# Drug Regulation

## Overview of Regulatory Trends in Biological Products

Jan 2018

Washington

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# Main Features of Biological Products and the Corresponding Regulations

# Main Features of Biological Products (1)

- The starting materials are bioactive substances, and some raw materials have limited availability (such as bacteria, virus, cells, plasma, etc.);
- The whole manufacturing processes of biological products are biological processes and strict aseptic operations are required;
- Some biological products are manufactured with virus  or growing bacteria requiring strict biosecurity system;
- Most of biological products are large molecular proteins or peptides, with complex molecular structures and lower stability. They are easier to be deactivated, susceptible for microbial contamination and enzymatic destruction, and unable to be processed by common methods (e.g. heat sterilization);
- Bioanalysis methods, used for product quality control, usually take a longer time, and contain complicated procedures with variability;

# Main Features of Biological Products (2)

- Higher "stability" is required for the raw materials, intermediates, finished products during transportation, storage and even use under "cold chain" system; quality control is implemented by process monitoring of the whole manufacturing processes, and requires a strict and comprehensive quality management system (QMS);

- With specific mechanisms and functions, biological products are often in connection with body's immune function, besides of the specialty of starting, complication of manufacturing processes, strictness of quality control, and variousness of using;

- Special political significance and public importance: Preventive biological products are different from other medicines as they target healthy people, so special considerations on safety and efficacy need to be taken. Special sources of blood products need special supervision of source plasma, etc.. Growth of antibody products and emergence of cell therapy products, security of clinical blood using by diagnostic reagents for blood screening…

# Stress and challenges in biological products from different perspectives

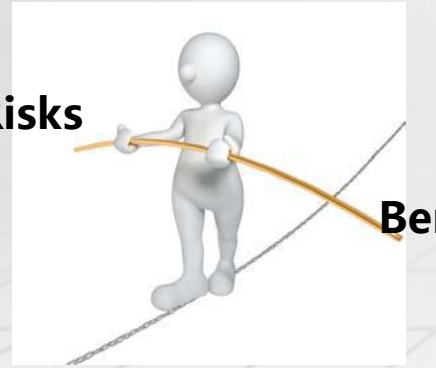
- Benefit of product launch
- Needs of R&D innovation
- Upgrade of process
- Ensuring capacity & yield
- Post-launch continuity mgt

**Enterprises**

- Developing the economy
  Fostering strategical emerging industry, encouraging development of biological medicine
- Ensuring people's well-being, maintaining stability
  Ensuring drug safety for the people
- Public health emergencies, Protection of national biosecurity

**Gov**

**Drug Registration**




**The People**

- Safety
- Accessibility
- Affordability
- Risk controllability, efficacy expectability

**Intl Demands**

- Harmonize and agree to differ in terms of regulatory
- Along with R&D and technique development
- Increase ability of evaluation continuously
- Regulatory information sharing
- Participate in international competition

# Special Regulations on Biological Products

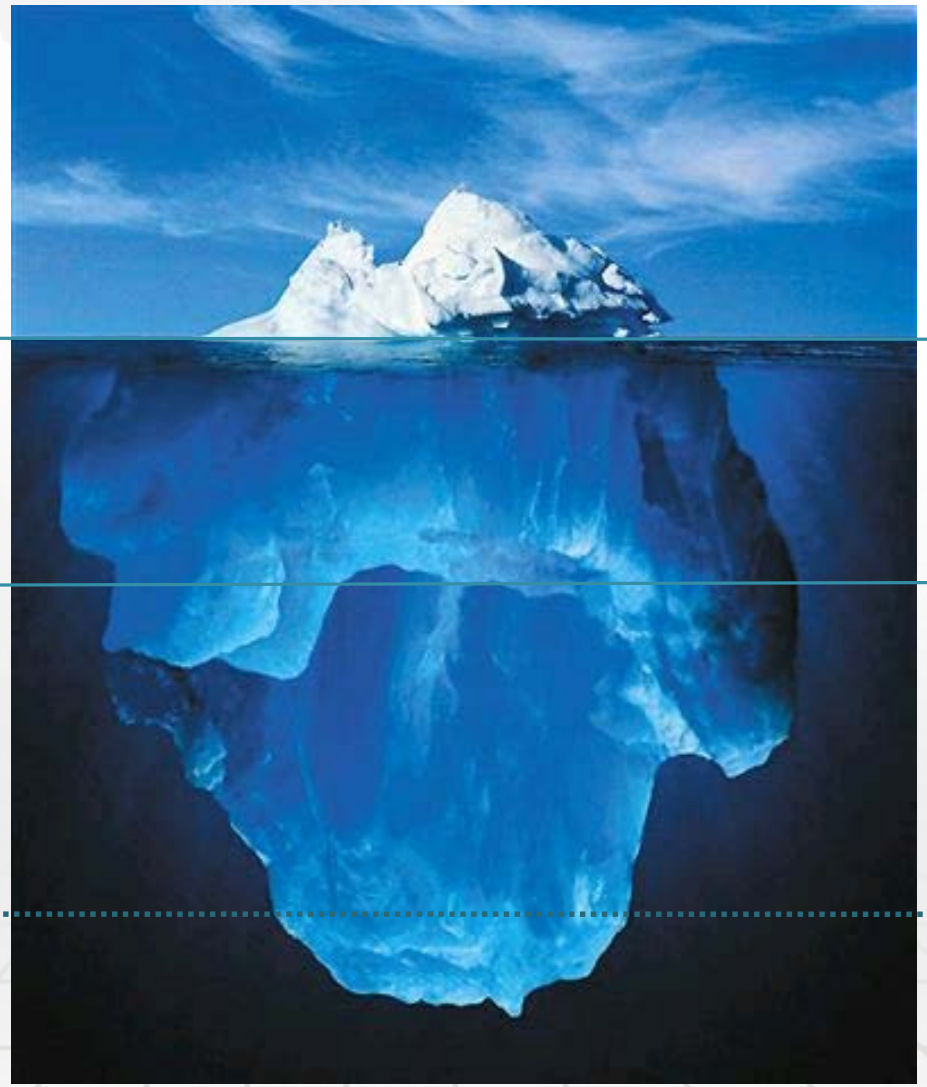
- Biological products belong to drugs, the drug regulations generally apply to them
- Biological products have special properties and different supervision approaches on registration, manufacturing, distribution, etc.
  - Different requirements on Clinical Trial Applications, New Drug Applications
  - Appointed quality control and inspection agencies
  - Current categorization: preventive biological products, therapeutic biological products and blood screening in vitro diagnostics. No categories for API and generics
  - Other focuses besides quality parameters: the ability of continuous production, batch-to-batch consistency, production stability, requirement for changing raw materials and excipients, distribution and transportation, post-marketing surveillance, etc.
  - Appendix on Biological Products, Blood Products in "Good Manufacturing Practice"
  - Some considerations on principle of exceptions …

