China's Regulatory Framework for Biological Products and the Latest Trend

Center for Drug Evaluation, National Medical Products Administration

Pharmaceutical Department of Biological Product

December 2022

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I. Laws, Regulations and Technical Evaluation Standard System

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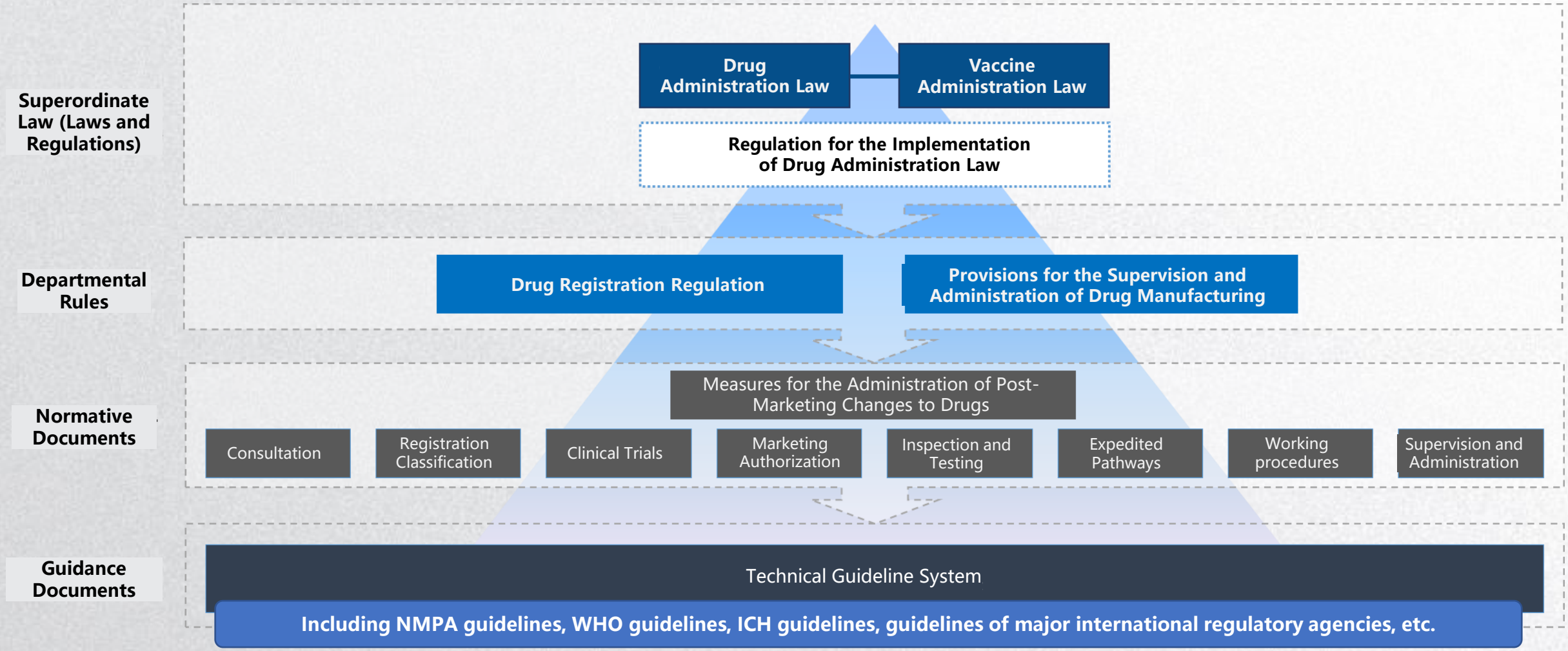
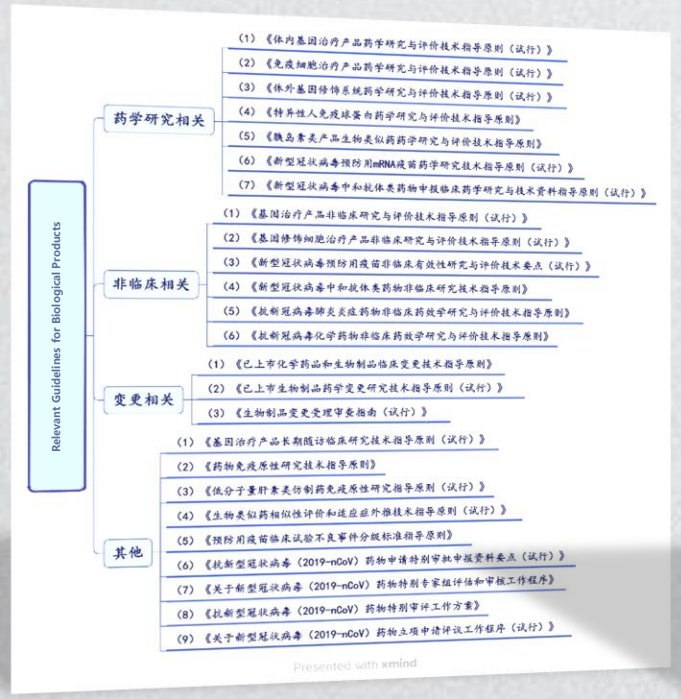
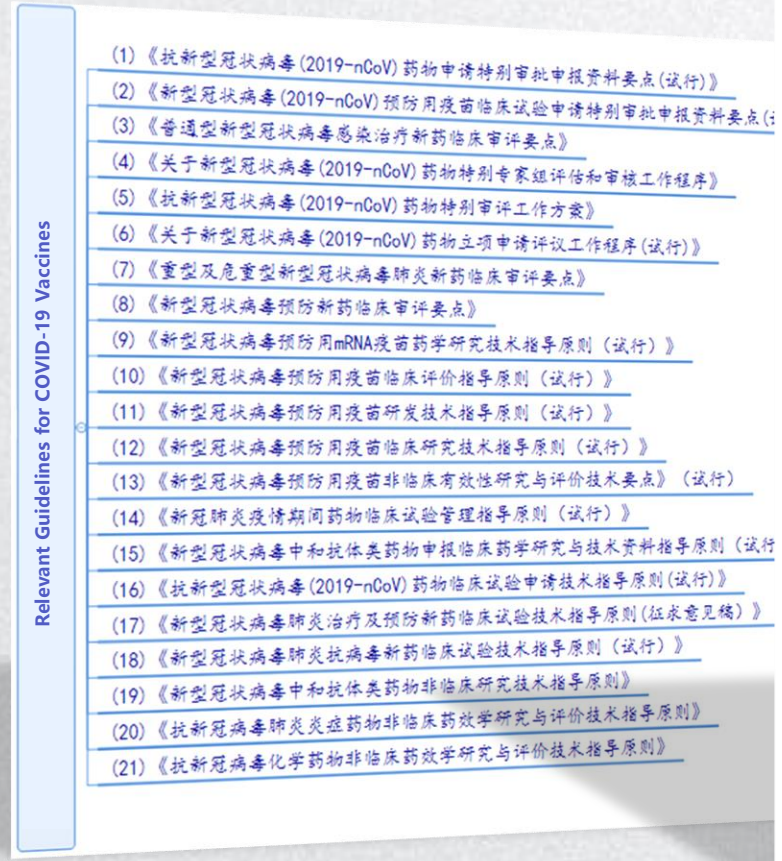
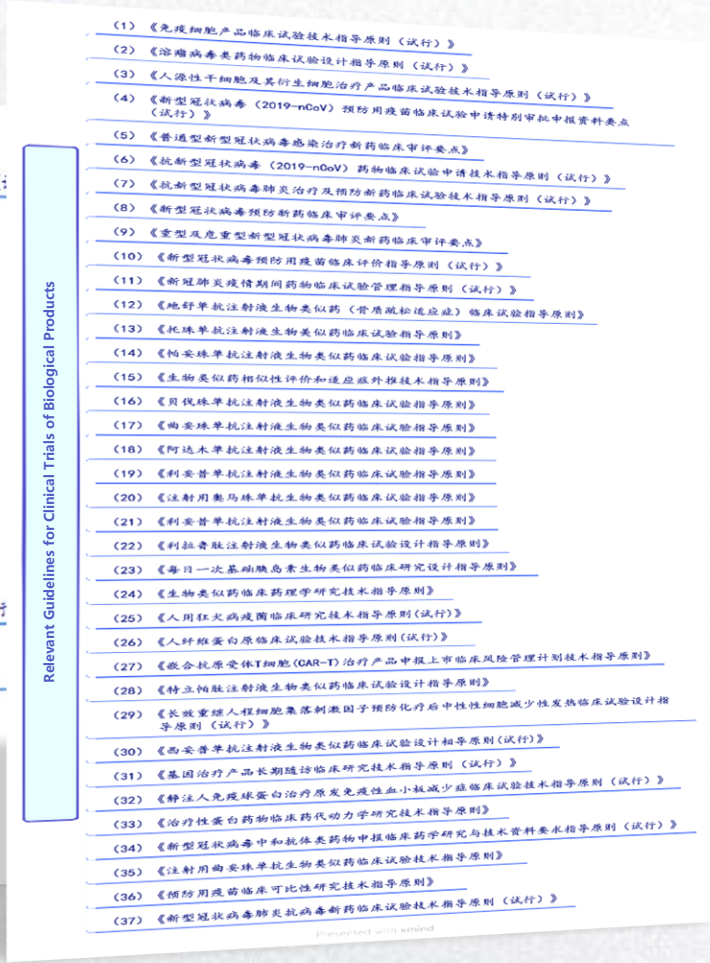


