# New LDT Pilot Regulations Key Takeaways

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In recent years, China is continuously exploring the regulations of LDT (Laboratory Developed Tests, as defined below). With the introduction of a series of new regulations, many outstanding multinational and local companies have participated in the research of LDT. At this stage, general provisions can no longer meet the demand of the practice of LDT industry. Recently, Shenzhen, Guangzhou, Hangzhou, Beijing and Shanghai have successively introduced favorable policies to support the development of LDT. In early 2023, the National Medical Products Administration of PRC ("**NMPA**") and the National Health Commission of PRC ("**NHC**") jointly issued the *Notice of Carrying Out the Pilot Program of Development and Use of Medical Institution Developed In Vitro Diagnostic Reagents* ("**National LDT Pilot Regulations**"). In March, Shanghai MPA and Shanghai Health Commission jointly issued the *Implementation Plan for the Pilot Program of Development and Use of Medical Institution Developed In Vitro Diagnostic Reagents* ("**Shanghai LDT Pilot Regulations**"). The introduction of National LDT Pilot Regulations and Shanghai LDT Pilot Regulations marks the beginning of the implementation stage of China's regulation on the LDT industry, thereto making the regulatory methodology clearer and taking a significant step to a more comprehensive and mature regulatory system in the future. This article will introduce the key aspects of the National LDT Pilot Regulations and Shanghai LDT Pilot Regulations and make comparison on the commonalities and differences between the two regulations, for the purpose of providing reference for the industry.

Laboratory Developed Tests, or namely LDT, originates in the United States and is a product differentiated from commercialized in vitro diagnostic ("**IVD**") products with marketing approval. Some clinical laboratories choose to develop and use LDT to fill in the gaps of marketed IVD products in diagnosing certain diseases in the market. In 1988, the U.S. Congress passed the bill of Clinical Laboratory Improvement Amendments, allowing the clinical laboratories' development and use of LDT.

In China, the official definition of LDT is a testing product used exclusively within the laboratories, which shall not be sold to other laboratories or medical institutions, but the results of which can provide guidance for clinical diagnosis and treatment, according to the *Technical Guidelines for the Application of Personalized Medical Testing of Sequencing Technology (Trial)* issued by the National Health and Family

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Planning Commission of PRC (the predecessor of the NHC).

According to Article 10 of the original *Regulations for the Supervision and Administration of Medical Devices* issued in 2000, the medical institutions can develop medical devices according to their own clinical needs and use them in their own institutions with the guidance of licensed physicians. However, this article is deleted in the revised versions of such regulation in 2014 and 2017. To sum up, despite the LDT programs have been carried out by some medical institutions for a long period, its legal and regulatory basis is not solid.

This situation persisted until 2021, when the currently effective *Regulations for the Supervision and Administration of Medical Devices (Revised in 2021)* were stipulated. Article 53 points out that, regarding IVD reagents for which no product of the same variety has been authorized for marketing in China, a qualified medical institution may, according to its clinical needs, develop and produce them by itself and use them within its own institution under the guidance of licensed physicians, which provides an official legal basis for LDT industry at the level of administrative regulations and started a new phase of development and regulation in China's LDT industry. However, the provision is rather general, and issues such as the criteria of "no product of the same variety has been authorized for marketing in China", the scope of "qualified medical institution", the understanding of "under the guidance of licensed physicians" and the boundaries of terms "in-house developed and produced" and "within its own institution" remain unclear and have caused many controversies and confusion in the practice. Accordingly, the series of pilot regulations mentioned above provide regulatory direction and pathway for the industry. We will introduce some key aspects of National LDT Pilot Regulations and Shanghai LDT Pilot Regulations in the following paragraphs.

## Overview of pilot regulations and regulatory authorities

### I. Issuing authorities and hierarchy of regulations

National LDT Pilot Regulations are directly issued by two ministry-level departments, respectively the NMPA and NHC. Although the medical institutions listed in such regulations are all in Beijing, the scope of pilot program also covers Shanghai since both Shanghai MPA and Shanghai Health Commission also appear as the receiving parties of the regulation. Shanghai LDT Pilot Regulations are jointly issued by Shanghai MPA and Shanghai Health Commission and are the implementation plan effective within Shanghai based on National LDT Pilot Regulations.

