China Launched Pilot Program on Segmented Production of Biological Products

On 21st October 2024, the National Medical Products Administration ("**NMPA**") issued the *Pilot Program for Segmented Production of Biological Products* ("**Pilot Program**") with immediate effect.

Segmented production of biological products is a manufacturing approach where the production process of biological drugs is divided into several stages, with each stage potentially being outsourced to different contract manufacturing organizations ("**CMOs**"). This approach involves breaking down the entire production cycle into specialized segments, such as upstream processing (cell culture and fermentation), downstream processing (purification and concentration), and final formulation and filling.

The Pilot Program is aimed at reducing costs and improving efficiency of pharmaceutical manufacturing for biological products.

1. Policy Background

Entrusted manufacturing or segmented manufacturing of biological products is not prohibited under the current Market Authorization Holder ("**MAH**") framework established by the *2019 PRC Drug Administration Law*. According to the *Comments Sought on the Implementing Regulations of the Drug Administration Law of the People's Republic of China* (issued on 9 May 2022 for public comments), segmented manufacturing is allowed for innovative drugs that have special needs for production process, facilities and equipment, and drugs with urgent clinical needs upon NMPA's approval.

According to the *Administrative Provisions on Vaccine Production and Distribution* (effective as of 8 July 2022), entrusted manufacturing of vaccines is allowed provided that special conditions are met and provided that the whole process is entrusted to one entity with one exception[1].

Before the issuing of Pilot Program, due to the lack of legal regulations or detailed guidelines, there has been little significant breakthrough in terms of segmented production of biological products. Consequently, in practice, it is difficult to obtain approval for biologics with segmented production process, especially for those international pharma firms with cross-border production practice.

2. Key Issues of the Pilot Program

a) Pilot Varieties

According to Article 2 (3) of the Pilot Program, in principle, the pilot varieties shall be innovative biological products, urgently needed biological products in clinical trial, or other biological products specified by the NMPA, including:

- multivalent and multicomponent vaccines;
- antibody-based biological products;
- antibody-drug conjugates ("**ADC**");
- glucagon-like peptide-1 ("**GLP-1**") analogs; and
- insulin-based biological products, etc.

For innovative biologics, segmented production can especially meet their needs for facilitating production process, shortening production cycle, and reducing investment costs for facilities. For example, producing ADC is particularly complex, involving steps for both chemical and biologics manufacturing. Involving CMOs to take on certain steps could reduce overall production costs and facilitating the whole production process.

The Centre for Drug Evaluation under NMPA issued the *Technical Requirements for the Pilot Registration Declaration for the Segmented Production of Antibody-Drug Conjugates* on 7 November 2024. We expect more details and requirements for other pilot varieties will be released.

b) Period and Covered Areas

The Pilot Program is set to run through to 31 December 2026. It applies to the following areas:

- the provincial-level administrative areas that have been assigned with the task to explore the segmented production of biological products; and
- the provincial-level administrative areas which has a biomedical industrial cluster, a real need for segmented production as well as strong regulatory capacity for biological products.

For the time being, it is still not clear which areas will be included in the Pilot Program. However, Beijing has already started the survey of needs of MAHs and research institutions[2]. In addition, Shanghai is also likely to be in the list because they have committed to introduce the segmented production policy earlier this year[3]. Shanghai further includes the provisions relating to segmented production into the *Shanghai Administrative Regulations on Drugs and Medical Devices* (Draft for public comments) issued on 29 November 2024. On 7 November 2024, the Ministry of Commerce issued *Several Measures to Support the Suzhou Industrial Park's Deepening of Comprehensive Pilot Projects for Opening-up and Innovation*, which allows Suzhou Industrial Park to select 1-2 enterprises to carry out pilot segmented production of biological products.

c) Requirements for Pilot Enterprises

According to Article 2 (2) of the Pilot Program, enterprises shall possess the ability of independent R&D, quality management, risk prevention and control, and proper compensatory capacity for the pilot varieties. NMPA clarified in a policy newsletter[4] that the pilot variety shall be the "originally developed products". This means those varieties under licensing deals or cooperative development might be excluded from the Pilot Program. However, this remains to be clarified in future regulations and policies.

According to Article 2 (2) of the Pilot Program, for CMOs, a comprehensive drug quality assurance system and at least three years of experience in commercial production of biologics are required. They shall jointly implement a unified quality management system with the MAHs.

Article 4 of the Pilot Program also emphasizes the obligations of MAHs and CMOs for product safety and quality, including:

- MAHs and CMOs must strictly adhere to the stipulations concerning entrusted manufacturing and primary responsibility of MAHs. A Pharmaceutical Good Manufacturing Practice ("**GMP**")

system encompassing the product full lifecycle, as well as relevant personnel shall be properly established or equipped.

- At least two technical personnel who are familiar with the manufacturing process and the Pharmaceutical GMP system should be dispatched to the CMOs for on-site instruction and supervision, so as to ensure that the quality management systems are aligned and effectively integrated. This is a stricter and more detailed requirement compared to the normal entrusted drug manufacturing model.

- In addition, MAHs shall establish management systems and procedures for liability compensation and have the compensatory capacity commensurate with the product risks, market scale, standards of compensation for personal injury and other factors.