The pillars to support the legal and regulatory system for life cycle management of drugs have been basically put up.

I. Laws, Regulations and Technical Evaluation Standard System







protect and promote public health

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II. China's Administrative Regulatory System for Biological Products

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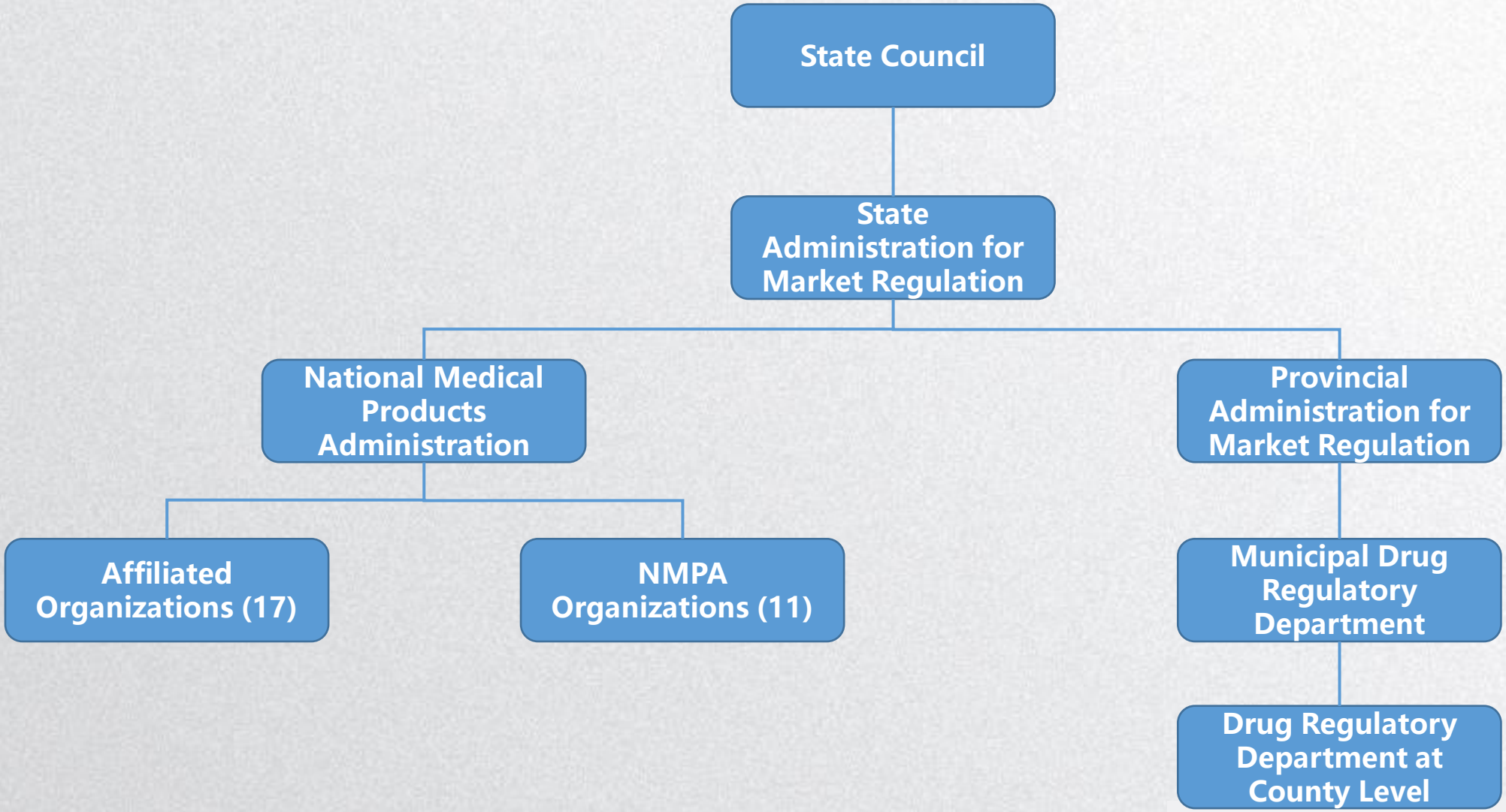

