China Life Science Sector Overview 2022:Wading into Deep Waters: Survive and Thrive

- Innovation-driven regulatory environment and economic downturn in the past year have urged life science companies to be more resilient and flexible to current regulatory and market changes.
- The Chinese government has cultivated an innovation-driven regulatory environment and provide unprecedented market incentives for orphan drugs and pediatric drugs.
- The legislative development in 2022 addressed various emerging issues in the industry, including cell and gene therapy regulation, cross-region or cross-border regulation, e-commerce regulation.

The Chinese government has been deepening its reform over the past year in order to foster evolving regulatory framework. Deeper reforms coupled with a chilled market means life science companies should prioritize their assets and re-position their business strategies in order to survive and grow stronger.

The legislative developments in 2022 continued to reinforce and foster the spirit and regulatory framework laid by the *PRC Drug Administration Law* (DAL) (中华人民共和国药品管理法), the *PRC Vaccine Administration Law* (VAL) (中华人民共和国疫苗管理法), the *PRC Medical Device Regulation* (MDR) (医疗器械监督管理条例) and the *Regulations for the Supervision and Administration of* (CSAR) (化妆品监督管理条例) between 2019 to 2021 to cultivate an innovation-driven environment and compliance culture for the life science sector.

I

What does not kill me makes me stronger

Innovation-driven regulatory environment and economic downturn in the past year have urged life science companies to be more resilient and flexible to current regulatory and market changes. Patient-centered market players who differentiate themselves with innovation and truly address unmet clinical need may survive and thrive.

- ***Cultivating an innovation-driven regulatory environment***

  In early-2022, the Chinese government announced its "14th Five-Year Plan for the Pharmaceutical Industry (2021-2025)" in February, which set the tone to call for innovation-driven development and breakthrough technologies for innovative pharmaceutical products and high-end medical devices.

In the same month, the Center for Drug Evaluation (CDE) of the National Medical Products Administration of China (NMPA) released a working procedure to accelerate the NDA review for innovative drugs. Following the *Technical Guidelines on Clinical Value-Oriented Trials for Oncology Drugs* in 2021, the CDE further published the following draft technical review guidelines to reiterate its review focused on the patient-centered and value-based drug development approach in 2022:

- Draft Technical Guidelines for Patient-centered Clinical Study Design;
- Draft Technical Guidelines for Patient-centered Clinical Study Conduction;
- Draft Technical Guidelines on Patient-centered Benefit-Risk Assessment for Clinical Trials; and
- Draft Technical Guidelines on Benefit-Risk Assessment for Innovation Drugs.

These drafts have been conceived as bearish news for me-too and fast follower products and bullish news for me-better, best-in-class and first-in-class products. Coupled with the chilled market in 2022 and the increasingly crowded pipelines, this regulatory evolution pushes pharmaceutical companies to the next level of innovation. Companies that can bring world-class products and play a bigger role in the international market may survive and stand out.

- ***Unprecedented Market Incentives for Orphan Drugs and Pediatric Drugs***

In May 2022, the Chinese government unveiled the long-awaited draft of the DAL Implementing Regulation, which among others and for the first time, grants orphan drugs up to seven years' market exclusivity and pediatric drugs up to a 12-month market exclusivity. Orphan drugs and pediatric drugs may enjoy such market exclusivity rights even when they are not patent-protected.

The increasingly crowded pipelines and competing environment make pharma companies swift in their intentions to niche markets so as to differentiate themselves. This unprecedented initiative proposed by the Chinese government under the DAL Implementing Regulation, if effective as it is, will greatly encourage the development of orphan drugs and pediatric drugs.

II

Wading into deep waters

The Chinese regulatory authority unveiled a considerable number of implementing rules in 2022 to deepen its reform in the life science and healthcare sector and foster the evolving regulatory framework formed during 2019 to 2021. The legislative development in 2022 addressed various emerging issues in the industry, including cell and gene therapy regulation, cross-region or cross-border regulation, e-commerce regulation, etc..