### II. Division of responsibilities among regulatory authorities

National LDT Regulations have made clear the regulatory duties of competent authorities:

- The national competent authorities (NMPA and NHC) are responsible for the organization and management of the pilot program, and the provincial competent authorities are responsible for the supervision at their administrative regions.
- The regulation maintains the division of regulatory responsibilities between MPA and Health Commission at all levels. MPA is responsible for supervising products, including the filing of pilot

products and post-filing quality supervision. The Health Commission is responsible for supervising medical institutions, including supervision of the use of pilot products by pilot institutions.

Additionally, both National LDT Pilot Regulations and Shanghai LDT Pilot Regulations emphasize pilot medical institution's responsibilities in quality safety and clinical use safety of its own LDT products.

## III. Tasks and expected results of pilot program

The pilot program emphasizes on fulfilling urgent clinical needs and protect patients' rights, as well as fulfilling the responsibilities of medical institutions, while the purpose of pilot program in Beijing and Shanghai are to create and form reproducible administration process and specific requirements and lay the foundation of a nationwide regulation of LDT. However, the pilot program herein is carried out in a narrow scope since the pilot medical institutions only involve a small number of hospitals but no independent clinical laboratories (ICLs) in both National LDT Pilot Regulations and Shanghai LDT Pilot Regulations. Shanghai Health Commission once provided a general direction for LDT pilot program in the *Notice of Carrying Out the Pilot Program of High-quality Development of Shanghai Public Hospitals* issued in 2022 that where conditions permit, hospitals may carry out pilot program of LDT in accordance with relevant regulations, and dozens of hospitals were enumerated as pilot institutions in the attachment of the notice. However, the Shanghai LDT Pilot Regulations specify a small-scale implementation, listing only four hospitals as pilot institutions.

Although ICLs are not included in the scope of pilot institutions in the pilot program released this time, we understand that, according to Article 53 of the *Regulations for the Supervision and Administration of Medical Devices*, if an ICL obtains a "Medical Institution Practice License", it can still explore ways to carry out LDT service in compliance as a legitimate medical institution. We also expect more hospitals and ICLs to be included in the LDT pilot scope in the future to meet the actual needs of clinical testing.

In addition, it is worth mentioning that, given the increasing attention to the real-world data (RWD/RWE), both the National LDT Pilot Regulations and the Shanghai LDT Pilot Regulations mention the exploration of the path of applying the clinical data generated during LDT use to IVD registration, forming a clear conversion pathway from LDT to IVD. This shows that the innovative development model of LDT to IVD conversion has been explicitly supported and encouraged. I n practice, one of the main reasons for the development of LDT service is to offset for the long registration period of IVD products and to meet clinical needs as a beneficial supplement to traditional IVD products. As commercial products with market approval and large-scale production and use, IVD products are more reliable in safety and should remain the mainstream of the testing service industry. Therefore, encouraging the innovative development model of LDT to IVD conversion essentially utilizes LDT as a pre-transition for IVD, which is conducive to the rational and orderly development of related products.

Moreover, the Shanghai LDT Pilot Regulations also emphasize the priority of meeting the clinical needs of pilot medical institutions in the diagnosis and treatment of rare diseases and birth defect diagnosis, which clarifies the focus and encouragement direction of LDT industry.

## The scope of pilot hospitals and varieties

### I. Scope and requirements of pilot hospitals

The National LDT Pilot Regulations list a total of six hospitals as pilot medical institutions, including Peking Union Medical College Hospital, Beijing Hospital, China-Japan Friendship Hospital, Cancer Hospital Chinese Academy of Medical Sciences, Fuwai Hospital Chinese Academy of Medical Sciences, and Peking University First Hospital. The Shanghai LDT Pilot Regulations list a total of four hospitals, including Fudan University Shanghai Cancer Center, Shanghai Children's Medical Center affiliated to Shanghai Jiao Tong University School of Medicine, Zhongshan Hospital affiliated to Fudan University, and Ruijin Hospital affiliated to Shanghai Jiao Tong University School of Medicine.