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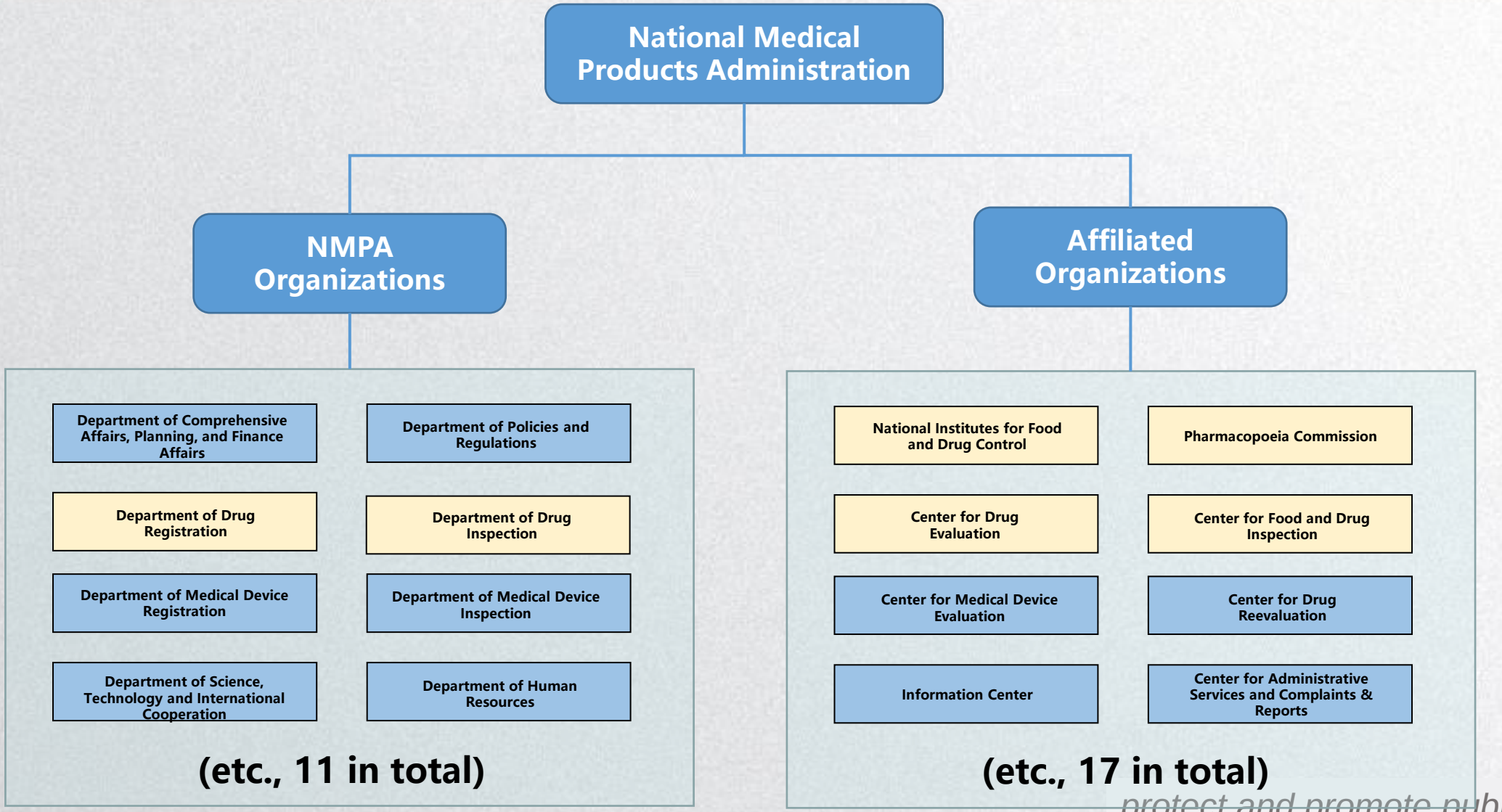

III. Improve the Management System for Review of Biological Products

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1. Establish a standard system for marketing of new drugs

- Refer to ICH E1 requirements
- Refer to the requirements of major international regulatory agencies
- Based on the actual situation of domestic R&D