- **Evolving Regulatory Framework in the Pharma Sector**

- **Policies and Guidelines on Cell and Gene Therapy.** 2022 has been a fruitful year for cell and gene therapy regulation. NMPA has proposed and/or finalized several policies and guidelines in this area, including:
  - Drug GMP - New Appendix for Cell Therapy;
  - Quality Management Guidelines for Manufacturing of Cell Therapies;
  - Technical Guidelines on Pharmaceutical Research and Evaluation of Immune Cell Therapies;
  - Technical Guidelines on Pharmaceutical Research and Evaluation of In-vitro Gene Editing Systems;
  - Technical Guidelines on Pharmaceutical Research and Evaluation of In-vivo Gene Therapies; and
  - Technical Guidelines on Clinical Trial Design Concerning Gene Therapy for Treating Hemophilia.

  These guidelines and drafts show the Chinese government's intention to promote the development of cell and gene therapies as encouraged by "14th Five-Year Plan for Bio-economy Development" issued by the PRC National Development and Reform Commission in May 2022.

- **New Era for Online Sales of Medicines**. After years of discussions, in September 2022, NMPA finally released the *Measures for Oversight of the Sale of Pharmaceuticals Online* (药品网络销售监督管理办法), which became effective as of Dec. 1, 2022. There has been a long-standing debate on the restriction of online sales of prescription drugs. The *Measures for Oversight of the Sale of Pharmaceuticals Online* finally give a green light, upon the condition that prescription drugs are visible and accessible to consumers only after the presentation of prescription by consumers. This differs from the current practices that consumers may view prescription drugs freely and only need to present the prescription upon payment.

  This new requirement echoes the so-called "most stringent" telemedicine rule issued in 2022, which prohibits the provision of Rx drugs to consumers before prescription, and the prescriptions must be issued personally by physicians instead of generated automatically by AI tools.

- **Breakthrough Cross-Border Contract Manufacturing in Greater Bay Area.** In June 2022, the Chinese government, as a pilot program, allowed cross-border manufacturing arrangement in the Guangdong-Hong Kong-Macao Greater Bay Area. Drug or device market authorization holders (MAH) in Hong Kong and Macau were permitted to engage in Contract Manufacturing Organizations (CMOs) in nine cities in the Guangdong Greater Bay Area including Guangzhou, Shenzhen and Zhuhai to provide CMO services for eligible drugs and devices.

  It has been NMPA's long standing position that MAHs may not outsource manufacturing activities for finished drug and device products cross-border. This means, traditionally, drug and device

products marketed by domestic MAHs in China must be locally manufactured; and those marketed by foreign MAHs in China must be manufactured overseas. Offshore companies (including Hong Kong and Macao companies) may not hold market authorization ("MA") in China for drug and device products that are locally manufactured in China.

This Pilot program provides Hong Kong and Macao MAHs opportunities to leverage manufacturing facilities and manpower within the Greater Bay Area. Though currently, only a limited number of pharmaceutical and device products are eligible in this program, which may help Chinese regulator gain experience in cross-border regulation and may pave the way for future opening.

- **Cross-Region Working Mechanism Among Local MPAs**. The rolling out of MAH system for drug and device products in recent years have boosted CMO and CDMO businesses in China. Increasingly biotech and medtech companies have resorted to CMO and CDMO services, while often time MAHs and CMO/CDMO may not be located within the same province. This creates the increasing need for cross-region manufacturing arrangement and regulation.

  Typically, drug and device manufacturing activities are primarily regulated by local Medical Products Administrations (MPAs). That is to say, MAHs and CMO/CDMOs must be primarily regulated by their respective local MPAs in the province when they are located. When MAH engages a CMO/CDMO that is located in a different province within China, it may call for joint-regulation by MAH's supervising MPA and CMO/CDMO's supervising MPA.

  To address the increasing need for such joint-regulation, the NMPA encourages local MPAs to accelerate and strengthen their cross-region working mechanism, which enables them to timely exchange information and coordinate on joint actions on a regular basis. For example, local MPAs may take joint-actions for on-site inspections required either before or after market approval, exchange information and provide support on product quality sampling and AE monitoring, and take joint enforcement actions against violations. The NMPA expects that this cross-region joint working mechanism among local MPAs would create seamless supervision over MAH and its CMO/CDMOs cross-regions.