Both the National LDT Pilot Regulations and the Shanghai LDT Pilot Regulations have requirements for the personnel and management system of the pilot hospitals. The key points can be summarized as follows:

**1. In terms of personnel:**

- The principal responsible person of the pilot hospital is fully responsible for the R&D, production, and use of in-house made reagents;
- Staffing with the project leader and quality leader for in-house made reagents. Both must be full-time staff of the institution, and the Shanghai LDT Pilot Regulations further clarify that the two positions must not be held by the same person;
- The project leader is responsible for the operation and management of the in-house made reagent project, including project establishment, research, verification, production, and use; and
- The quality leader is responsible for the establishment and operation of the quality management system for in-house made reagents, product release, and other quality management tasks.

**2. In terms of institutional management systems:**

- Set up necessary internal management institutions with the corresponding personnel, site, conditions, and capabilities;
- Establish a corresponding quality management system and internal review system;
- Set up corresponding academic review boards and ethics committees;
- Establish a management system to prevent the risk of in-house made reagent use, including adverse event monitoring system;
- Establish an in-house made reagent information management system to conduct full traceability and dynamic management of the R&D, production, and use of in-house made reagents throughout the process; and
- Have corresponding diagnostic and therapeutic subjects and practicing physicians.

## II. Academic review in addition to ethics review

It is worth noting that in the pilot program, in addition to requiring pilot medical institutions to establish ethics committees for ethics review in accordance with the relevant requirements of the *Measures for the Ethics Review of Biomedical Research Involving Human Subjects, Measures for the Ethics Review of Life Science and Medical* Research *Involving Human Subjects* and *Good Clinical Practice for Medical Device Trials*, it also requires medical institutions to establish an academic review system to review the necessity, scientific soundness, and safety of LDT projects. The Shanghai LDT Pilot Regulations specifically state that the personnel composition of the academic review institution should be adapted to the LDT R&D and production, and the academic committee should consist of personnel with deputy senior professional or above in various fields such as clinical, testing, and management. The content of the academic review to be conducted includes but is not limited to:

- Whether it is scientific and feasible, and the clinical application is irreplaceable;
- Whether it can ensure safety, effectiveness, and quality control;
- Whether it has the conditions and capabilities to carry out in-house made reagents;
- Whether risk prevention and control measures have been established for potential risks;
- Whether quality control measures have been established for the use process; and
- Whether the production process can meet the relevant requirements of the quality management system.

From the perspective of personnel composition, the academic review committee should be composed of personnel with professional and technical tittle of vice-senior level (副高级) or above in different specialties such as clinical, laboratory, and management, while the ethics committee, according to the provisions of the *Measures for Ethics Review of Life Sciences and Medical Research Involving Humans*, should be composed of experts in the fields of life sciences, medicine, bioethics, and law, and experts from outside the institution. Therefore, there are certain differences in personnel composition requirements between the two committees, and we understand that if a single committee is to undertake the responsibilities of both the academic review and the ethics committee, it must have the personnel who to meet the corresponding requirements of each.

## III. Scope of pilot varieties

According to Article 53 of the *Regulations for the Supervision and Administration of Medical Devices*, LDT products should be IVD reagents for which there are "no products of the same variety has been authorized for marketing in China". However, the regulations do not provide specific criteria and subject for determination. The National LDT Pilot Regulations and Shanghai LDT Pilot Regulations clarify the criteria and subject for determining whether there are "no products of the same variety has been authorized for marketing in China", stipulate that the scope of pilot varieties shall be regulated through guidance catalogs, and supplement quality management requirements for the products of pilot varieties.