2. Improve guidelines for drug R&D and evaluation

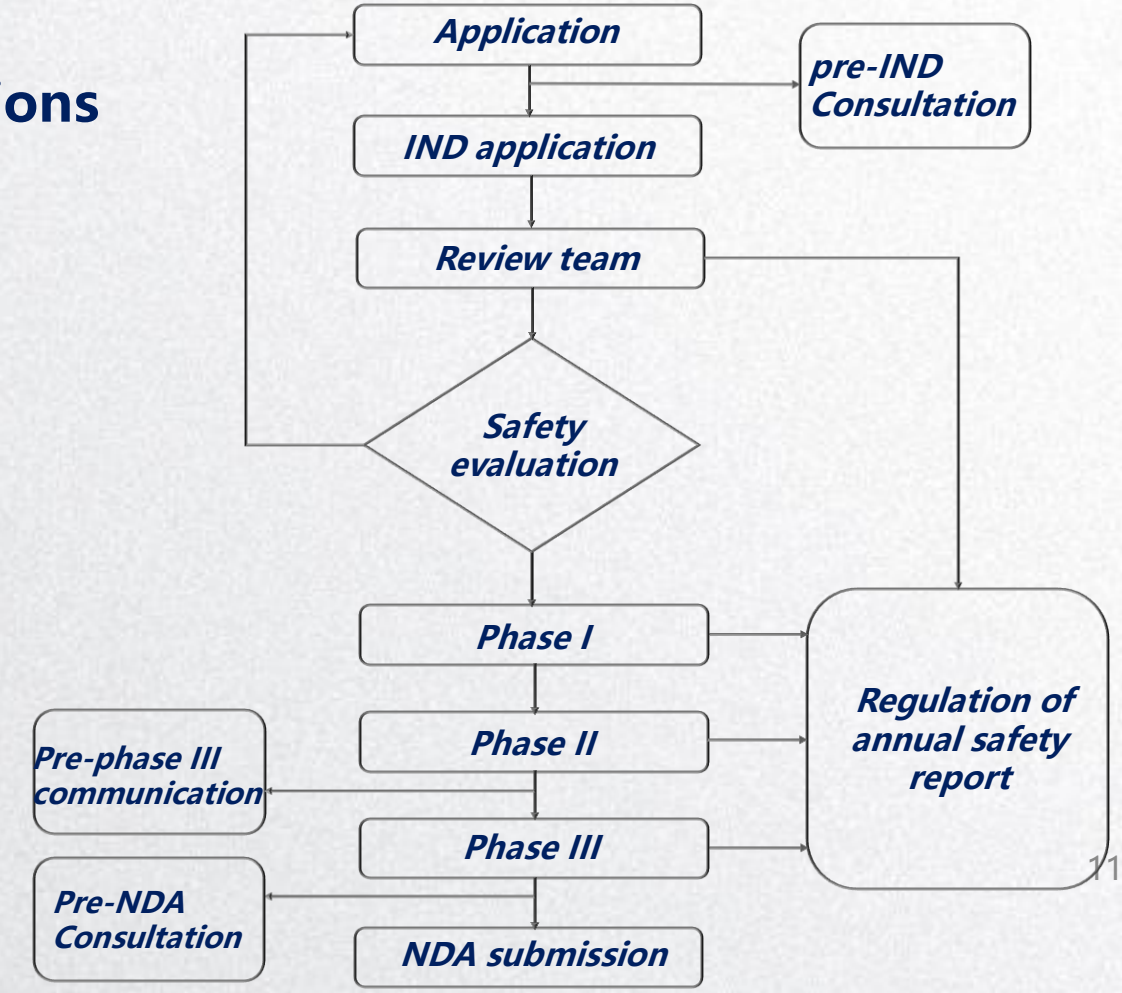
Relevant guidelines for biological products published in latest three years (as of July 30, 2022)

Classification of Guidelines	CMC	Nonclinical	Clinical	Changes	COVID-19	Others
Number of Guidelines	11	6	40	3	21	10

3. Optimize the review and approval procedures

III. Improve the Management System for Review of Biological Products

- **Optimize the management of applications for clinical trials (convergence)**
  - Higher requirements on application dossiers
  - Strengthen pre-IND/pre-NDA communication
  - Implied license system for clinical trial application
    - **60-day implied license**



