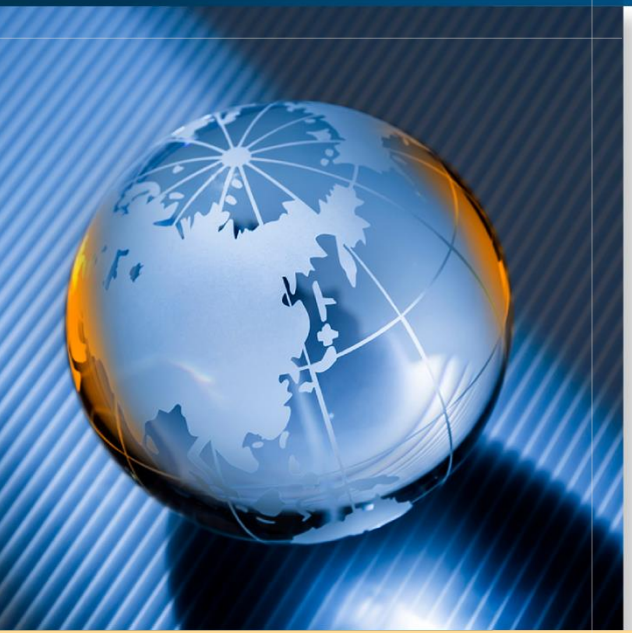

CHINA: RECENT UPDATES IN THE REGULATORY REGIME FOR IVD/COMPANION DIAGNOSTICS

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AGENDA

- Brief Introduction to IVD and CDx
- Main Updates in the Regulatory Regime for IVDs/CDx
- Overview of HGR and Data Protection Regulations

Brief introduction to IVDs and CDx

- **Categories of IVDs**:
  - IVDs regulated as drugs: IVDs used for blood source screening and IVDs labeled with radionuclides.
  - IVDs regulated as medical devices: IVDs other than those regulated as drugs.
- **Definition of IVDs and CDx**:
  - IVDs regulated as medical devices include any reagent, kit, calibrator, quality control product and so on, whether used alone or in combination with instrument, apparatus, appliance and system, intended to be used in vitro for the examination of human specimens during the prediction, prevention, diagnosis, treatment monitoring, prognostic observation of disease, and health status evaluation.
  - CDx are instrument for evaluating the safety and efficacy of related medicinal products, and are mainly used, before and/or during treatment, to identify patients who are most likely to benefit from related medicinal products and patients who may have an increased risk of serious adverse reactions due to the treatment.
- **Classification of IVD and CDx**:
  - IVDs are divided into three classes – Class I, II, III – with the risk level from low to high.
  - CDx are regulated as Class III IVDs.

Main Updates in the Regulatory Regime for IVDs

- **Administrative Measures for the Registration and Record-Filing of IVDs ("Order 48")**
  - Order 48 was promulgated by SAMR and became effective as of October 2021.
  - As a supporting regulation of Order 739 (the Medical Device Regulations), Order 48 outlines the registration/record-filing requirement for IVDs, including pathways (*regular approval vs. accelerated approval*), procedures requirements (*e.g., clinical evaluation, type testing, QMS inspection*), statutory time. It also clarifies the obligations of the marketing authorization applicant and regulatory authorities (e.g., NMPA, CMDE, CFDI).
  - Class I --- record-filing; Class II and Class III --- registration.
- **Classification Rules for IVDs ("2021 Classification Rule")**
  - Promulgated by NMPA and effective since October 2021, the rules identify factors that may affect the determination of IVDs' risk level, define the scope of each class of IVD products, and enumerate the types of reagents under each class.
  - To implement the 2021 Classification Rules, NMPA now is amending the IVDs Classification Catalog. In March 2023, NMPA issued a draft version to solicit public comments.