Biological product industry is on its good day growing rapidly, appears significant political, economical and social values, requirements on tech, process, quality control, capacity and management, etc., are daily updated, its development relies on the overall strength

Take for example vaccines, the integrated national regulatory agencies are assessed in terms of the seven functions: regulatory system, marketing & manufacturing authorization, post-marketing surveillance and adverse reaction monitoring,  regulatory inspections, clinical trials, lot release, and laboratory management. In March 2011, it was the first time that the former SFDA passed WHO's assessment on National Regulatory Authority. With the growth of biological product industry including vaccines, WHO increases the requirements on national regulatory authority, and further strengthens the quantified indicators on the indispensable abilities of qualified regulatory system.  In October 2011, WHO introduced the concept of "Maturity Levels" to regulatory capacity of oversight for vaccines, and further developed the concept and applied to the assessment of regulatory capability of oversight for vaccines. In April 2014, CFDA was re-accessed by WHO and passed the re-assessment in July 2014.

World Health Organization

Release Tests
(Specifications)



Extended
Characterization
(Process & Product)

Process Control

- Procedures
- Materials
- In-process testing
- In-process monitoring
- Validation

Unknown
Learned over time-
update control strategy

*Consistency*

*Equivalence*

*Comparability*

Finished-Product management

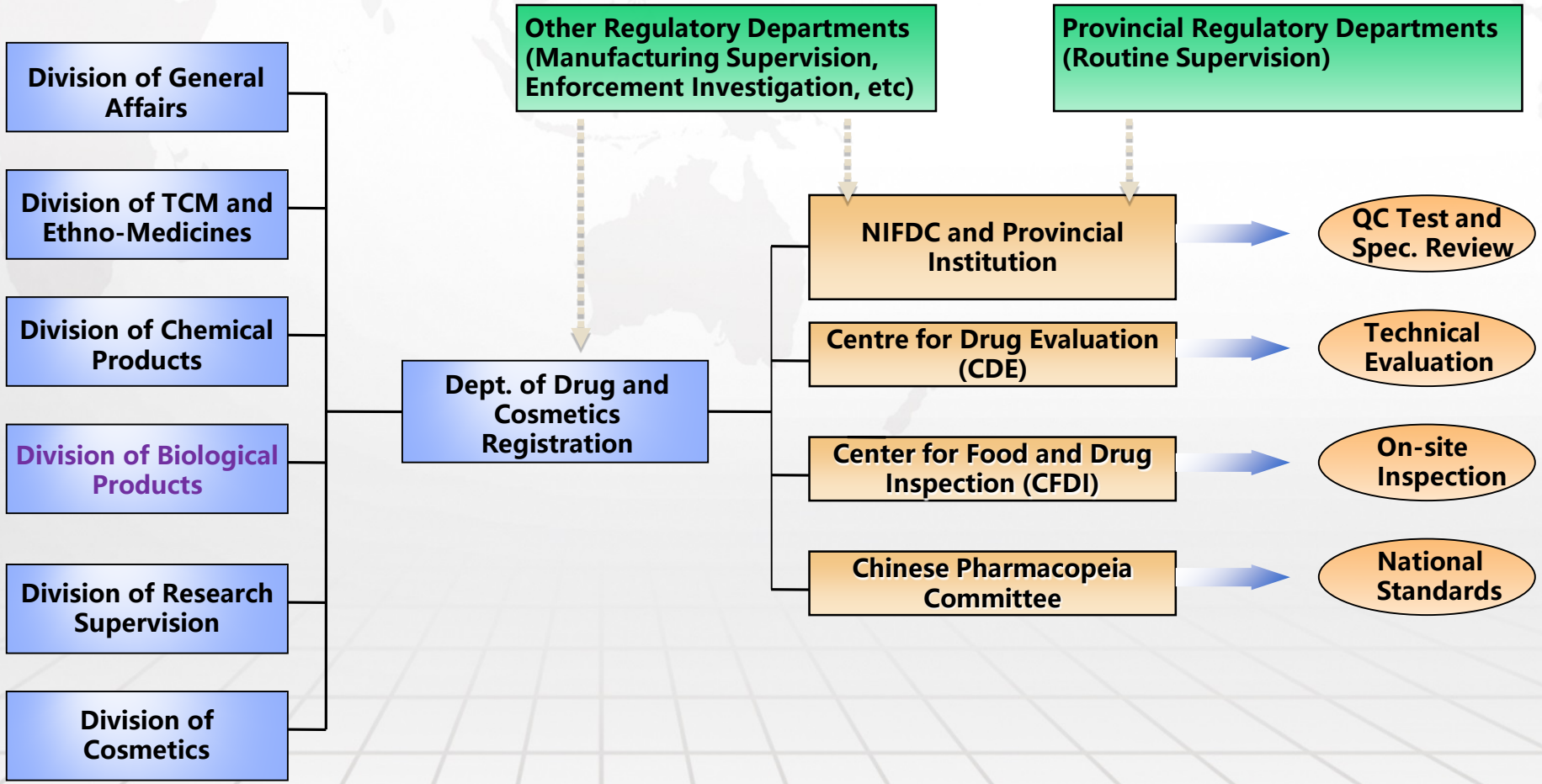
In-Process Controls

integrated supervision chain:
Including lot release

**Who is the steersman – the applicants are actually the Key person for quality of products**

# Progress in Reform of Review & Approval Mechanism

# Main Organizations and Technical Supportive Units for Registration Management



# Evolution of Biological Product Registration Regulations

## Initial Stage

➢Some Provisions on Drug Administration (1963, Ministry of Health, Ministry of Chemical Industry, Ministry of Commerce)

➢Interim Provisions on Administration of New Drugs (1965, Ministry of Health, Ministry of Chemical Industry)

➢Drug Administration Regulations (Trial Implementation) (1978, the State Council)

➢Provisions for New Drug Administration (1979, Ministry of Health)