III. Improve the Management System for Review of Biological Products

- **Focus on the design of procedures for unmet clinical needs (convergence)**

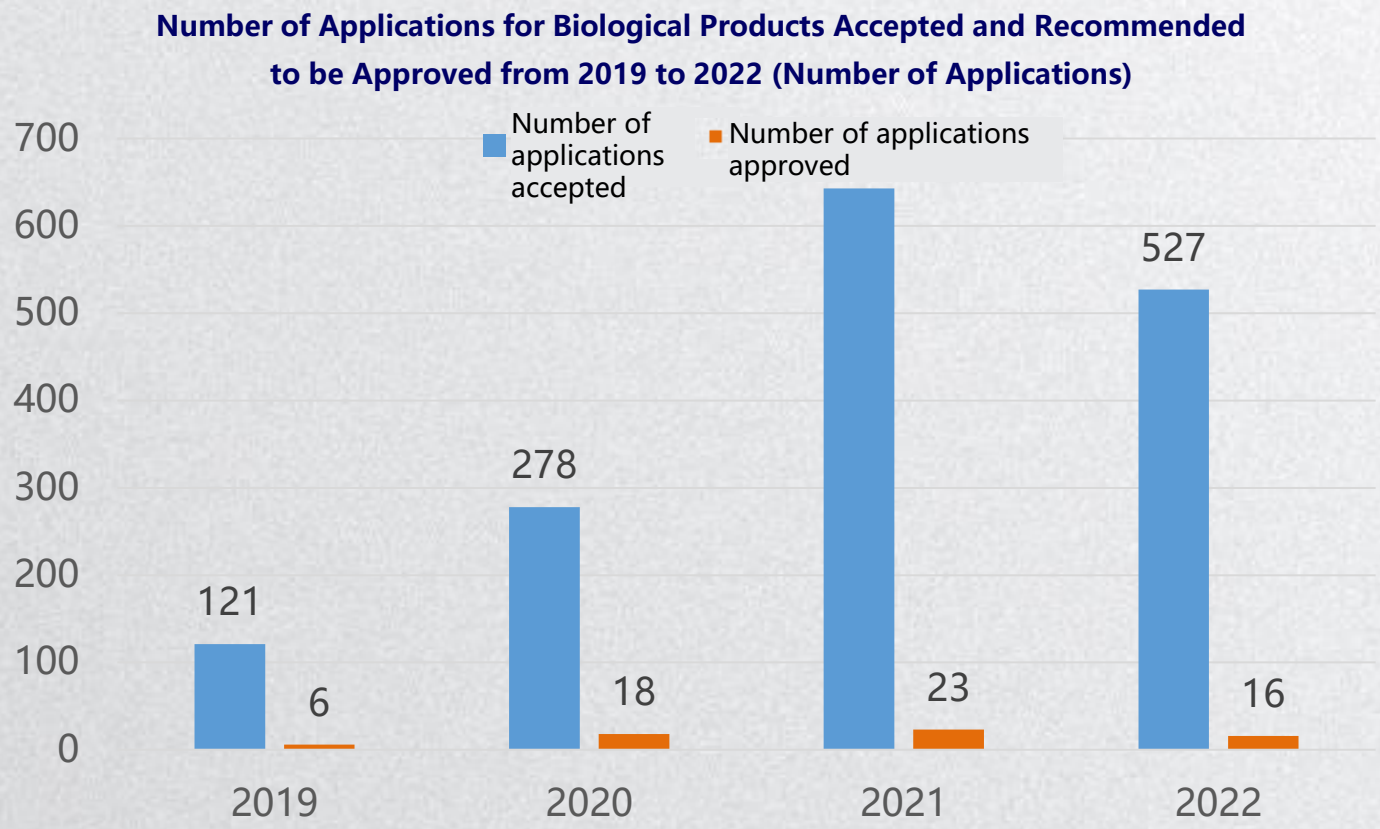
	Breakthrough Therapy Designation	Conditional Approval Designation	Priority Review Designation
Application Stage	**Clinical trial stage**	**Clinical trial stage**	**Marketing authorization application stage**
Scope of Application	Innovative drugs or modified new drugs that prevent and treat serious life-threatening diseases or diseases that significantly affect the quality of life, and for which there are no available effective prevention and treatment methods, or preliminary clinical evidence indicates that the drug can demonstrate notable clinical advantages	(1) Drugs for the treatment of diseases that are seriously life-threatening and for which there is no effective treatment, with available data from clinical trials that have confirmed the efficacy and predicted the clinical value (2) Drugs that are urgently needed in public health, with data from clinical trials that have demonstrated the efficacy and predicted the clinical value; (3) Vaccines that are urgently needed to deal with major public health emergencies or other vaccines that are determined to be urgently needed by the National Health Commission, and the benefits have been assessed to outweigh the risks	(I) Drugs in shortage and urgently needed in clinical settings, innovative drugs and modified new drugs for the prevention and treatment of major infectious diseases or rare diseases; (II) New products, dosage forms and strengths of pediatric drugs in line with the physiological characteristics of children; (III) Vaccines and innovative vaccines urgently needed for disease prevention and control; (IV) Drugs granted BTD; (V) Drugs seeking marketing approval are compliant with requirements for conditional approval; (VI) Other circumstances subject to priority review and approval specified by NMPA
Support of Policies	1.Communication and guidance 2. Rolling submission of dossiers 3. Priority review	1.Communication and guidance 2.Early approval 3. Priority review	1. Rolling submission of dossiers 2. Shorten the review timeline 3. Priority inspection and testing

III. Improve the Management System for Review of Biological Products

- **Optimize the review and approval process --- adjust the time of initiating inspection and testing**

III. Improve the Management System for Review of Biological Products

- **Acceptance and approval of application for biological products**



- The number of applications for biological products accepted from 2019 to 2021 showed an increasing trend, with an average annual growth rate of 26%; the number of applications accepted in 2021 was about twice that of 2019;

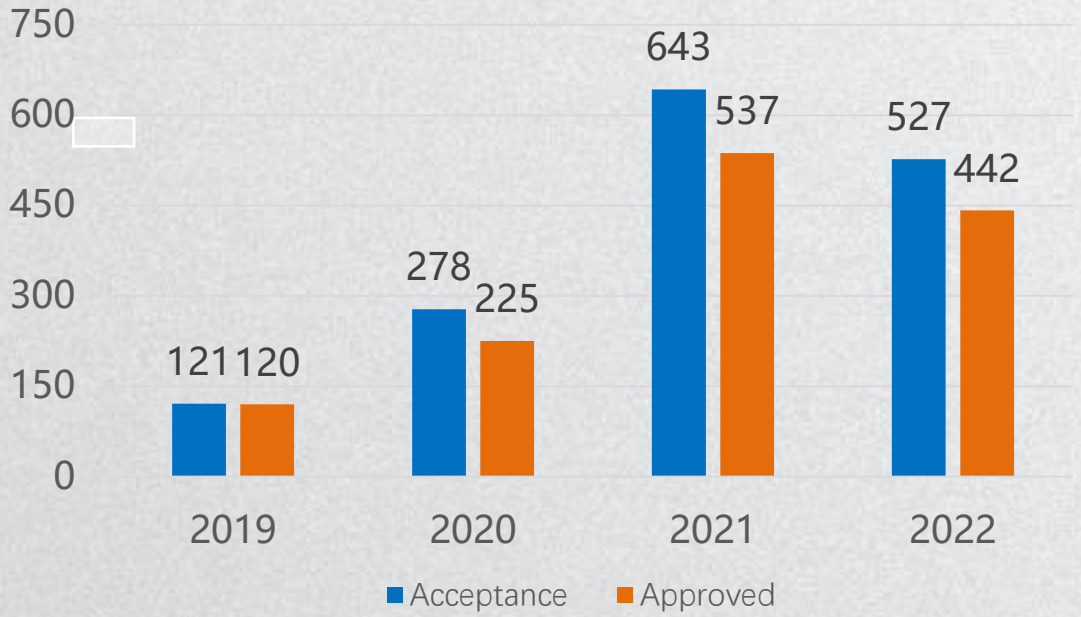
- The number of applications for biological products recommended to be approved from 2019 to 2021 showed an increasing trend, with an average annual growth rate of 29%; the number of applications recommended to be approved in 2021 was 2.16-fold that of 2019.