On 1st November 2024, the Centre for Food and Drug Inspection of NMPA issued the *Guidelines for On-site Inspection of Segmented Production of Biological Products* ("**Guidelines**"). Segmented production will inevitably give rise to new risks in terms of quality and efficacy of drugs, for instance during the transportation of drugs between different manufacturers. It may also bring new challenges for MAHs, for instance in terms of specifying obligations and liabilities among different entities. The Guidelines have included requirements for these aspects.

d) Application

Applicants for drug registration (including domestic enterprises designated by overseas applicants to handle drug registration matters for imported drugs) ("**Registration Applicants**") and MAHs (including domestic enterprises designated by foreign MAHs to fulfill MAH's obligations) shall submit its application to the provincial medical product administration ("**PMPA**") by 31st December 2025. This means the Pilot Program also applies to imported drugs, and cross-border segmented production of biological products will be possible.

The PMPA shall carry out a preliminary selection of pilot enterprises and varieties and, on an "one product, one policy" basis, develop the provincial pilot program and supervision plan for the approval of the provincial government. Where the MAHs/Registration Applicants and CMOs are in different provinces, the pilot program and supervision plan shall be jointly developed by concerned PMPAs and shall be approved by the provincial government of the MAHs/Registration Applicants. NMPA shall have a final assessment and decision on the provincial pilot program, supervision plan, regulation capacity of PMPAs, as well as the pilot enterprises and pilot varieties.

If it is determined that the relevant meet the requirements of the Pilot Program, the Registration Applicant, MAH and entrusted CMO(s) shall apply for the Drug Manufacturing License or its modification. The Drug Manufacturing License of the Registration Applicant or MAH shall specify the production address of the stock solution as well as the preparation, while the Drug Manufacturing License of the entrusted manufacturer of the stock solution and/or preparation shall specify the production address of the stock solution and/or preparation respectively.

e) Post-market Supervision

To meet the new challenges of segmented production, according to the Pilot Program, PMPAs shall conduct annual comprehensive inspections and sampling inspections of pilot varieties, urge pilot enterprises to fully implement their primary responsibilities for product quality and safety. The pilot-related enterprises and varieties will be the key targets of supervision and PMPAs will conduct no less than one comprehensive GMP compliance inspection per year for pilot varieties. However, it remains to be seen how the cross-regional regulation will be coordinated and implemented.

3. Suggestions

The Pilot Program responds to the widespread call for segmented production. It brings benefits for the biological products production industry in terms of specialization of labor, improving production efficiency, ensuring the supply of important and scarce products, facilitating the early development and market launch of innovative drugs etc. In a cross-border context, segmented production creates

more options for international biological products enterprises. It enables such enterprises to allocate their resources more flexibly on a global scale. For those pharmaceutical enterprises who plan to engage in segmented production of biological products, upon approval by relevant authority, they need to pay more attention to the strict requirements in relation to segmented production to be all complied with, and the safety, efficacy, and quality of the biological products shall not be negatively affected due to such segmented production.

In case you have questions or for further information, please contact the authors of this newsletter:

Nicolas Zhu
Partner
Head of Lifesciences Sector Group
CMS, China

T + 86 21 6289 6363
E Nicolas.Zhu@cmslegal.cn

Laila Lu
Associate
CMS, China

T + 86 21 6289 6363
E Laila.Lu@cmslegal.cn

CMS Hasche Sigle Shanghai
Representative Office (Germany)
3108 Plaza 66, Tower 2
1266 Nanjing Road West
Shanghai 200040, China

CMS Cameron McKenna LLP Beijing
Representative Office (UK)
Room 1909, China Youth Plaza,
No. 19 Dongsanhuan North Road,
Chaoyang District
Beijing 100026, China

---

[1] An MAH may apply for entrusted production of vaccine varieties meeting one of the following circumstances:
1) the reserve requirements set forth by the industrial and information technology authority under the State Council cannot be met based on the MAH's existing production capacity;
2) the health administration department under the State Council proposes an urgent need for disease prevention and control and the demand cannot be met based on the MAH's existing production capacity; and
3) production of multivalent and multicomponent vaccines.

The scope of the entrusted production shall be the entire process of vaccine production. If it is necessary to entrust an entity to produce multi-component or multi-dose vaccines, the production stage of the solution or the preparation can be entrusted with the consent of the NMPA (Article 12 of the *Administrative Provisions on Vaccine Production and Distribution*).

[2] According to the *Notice of the Beijing Municipal Drug Administration on Organising a Survey of the Demand for Segmented Production of Biological Products* (北京市药品监督管理局关于组织开展生物制品分段生产需求调查的通知)

[3] According to the *Notice of the Shanghai Municipal Drug Administration on Issuing the Several Measures for Continuous Benchmarking Reform to Create a First-Class Business Environment in the Field of Drug Regulation* (上海市药品监督管理局关于印发《关于对标改革持续打造药品监管领域一流营商环境的若干措施》的通知)

[4] Source: https://www.nmpa.gov.cn/xxgk/zhcjd/zhcjdyp/20241022112538156.html