- Criteria for Variety Determination: whether there are substantial differences in technical principles, intended uses, or fundamental improvements in clinical performance of the product, and whether the product exhibits significant differences or create new values in clinical diagnostic application;
- Authority for Determination: NMPA, in conjunction with the NHC, will organize expert discussions to make decisions;
- Guidance Catalog: pilot medical institutions shall submit materials for recommended pilot varieties through provincial MPA, and the NMPA, in conjunction with the NHC, will organize expert validation and form a pilot variety guidance catalog to regulate LDT pilot work;
- Supplementary Quality Requirements: the technical maturity and clinical significance of the relevant products of pilot varieties shall be clear, and there are clinical guidelines recommended by domestic or foreign clinical treatment guidelines or clinical research indicating clinical application conditions.

Additionally, compared to the National LDT Pilot Regulations, the Shanghai LDT Pilot Regulations provide further clarification on the requirements for submission materials for pilot varieties to MPA, making it highly practical.

## Requirements for the use of LDT products

The pilot policy stipulates that specific reagents developed and used by medical institutions shall be subject to filing administration and sorts out detailed regulatory rules with respect to R&D, production, and use. When using LDT products, pilot medical institutions are required to strictly adhere to these rules, while non-pilot medical institutions can also take note of the relevant regulatory requirements and implement them as appropriate.

### I. Filing administration of LDT products

In addition to pilot varieties regulated by guidance catalogs, the pilot policy further stipulates that medical institutions should apply for filing procedures to the provincial MPA before developing and using specific LDT products. The policy further specifies relevant regulatory requirements, including the requirement of filing materials, procedures, and the requirements and procedures for amending or canceling filings as needed.

As aforementioned, the filing of LDT products is primarily supervised by the provincial MPA, but the provincial Health Commission also serves as a crucial regulatory authority for LDT. According to the pilot policy, the provincial MPA is required to promptly submit filling information to the NMPA and notify the Health Commission of the same level. Furthermore, the Shanghai LDT Pilot Regulations stipulate that although pilot products shall be filed by the provincial MPA, the MPA shall collaborate with the same-level Health Commission to conduct assessments prior to filing. It's worth noting that the provincial MPA and the provincial Health Commission both retain important supervisory responsibilities during the post-filing inspections of pilot products. Both the National LDT Pilot Regulations and the Shanghai LDT Pilot Regulations specify the inspection contents, timing, and mutual notification requirements for the two regulatory authorities regarding post-filing inspections of LDT products within

their administrative regions.

**1. Inspection Items and timeline of post-filing inspections by MPA**

- Inspection Items: whether filing materials meets the regulatory requirements, whether the developed product is consistent with filing information, and whether develop and production process complies with GMP;
- Inspection Timeline: on-site inspection towards filed products within 3 months after filing, and at least one supervision inspection of the pilot medical institution at the 6th and 12th months, respectively, after the pilot program carried out (or after filing as stipulated in the Shanghai LDT Pilot Regulations).

**2. Inspection items and timeline of post-filing inspections by health commission**

- Inspection Content: whether the medical institution meets the requirements of the qualification conditions and whether the products are used in accordance with the regulatory requirements;
- Inspection Timeline: inspection of medical institutions at the 6th and 12th months, respectively, after the pilot program carried out (or after filing as stipulated in the Shanghai LDT Pilot Regulations).

## II. Production requirements for LDT product

According to the pilot policy, when medical institutions produce their own LDT products, they should comply with the requirements of the Good Manufacturing Practice (GMP) for medical devices, ensuring that the quality management system is effectively implemented and that the products are produced strictly in accordance with the filed technical requirements to ensure that the in-house made reagents meet such technical requirements. We understand that the requirements of the pilot policy are relatively strict, and in practice, medical institutions may find it difficult to comply with the GMP for medical devices. Therefore, it is highly likely that they will need to outsourced production.