Note: The statistical data is as of October 2022. Including IND, NDA, supplemental application, and license renewal application of imported drugs

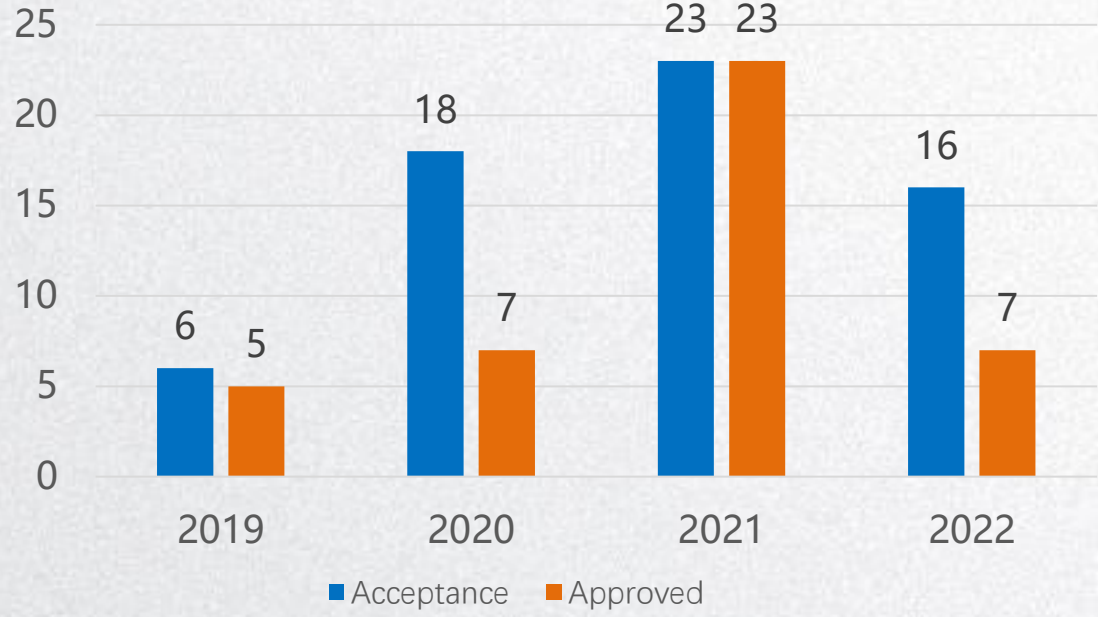
III. Improve the Management System for Review of Biological Products

- **Acceptance and approval of IND applications and NDAs for innovative biological products**

Number of IND Applications for Innovative Biological Products Accepted and Recommended to be Approved from 2019 to 2022 (Number of Applications)



Number of NDA Applications for Innovative Biological Products Accepted and Recommended to be Approved from 2019 to 2022 (Number of Applications)



Note 1: Innovative drugs: Drugs whose applications are accepted as per requirements for Class I biological products as prescribed in current *Drug Registration Regulation* (Decree No. 27 of the State Administration for Market Regulation) and the original *Drug Registration Regulation* (Decree No. 28 of the State Food and Drug Administration).

Note 2: The statistical data is as of October 2022.

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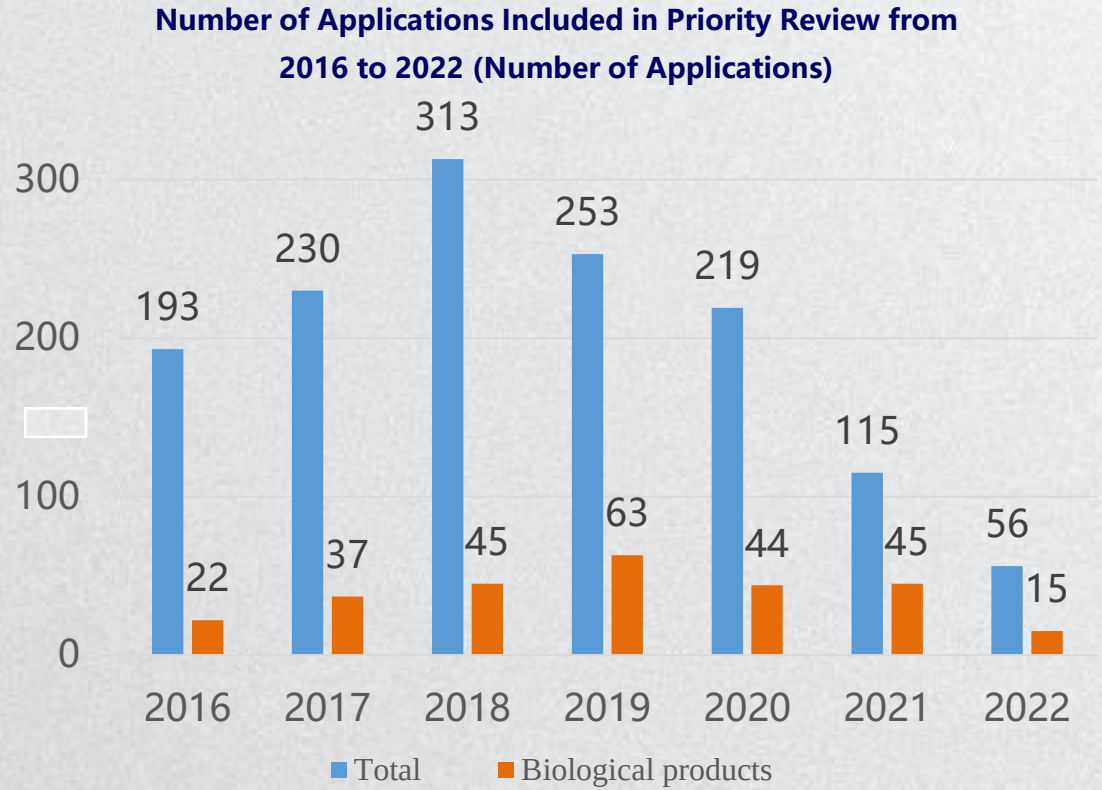