Main Updates in the Regulatory Regime for IVDs

- **Technical Guidance for IVDs Clinical Trials ("2021 IVD GCP")**
  - The 2021 IVD GCP was issued by NMPA and became effective as of September 2021. Compared to the IVD GCP issued in 2014, the 2021 IVD GCP proposes more specific and detailed requirements on IVDs clinical trials for registration purposes in China. Key changes include:
    - **Clinical trials design.** 2021 IVD GCP describes two types of IVD clinical trial design (observational study vs. interventional study) and requires sponsors to select the appropriate approach in accordance with the characteristics and intended uses of the relevant products.
    - **Sample size requirement.** 2021 IVD GCP removes the rigid requirement on sample size (e.g., at least 1000 samples for Class III IVD and 200 samples for Class II IVD) and allows sponsors to estimate minimum sample size estimates based on statistical analysis.
    - **Quality control requirement.** 2021 IVD GCP adds a whole chapter on quality control management, emphasizing that the IVDs clinical trials should be carried out in accordance with the medical device GCP. Such requirement can also be found from the medical device GCP revised in 2022.
    - **Informed consent requirement.** 2021 IVD GCP deletes the circumstances under which an informed consent can be waived and requires investigators to obtain informed consent from clinical trial subjects.

Common Issues Found in IVD Clinical Trials

- **The CMDE recently shared the following common issues discovered during the on-site inspection of IVDs clinical trials:**
  - Inconsistency or un-traceability of clinical trial data [36.75%]
  - Deviation from clinical trial protocol [25.64%]
  - Fabrication of original data or incomplete original data [15.38%]
  - Study device management [10.26%]
  - Insufficient site preparation before clinical trials [6.84%]
  - Inadequate protection for study subjects [3.42%]
  - Management of biological specimens [1.71%]

Main Updates in the Regulatory Regime for IVDs

- **Catalog of IVDs Exempted from Clinical Trials ("Trial Exemption Catalog")**
  - Article 37 of Order 48 provides a legal basis for exemption of clinical trials for IVDs with specific characteristics (clear working mechanism, mature design and production process, no records of SAE, etc.)
  - This Trial Exemption Catalog was promulgated by NMPA in 2021 and came into effect from October 1, 2021.
  - A total of 423 Class II and Class III IVDs are exempted from clinical trials.
- **Technical Guidance for Clinical Evaluation of IVDs Exempted from Clinical Trials**
  - This guidance was issued by NMPA in September 2021 and applies to the clinical evaluation of IVDs included in the Trial Exemption Catalog.
  - IVDs eligible for clinical trials exemption can demonstrate compliance with the use requirements or intended use in one of the following two ways:
    - Establishing equivalence with products that are already approved for marketing in China by comparing their intended use, basic principles, performance indicators, positive judgement values and reference intervals, etc..
    - Conducting comparative analysis with a reference measurement procedure or diagnostic accuracy standard and the result of comparison displaying good consistency.

Main Updates in the Regulatory Regime for IVDs

- **Technical Guidance for Using Overseas Clinical Trials Data of IVDs**
  - In December 2021, NMPA released this guidance as a supplement to the Technical Guidance for Accepting Overseas Clinical Trials Data of Medical Devices released by NMPA in 2018.
  - When using overseas clinical trials data for the initial registration or change application of IVDs, the applicants should analyze:
    - the difference between the GCPs adopted in China and overseas to determine whether the clinical evidence meets the compliance requirements; and
    - the key design elements of clinical trials conducted in and outside of China to determine whether the clinical evidence meets the scientific requirements.
- **Circular on Requirements for IVDs Registration Application Dossiers and Format of Approval Documents**
  - The latest version came into effect on January 1, 2022 as a supporting rule of Order 739 and Order 48.
  - Attachments 4, 5, and 6 of the Circular explain in detail the application dossiers requirements for the initial registration, re-registration and change application of IVDs.

Main Updates in the Regulatory Regime for CDx

CMDE has issued three technical guidelines on CDx for oncology drugs in 2021 and 2022.

- **Technical Guidance for Registration Review of Clinical Trials of Originator CDx Co-developed with Anti-tumor Drugs (June 2022)**
  - **Scope of Application**:
    - Joint development of CDx and anti-tumor drugs in the process of preclinical and clinical research. The joint research data can be used to support the marketing application of both the CDx and the oncology drug.
    - Subsequent development of CDx relying on the Clinical Trial Assay ("CTA") adopted in the clinical trials for oncology drugs.
    - Marketed products being chosen as the CDx in the development of oncology drugs. The clinical research results can support the registration application for the oncology drug and the change application for the CDx.
  - **Priority review**:
    - CMDE encourages the co-development and co-registration of oncology drugs and their CDx; a simultaneous review mechanism has been implemented by CDE and CMDE.
    - If an oncology drug has been admitted into fast-review track, its co-developed CDx is also eligible for priority review pathway.

