreted as the "collaborating parties" and thus the data exchange between them can also be exempted from additional data sharing reporting. After the

effectiveness of the *Implementation Rules* and the *New Administrative Guidelines*, it is necessary to further observe whether parties other than the sponsors and the leading sites can also be exempted from the data sharing reporting and backup procedures.

Regarding the national security review, the *New Administrative Guidelines* clearly state that if the MOST, during its formal review process of data sharing reporting, believes that the application for external provision or access opening of HGR information meets the requirements for national security review, the national security review procedure will be carried out. Accordingly, we understand that the initiation of the national security review will be determined by the MOST during the formal review stage of data sharing reporting, and the applicants are not required to voluntarily submit a separate application for national security review.

Approval of exporting HGR materials

The *New Administrative Guidelines* have further refined the application material requirements for the approval of exporting HGR materials. In comparison to the previous guidelines, the *New Administrative Guidelines* additionally stipulate that the applicant should submit research protocol, agreements on the disposal of remaining HGR materials (if involved), and proof of the legitimate source of HGR materials (if applicable), etc. The *New Administrative Guidelines* also emphasize that the submitted research protocol should encompass the entire process of sample utilization, reflecting the enhanced regulatory requirements outlined in the *HGR Regulations*, such as the need for reasonable use in exports and ensuring no harm to China's public health, national security, and social public interests.

Approval procedure for international collaboration scientific research

Regarding major/non-major changes in the approval of international collaboration scientific research ("**ICSR**"), the *Implementation Rules* provide specific criteria for determining non-major changes and clearly outlines some non-major change situations, including situations where the changes in total cumulative quantity do not exceed 10% of the approved HGR quantity. The *New Administrative Guidelines* further explain this provision, emphasizing that the term "changes" only pertain to quantity increases while reductions in quantity are exempted from regulations. Regarding the involvement of different types of HGR, the *New Administrative Guidelines* state that the inclusion of a new type of HGR should be declared as a major change, regardless of its quantity. Furthermore, if any one type of HGR undergoes a cumulative change in the total amount exceeding 10%, it should also be declared as a major change. Finally, the *New Administrative Guidelines* emphasize that if multiple non-major changes result in a cumulative change in a quantity exceeding 10% of the initially approved quantity, all non-major change amounts should be accumulated and declared as a major change when declaring the current change that exceeds the 10% threshold of the initial approval amount.

Regarding application materials for ICSR approval, it is worth noting that the *New Administrative Guidelines* require sponsors, leading sites, CROs, and third-party laboratories to submit the executed versions of international collaboration agreements. This is because of the increased pass rate of actual ICSR approval. Previously, the pass rate for ICSR approval was lower, and requiring the submission of executed versions of collaboration agreements may have resulted in a significant number of applicants

who failed to pass ICSR approval to breach their agreements. While this is no more the case, the MOST clearly states in the *New Administrative Guidelines* that sponsors, leading sites, CROs, and third-party laboratories shall submit signed and stamped versions of international collaboration agreements. Nevertheless, there are currently no such requirements for other participating parties besides these four collaborating parties.

Filing procedure for international collaboration clinical trials

The *Implementation Rules* have stipulated that HGR can be tested, analyzed and disposed of in domestic institutions designated by clinical trial protocols in international collaboration filing projects. Although the *New Administrative Guidelines* do not provide further explanation regarding the “domestic institution” designated by the clinical trial protocol, we understand that the term "domestic institution" here may also include foreign-invested institutions in China, rather than merely referring to Chinese Parties under the HGR supervision regime.

Regarding change procedures for international collaboration filing, the *New Administrative Guidelines* align with the *Implementation Rules* in determining major and non-major filing changes and outline specific major change situations, including changes in types, quantities, uses, partners, research protocols, research content, or research purposes. It is worth noting that non-major changes for ICSR approval do not apply to international collaboration filing. Therefore, if there is a change in the total cumulative quantity of HGR that does not exceed 10% of the HGR quantity stipulated in the international collaboration filing, it may still fall under the category of a major change and shall undergo the necessary filing change procedures.

Regarding the application materials for international collaboration filing, the same requirements as the previous guidelines remain in place. Applicants are required to provide signed and stamped versions of international collaboration agreements.

Conclusion

The *New Administrative Guidelines* have further refined some key definitions and scope such as HGR materials and HGR information and provide more detailed operational requirements for approval, filing and reporting procedures regarding HGR-related activities. While responding to some major concerns from the industry, the *New Administrative Guidelines* also leave the regulatory authorities with room for discretion on specific cases. Therefore, we understand that when carrying out HGR-related activities, such as collection, biobanking, exportation, data sharing, etc., relevant parties should strictly fulfill relevant compliance requirements and obligations based on the regulations and guidelines.

As mentioned in previous articles, the existing regulations on HGRs in China have heightened the regulatory supervision of HGR-related activities. Therefore, we understand HGR compliance is increasingly important for relevant business activities, and suggest relevant parties continue to pay attention to the evolving regulatory requirements and trends. We will keep a close eye on the regulations in HGRs.

Important Announcement

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