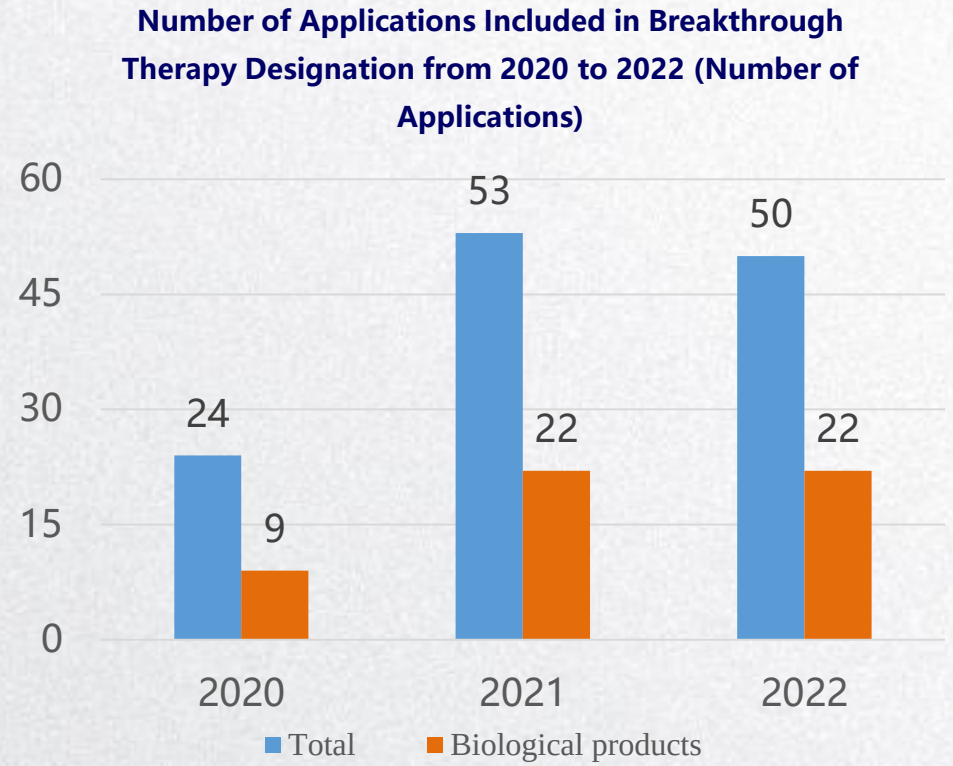

Note: The data of applications included in priority review is as of September 2022; the statistical data of applications included in breakthrough therapy designation is as of October 2022.

- **According to the *Working Procedures for Review and Approval of Applications for Conditional Approval of Drug Marketing (Interim)*, as of September 30, 2022, 68 products have been conditionally approved, including 25 biological products, involving 38 indications.**

IV. Technical Review of Vaccines in Emergency

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▪ Laws and Regulations

Vaccine Administration Law (issued in 2019)

For vaccines which are used to respond to major public health emergencies or other vaccines which are urgently needed as identified by the competent health department under the State Council, the drug regulatory department under the State Council may grant conditional approval on registration application if benefits of those vaccines outweigh risks based on evaluation.
When particularly major public health emergencies or other emergencies which seriously threaten public health occur, the competent health department under the State Council shall propose recommendations on the urgent use of vaccines based on the need of infectious disease prevention and control, and after evaluation organized by the drug regulatory department under the State Council, the permission for the urgent use within certain scope and period shall be granted.

Special Review and Approval Procedures for Drug Registration (SFDA Decree No.21)

According to the principle of unified leadership, early involvement, expeditiousness and efficiency, and scientific review and approval

Carry out special review and approval of drugs for handling public heath emergencies

Supportive Documents by CDE for Decree No.21

One program, two procedures, and one good practice

- CDE Working Program for Special Review and Approval of Anti-Covid 19 Medicines
- Working Procedure for Review of Application for Project on Anti-Covid 19 Medicines
- Working Procedure for Assessment and Review by the Ad Hoc Expert Group on Anti-Covid 19 Medicines
- NMPA Good Practice on Expert Meetings on Anti-Covid 19 Medicines

IV. Technical Review of Vaccines in Emergency

■ Establishment of a standard system for the development, review and approval of COVID-19 vaccines

Technical Guidelines and Requirements For Application Dossiers

More targeted technical guidelines (interim) and requirements for application submission in response to COVID-19 pandemic

- Technical Guidance for Research of Prophylactic Vaccines for SARS-CoV-2 (Interim)
- Technical Guidance for CMC Studies of Prophylactic mRNA Vaccines for SARS-CoV-2 (Interim)
- Technical Essentials for Non-Clinical Effectiveness Study and Evaluation of Prophylactic Vaccines for SARS-CoV-2 (Interim)
- Technical Guidance for Clinical Studies of Prophylactic Vaccines for SARS-CoV-2 (Interim)
- Guidance for Clinical Evaluation of Prophylactic Vaccines for SARS-CoV-2 (Interim)
- Requirements for the Dossiers for Clinical Trial Application of Prophylactic Vaccines for SARS-CoV-2 (Interim)
- Essentials for Technical Review of Prophylactic Vaccines for SARS-CoV-2 (for internal use)

In view of the rapid development of new biomedical technologies and the limited understanding of the biological characteristics of SARS-CoV-2, these technical guidelines will be continuously improved and updated in due course with the deepening of research and the accumulation of relevant research data.