Main Updates in the Regulatory Regime for CDx

– **Accepting Overseas Clinical Trial Data**:

For CDx co-developed with the an oncology drug in overseas clinical trials or international multi-center clinical trials including China:

Oncology Drug Clinical Trial	CDx Used in the Clinical Trial	Clinical Value of CDx
All overseas clinical trial data are accepted by the CDE to support the registration of the drug	Using the same CDx	Clinical trials data of the oncology drug
Parts of overseas clinical trial data + parts of domestic clinical trial data	Using the same CDx in clinical trials conducted in and outside of China	
	Using different CDx in clinical trials conducted in and outside of China	Bridging tests of overseas clinical trials + drug clinical trials conducted within China

Note: The rules for and conditions to accepting overseas clinical trials data for drug registration in China should refer to the '*Technical Guidance for Accepting Drugs Overseas Clinical Trials Data*' released by CDE in 2018.

Main Updates in the Regulatory Regime for CDx

- **Technical Guidance for Registration Review of Clinical Trials of Non-Originator CDx for Oncology Drugs (December 2021)**
  - **Scope of Application**:
    - Specifying the general requirements for clinical research of non-originator CDx.
    - Non-originator CDx refer to the CDx that are developed by the IVD manufacturers to support oncology drugs that have already been approved for marketing.
    - This Guidance will apply when the following conditions are met:
      - The marketed oncology drug(s) for companion use has been determined during R&D stage;
      - Consistent biomarkers with the originator CDx;
      - Consistent applicable populations and sample types with the originator CDx;
      - Comparability of analytical performance with the originator CDx.
  - **Clinical Trials Requirements**:
    - Purposes: 1) determining clinical performance; 2) determining companion diagnostic uses
    - Design: 1) following the 2021 IVD GCP to evaluate clinical performance; 2) conducting consistency comparison, bridging tests, or observation studies on efficacy to determine companion diagnostic uses.

Main Updates in the Regulatory Regime for CDx

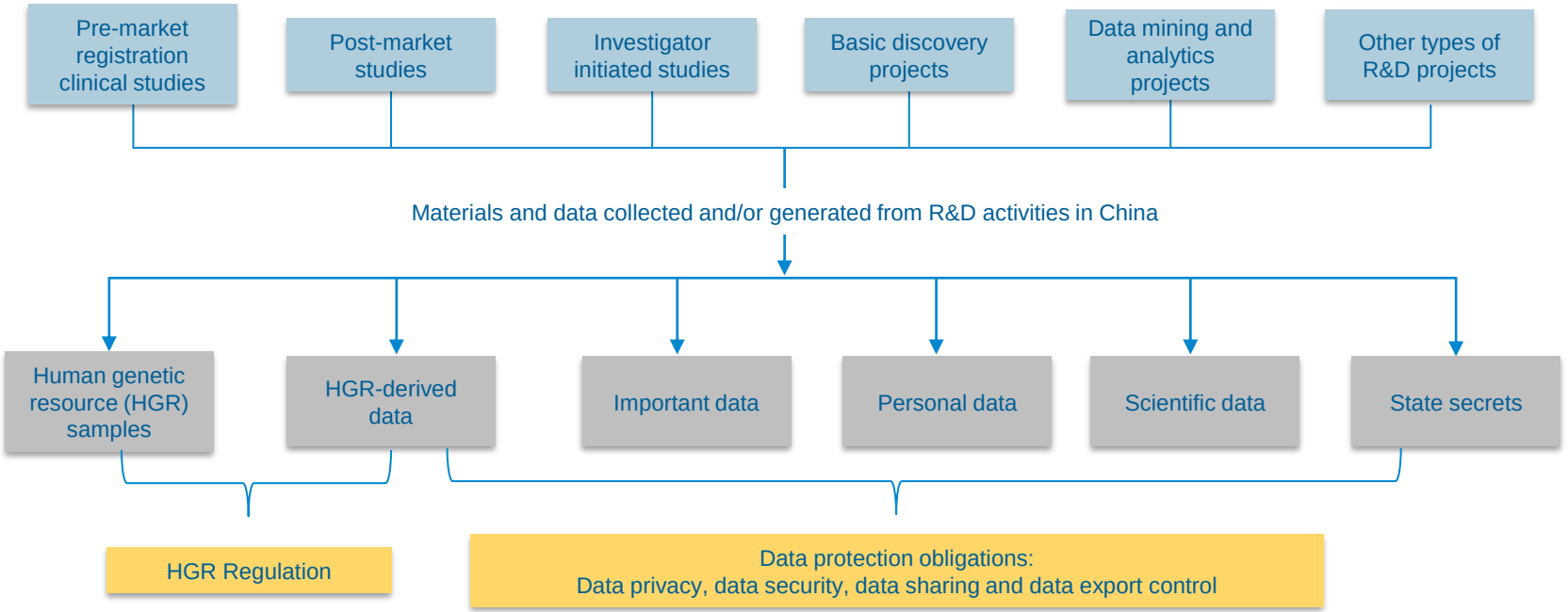
- **Guideline for Technical Review and IFU Update for Oncology CDx Based on the Same Group of Therapeutic Drugs (April 2021)**