- **Strengthened Regulation for Vaccines.** Following the release of the "most stringent" VAL, the NMPA finalized one key VAL implementing rules: the *Provisions for the Administration of the Manufacturing and Distribution of Vaccines* (VMDR) (疫苗生产流通管理规定) in July 2022. Among others, VMDR
  - sets a high entry threshold by strictly controlling the number of vaccine manufacturers in China;
  - requires vaccine MAHs to have manufacturing capability, which means that vaccine companies only having R&D capabilities may not become a vaccine MAH;
  - only allows vaccine MAHs to outsource manufacturing activities in very limited circumstances (for example, on the government's demand for public needs or for multivalent

vaccines); and

- for imported vaccine products marketed by a foreign MAH in China, requiring foreign MAHs to only engage an adequate general local distributor for one imported product.

- **Evolving Regulatory Framework in the Medtech Sector**

- **New Rules on Device Manufacturing and Distribution.** Following the release of the MDR in 2021, the NMPA issued the two major MDR implementing rules in 2022: the *Measures for the Oversight of the Production of Medical Devices* (MDMR) (医疗器械生产监督管理办法) and the *Measures for Oversight of the Dealing in Medical Devices* (MDDR) (医疗器械经营监督管理办法). MDMR and MDDR reinforce the MAH system launched by MDR, and further streamline the device regulatory approval procedure. For example,

  - MDMR now allows CMOs to apply for a Device Manufacturing Permit in reliance on MAH's device registration license instead of holding a product registration license by itself. MDMR no longer restricts MAHs from only engaging one CMO at a time. Generally, MAHs have freedom to engage multiple CMOs for one product to the extent commercially desirable.

  - MDDR exempts certain low-risk class II medical devices from Device Distribution Notification with the supervising regulatory authority. Further, MDDR simplifies submission dossiers required for a Device Distribution Permit or a Device Distribution Notification, and shortens the application review timeline from 30 working days to 20 working days.

- **New Device GCP.** The NMPA released the new Medical Device GCP in March 2022, which became effective on May 1, 2022. In line with the spirit of the MDR, the new Medical Device GCP emphasized the regulatory obligations and responsibilities that should be assumed by a device sponsor. Medical Device GCP requires device sponsors to establish an appropriate quality management system that can appropriately cover the whole process of clinical trials sponsored by them. This echoes the responsibilities assumed by MAHs under the MDR throughout the entire device life cycle from development to commercialization.

- **Updated Risk-Based Regulatory Approach.** NMPA consolidated and strengthened its risk-based regulatory framework to regulate medtech companies in 2022. Specifically, NMPA grouped device companies into four grades based on their risk level as follows:

Risk Level	Grading	Companies and Products	Inspections
High Risk	Grade 4	▪ Devices on the priority monitoring list ▪ Companies having serious inadequate quality management	▪ Full-item inspection at least once per year

		system ▪ Companies with really poor credentials	
Medium to High	Grade 3	▪ Class III devices but not on the priority monitoring list ▪ Companies having inadequate quality management system ▪ Companies with poor credentials	▪ Full-item inspection at least twice per year ▪ Regular inspection at least once per year
Low to Mediam	Grade 2	▪ Class II devices but not on the priority monitoring list	▪ Regular inspection at least twice per year
Low Risk	Grade 1	▪ Class I devices	▪ 25% sampling inspection per year

▪ **Evolving PRC Cosmetics Regulatory Framework**

With the unveiling of CSAR in 2021, the cosmetic regulation entered into a new era. A series of implementing rules come into effect in 2022 to implement and supplement CSAR.

- **First Cosmetics Online Sales Rules.** E-commerce for cosmetic products has experienced exponential growth in recent years, which called for systematical regulation to guide online sales activities. In August 2022, the NMPA published the draft *Measures for the Regulation of Online Dealing of Cosmetics* (化妆品网络经营监督管理办法) to specifically regulate cosmetic-related e-commerce activities. In particular, the draft highlights cosmetic companies' obligation to fully, truthfully, accurately and clearly disclose information on the labels of cosmetic products, and obligates cosmetic companies to timely take corrective actions to control and mitigate risk.