IV. Technical Review of Vaccines in Emergency

▪ Initiatives for Accelerating Research and Development

Working Mechanisms	Description of Mechanisms
Technical standards first	• The technical guidelines guiding technical research and the preparation of application dossiers have been drafted. • The essentials for technical review of common changes have been drafted.
From "orderly" to "simultaneously"	• Simultaneously conduct testing, inspection and review • Simultaneously conduct MAH's release testing and registration testing (by the national lab (NIFDC)) to complete drug testing required by China's Regulations within 21 days
Continuous communication	• Establish a dedicated review team and a dedicated contact system • Enhance communication with applicants; CDE's involvement at early stage; regular follow-up; and feedback to applicants' questions within 24 hours
Rolling submission of dossiers	• Applicants can submit updated data and responses to supplementary questions about dossiers on a rolling basis, and timely feedback can be given on dossiers submitted through rolling submissions to achieve "end of review at the end of research and development" • Some study data may be submitted after on-site inspection/testing
Accelerated clinical trials	• Changes in clinical trial modes and design: seamless design, etc. • Clinical interim analysis is supportive of conditional approval for marketing
Regulatory flexibility and post-marketing requirements based on risk assessment	• Post-marketing risk management plan and continued monitoring, timely update of IPC, stability study data, etc. • Risk management and control of post-marketing changes
Formation of the ad hoc expert group	• Form an ad hoc expert group composed of academicians and experts in the fields of CMC, pharmacology and toxicology, and clinical sciences to provide solid technical support for review and approval in emergency

IV. Technical Review of Vaccines in Emergency

- **Early Stage CMC Requirements and Stage Appropriated Considerations in Emergency**

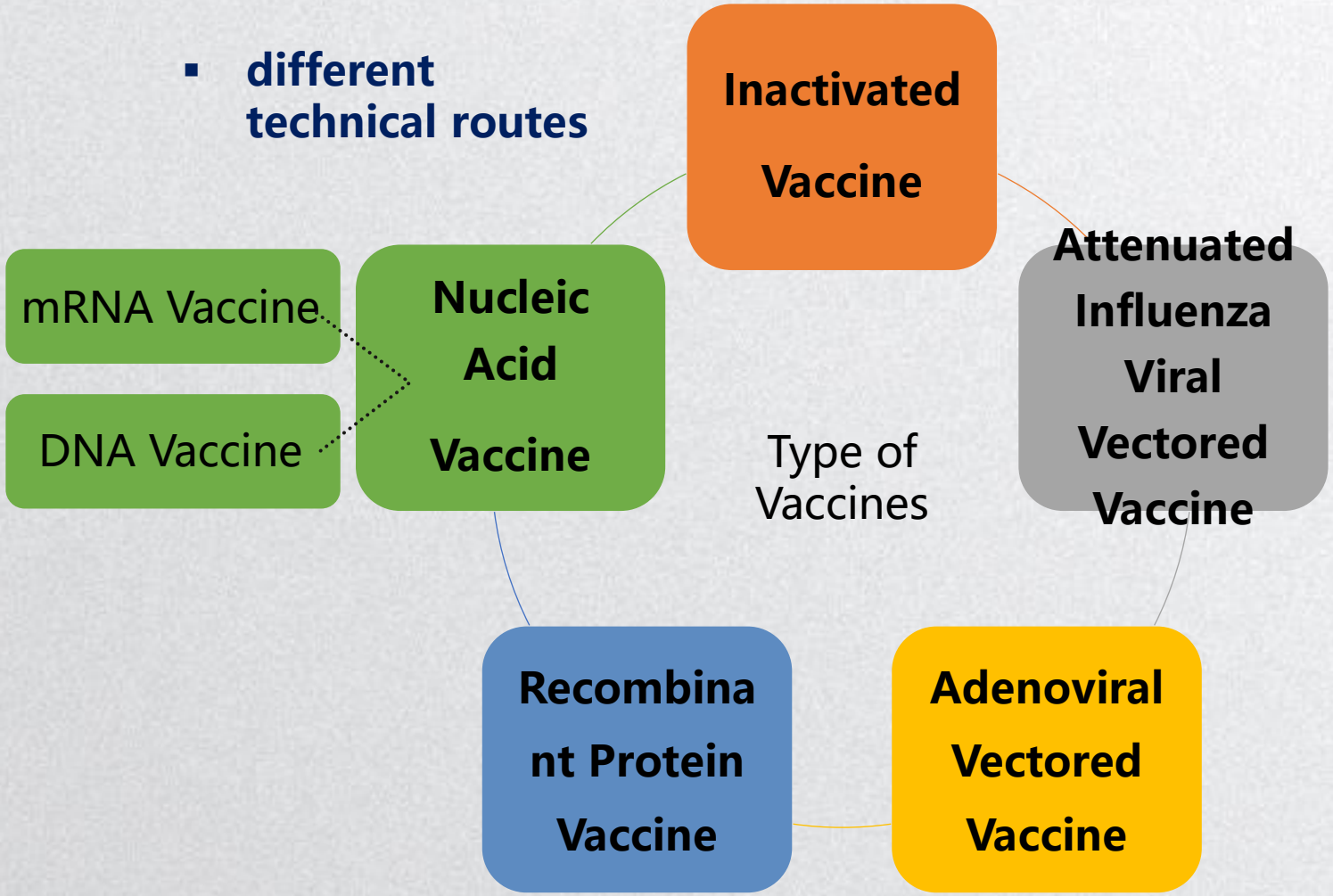
  - Staged, progressive considerations
  - Overall coordination
  - Good identification at R&D stage
  - Advance comparability study design and sample retention

  - Seed banks: primary seed banks may be used for clinical trial sample preparation; consider the use of accelerated testing methods
  - Manufacturing process: platform-based process development; it is recommended to study as many process control parameters as possible to accumulate product knowledge and process knowledge, and to lay a foundation for possible issues in the scale-up and their comparability studies; the reduction of control parameters would not be considered until adequate accumulation and validation work is completed.
  - Quality characteristics study: staged submission
  - Specifications: focus on the comprehensiveness of testing items; progressive confirmation of standard limits

IV. Technical Review of Vaccines in Emergency

- **Technical Challenges to CMC Review**

- **different technical routes**



- **Others:**
  - Use of Novel Adjuvants
  - Development of Novel Viral Vectors
  - Application of Novel Drug Delivery System
  - Use of Novel Drug Delivery Devices

Conclusion

- Guided by unmet clinical needs
- Based on China's biopharmaceutical R&D ecology
- Regulatory convergence and harmonization of standards
- Establish a standard system for new drug marketing
- Challenges and breakthroughs arising from the emergency

CDE

Thanks For Your Attention !

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