The pilot policy innovatively provides for a system of outsourced production of LDT products. Article 53 of the *Regulations for the Supervision and Administration of Medical Devices* stipulates that LDT products shall be "in-house developed and produced" by medical institutions. On the basis of the aforementioned regulations, both the National and Shanghai LDT Pilot Policies have innovatively established that medical institutions, in addition to in-house made LDT products, may also commission qualified medical device manufacturers to produce them. Compared to the National LDT Pilot Regulations, the Shanghai LDT Pilot Regulations take a step further in exploring the outsourced production system. While the National policy stipulates that pilot hospitals shall develop and produce their own reagents, and only outsource the production if they lack the capacity to do so, the Shanghai policy clarifies that pilot hospitals only need to have the ability to develop reagents, and can freely commission qualified medical device manufacturers to produce LDT products. Regarding the commissioning of production, the following points should be noted:

**1. Qualification requirements for outsourced production companies**

- possess a Medical Device Manufacturing License, with the scope of production including Class II or Class III IVD reagents;
- possess relevant production experience of similar IVD reagents.

**2. Outsourced contract and quality agreement arrangements**

- medical institutions shall sign commissioning contracts and quality agreement with outsourced production companies to clearly define the rights and obligations of both parties with respect to the protection of quality and safety of in-house made reagents.

**3. Responsibilities and obligations of medical institutions**

- supervise the production process of the outsourced production companies;
- be responsible for ensuring the quality of reagents produced by the outsourced production companies.

**4. Responsibility and obligations of outsourcing production companies**

- produce the reagents in accordance with relevant laws and regulations, GMP for medical device, mandatory standards, product technical requirements, outsourced contracts and quality agreements;
- be responsible for the production of the reagents;
- be subject to supervision by the commissioning medical institution.

The pilot policy also specifies the release requirements for clinical-use LDT products, stating that medical institutions are responsible for releasing finished products and shall establish product release and use procedures, the criteria and conditions of which being made clear. LDT products can only be used in clinical setting after the authorized release personnel have been audited and confirmed in accordance with the requirements of the quality management system.

## III. Requirements for the use of LDT products

According to the National LDT Pilot Regulations, the specific use requirements of LDT products include under the guidance of licensed physicians, registering or filling supporting medical device in compliance, establishing sound patient rights protection, risk control and adverse event management systems, and fulfilling regular reporting obligations on product use to the provincial MPA. The Shanghai LDT Pilot Regulations are more comprehensive and strict than the National LDT Pilot Regulations, which supplement regulatory requirements and provides more detailed provisions. Specifically, the regulations supplement the requirement for medical institutions to recall products in the adverse events when necessary and establish record system for developing, producing, and using reagents, maintaining relevant documentation for a minimum of three years.

Notably, according to the Shanghai LDT Pilot Regulations, the scope of “its own institution” (i.e., the

medical institution producing respective reagents) does not include medical institution consortium or other medical institutions in the group. In-house made reagents should only be used within "its own institution" and clearly identified on the packaging label as such. Article 53 of the *Regulations for the Supervision and Administration of Medical Devices* stipulates that LDT products can only be used within "its own institution" without providing clear clarification on the term's meaning and scope, which has attracted widespread attention from the industry.

In the current LDT industry, different business models exist, such as cooperations between R&D entities and medical institutions within a medical consortium, medical institutions partnering with ICLs on LDT service, and medical institutions establishing in-house laboratories in collaboration with other enterprises to conduct LDT service. The compliance of these business models largely depends on regulatory understanding of the meaning and scope of "its own institution," which is significantly important for the development of LDT service. It's clear that the Shanghai LDT Pilot Regulations have quite stringent regulatory requirements, restricting the use of LDT products to within the medical institution itself. We understand that in the early stages of the pilot program, regulatory authorities may tend to adopt a more cautious and conservative regulatory methodology. As the regulatory system evolves and matures, corresponding regulations may become more flexible and adaptable, and we'll keep a close eye on it.

## Conclusion

Given the vigorous demand for LDT in clinical practice, China's exploration of LDT regulatory policies has entered a new stage in recent years. The pilot policies implemented in Beijing and Shanghai undoubtedly provide an important blueprint for the development of a mature LDT regulatory system and pave the way for future exploration. Although the current LDT pilot policies are rather cautious, we understand that it is in line with China's experience in regulating LDTs at this stage. These policies will help to explore and develop sound regulatory frameworks for LDT under controllable risks. We believe that with the accumulation of positive regulatory experience, future policies will become more flexible and open, to meet the demands from different regions and enterprises.

## *Important Announcement*

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