- **First Cosmetics GMP.** NMPA released the *Cosmetic Good Manufacturing Practice* (Cosmetic GMP) (化妆品生产质量管理规范) in January 2022, which became effective on July 1, 2022. This was the first Cosmetic GMP in China that provides comprehensive guidance on the cosmetic manufacturing process. In particular, to address the prevailing contractual manufacturing in the cosmetic industry, the Cosmetic GMP has a chapter specifically for contract manufacturing, which clarifies the responsibilities between MAHs and CMOs in terms of product quality and safety. MAHs need to establish an appropriate quality management system with adequate personnel and facilities that can competently supervise CMO's activities and product releases.

- **First Cosmetic AE Rules.** The NMPA, for the first time, issued the *Measures for the Monitoring of Cosmetic Adverse Effects* (**Cosmetic AE Measures**) (化妆品不良反应监测管理办

法) in February 2022, which became effective on Oct. 1, 2022. This was a major legislative milestone for cosmetic adverse effects (AE) regulation.

It specifies and standardizes the procedures for AE monitoring, reporting, evaluation and investigation. It emphasizes cosmetic MAHs' primary responsibility for the quality and safety of their cosmetic products throughout the whole life cycle, and regulatory obligations to proactively monitor, collect, evaluate AEs and take timely risk control measures against AEs.

MAHs must investigate the root cause of AEs with consideration to the potential risk arising from raw materials, product formulation, manufacturing process, quality management, storage and transportation. The Cosmetic AE Measures urge cosmetic companies to take into account AE monitoring and evaluation as an importation part of their product quality and risk management system throughout the whole product life cycle.

III

Biosafety and HGR regulation: be prepared for routine inspections as the new normal

After the implementation of the *PRC Regulations for the Administration of Human Genetic Resources* (HGR Regulations) (中华人民共和国人类遗传资源管理条例) in 2019 and the *PRC Bio-Safety Law* (中华人民共和国生物安全法) in 2020, the PRC Ministry of Science and Technology (MOST) unveiled the long-expected *Draft Implementation Rules* for the HGR Regulations (Draft HGR Implementing Rules) (人类遗传资源管理条例实施细则) for public comments in March 2022.

Notably, half of the Draft HGR Implementing Rules introduces a multi-level, risk-based and systematical approach to supervising and inspecting activities involving Chinese human genetic resources (HGRs) and elaborating on the working procedures therein.

If the Draft HGR Implementing Rules become effective in its current form, it is expected that local counterparts of MOST will play an important role in HGR enforcement and will conduct multi-level overarching HGR inspections on companies located within their jurisdiction, including:

a. annual regular inspections;
b. prioritized inspections on high risk companies (such as companies being penalized for HGR violations in the past three years, companies that failed to take timely corrective actions and companies with poor credentials);
c. randomized sampling inspections; and
d. for-cause inspections.

Companies with good credential and performance would receive less HGR inspections. Life science companies should be prepared for frequent routine HGR inspections in the future, including taking corrective action to address history compliance issues (if any) and building up or improving HGR

policies and systems to ensure HGR compliance on an ongoing basis.

Other notable highlights of the Draft HGR Implementing Rules include:

1. It "narrowed" the scope of HGR information by emphasizing on human gene and genome data.

2. It clarifies the "actual control" test for a foreign party under the HGR Regulations, pursuant to which VIE would be deemed as a foreign party from an HGR regulation perspective, as VIE typically is an entity actually controlled by a foreign party through VIE contractual arrangement.

3. It clarifies the circumstances that would trigger security review for HGR information export, including exporting exome or genome sequencing information of over 500 subjects, and exporting HGR information of important genetic families or from specific regions.

4. More registrational trials would be eligible for a simplified notification procedure with MOST.

5. HGR collection approvals would no longer be required for registrational trials that do not involve HGRs from an important genetic family or specific regions.

6. Non-material changes of a clinical trial would enjoy a simplified approval or notification procedure.

In 2023, with the removal of pandemic control measures and re-opening up to the world, we expect the recovery of the market and closer cross-border collaborations. Chinese life science companies are thrilled to show their innovation and resilience to embrace a better 2023. With more legislative developments to enrich and foster the regulatory framework in the life science sector, life science companies learn to adapt to the new era of the innovation-driven and compliant regulatory environment.