  It used to be a common practice to approve a CDx for companion use with a specific drug. Under the Guideline, the IFU for an Oncology CDx can be updated to allow the use for same group of therapeutic drugs when certain conditions are met.

  – **Scope of Application**:
    - Scientific evidence shows that a tumor detection reagent is suitable to be used for same group of therapeutic drugs.
    - Same group of therapeutic drugs refer to at least two NMPA approved oncology therapeutic drugs with the same mechanism of actions, same biomarkers, and the same applicable population.

  – **Factors to consider**:
    - Evaluating all possible differences to ensure appropriate extrapolation
    - Specifying the same group of therapeutic drugs
    - Clear biomarkers and the mechanism of actions of the therapeutic drugs
    - Well-established clinical performance and efficacy data

Overview of HGR and Data Protection Regulations



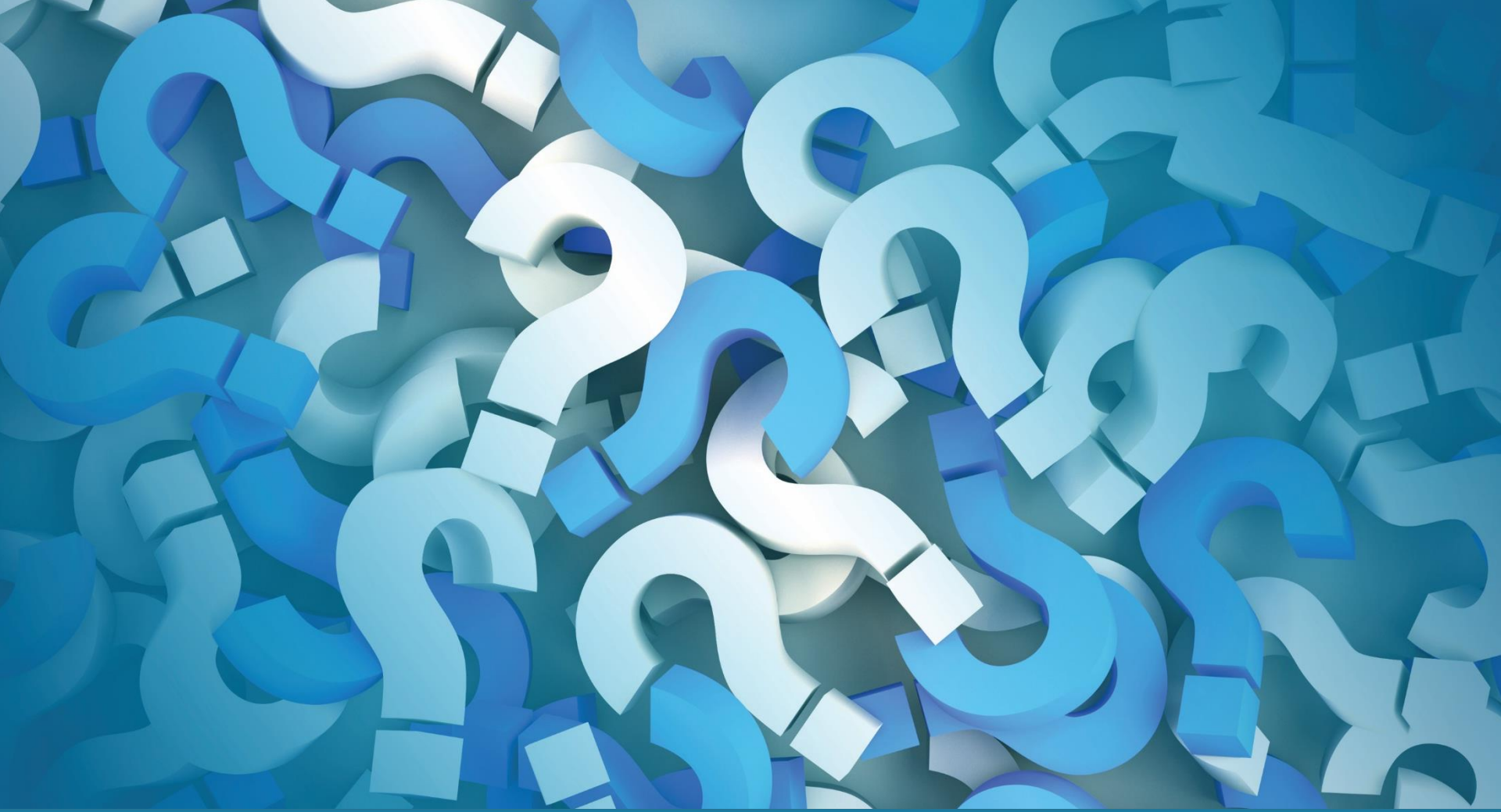
Overview of the HGR Regulation

- China's State Council, the country's top administrative authority, released the Regulation of Human Genetic Resources (the "HGR Regulation") on May 28, 2019, to replace the previous tentative rules issued in 1998.
- The HGR Regulation, which became effective as of July 1, 2019, illustrates the Chinese government's clear intent to position the regulation of HGRs as one of its national security priorities.
- The HGR Regulation closely scrutinizes all HGR-related researches from upstream collection of human bio-specimens to downstream utilization and sharing of HGR samples and any data derived therefrom.
- The HGR Regulation formalizes the approval requirements pertinent to research collaborations between Chinese and foreign-owned or controlled entities to avoid uncertainty during the approval process.

- The HGR Regulation also significantly increases and expands penalties for various violations.

Overview of the Data Protection Regulations

Evolving legislation	▪ In recent years, the Chinese government has issued a set of laws, regulations and guidelines to specify personal information protection and data privacy and security requirements, including Personal Information Protection Law (PIPL), Data Security Law, Measures for the Security Assessment of Outbound Data Transfer, etc. ▪ Cross-border transfer of data (e.g., personal information, important data) has become the focus of administrative supervision. ▪ Unlike GDPR or HIPPA, the Chinese legislation emphasizes the importance of safeguarding national security. The Chinese government has positioned health and medical data (including population demographics and genetic information) as one of its national security priorities.
Active enforcement	▪ Various cybersecurity regulators from national, provincial, and local levels have initiated enforcement actions in China. - Didi, China's ride-hailing conglomerate, was fined RMB 8.026 billion (US$1.2 billion) for unlawful collection and processing of passengers' information in violation of the Cybersecurity Law, the PIPL, and the Data Security Law. ▪ Companies need to review their cybersecurity compliance and be prepared to respond to investigations (categorize and segregate systems containing sensitive IP or information, providing trainings, implementing SOPs for handling dawn raids).



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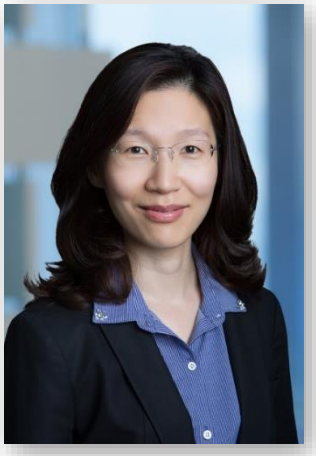

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Practice

Katherine assists pharmaceutical, biotechnology, and medical device companies on a wide range of commercial and regulatory matters. Before entering into private practice, Katherine served as the head of AstraZeneca's legal department in the Asia-Pacific region. She is named on Chambers Asia-Pacific and Greater China's Leading Lawyer in Life Sciences (2011-2023), Legal 500 Asia Pacific's Leading Individuals in Life Sciences (2019-2023), China Business Law Journal's The A-List of China's Top 100 Lawyers (2019, 2021-2022), and Global Law Experts' Life Sciences Regulatory Expert of the Year in China, Product Registration Expert of the Year in China, and GxP Compliance Expert of the Year in China (2021).