➢……

## Development Stage

➢Drug Administration Law of People's Republic of China （1985, NPC legislation）

➢Provisions on New Drug Review and Approval (1985, Ministry of Health)

➢Provisions on New Biological Product Review and Approval (1985, Ministry of Health)

➢Measures for Implementation of Drug Administration Law of People's Republic of China (1989, Ministry of Health)

➢Administrative Punishment Provisions for Drug Administration (Interim) (1992, Ministry of Health)

➢Regulation of Biological Product Administration (1993, Ministry of Health)

➢ ……

## Improvement Stage

➢Provisions on New Drug Review and Approval, Provisions on New Biological Product Review and Approval, Provisions on Import Drug Administration, Provisions on Protection and Technical Transfer of New Drugs (1999, SFDA)

➢Drug Administration Law of People's Republic of China (2001, NPC legislation)

➢Regulation for Implementation of Drug Administration Law of People's Republic of China (2002, the State Council)

➢Drug Registration Regulation(2002; 2005; 2007, SFDA) Biological products were categorized as drugs under the unified management as for traditional medicines, chemical drugs

➢ Drug Label and Package Insert Management Regulation (2006, SFDA)

➢ Regulation for Lot Release of Biological Products（2004，SFDA）

➢……

## Reform Stage

➢State Council released Opinions on Reforming the Evaluation and Approval System for Drugs and Medical Devices in Aug 2015, initiating the reform

➢Revising on Drug Administration Law, Drug Registration Regulation and Regulation for Lot Release of Biological Products was conducted in parallel

➢Updates and changes on institution, system, procedure and operation

➢Tremendous strengthening of various supervision measures:
Inspections to clinical trials, re-evaluations and process inspections to marketed products

➢ ……

# **Reform of Drug Review and Approval** – Policy setting

**State Council released *Opinions on Reforming the Evaluation and Approval System for Drugs and Medical Devices* in Aug 2015, initiating the reform. The core is to improve drug quality, to realize the safety, efficacy and quality controllability of marketed drugs through reforming, so the international advanced level can be achieved and the public medical needs can be met.**

**No. 44**

国务院文件

国发〔2015〕44号

国务院关于改革药品医疗器械
审评审批制度的意见

各省、自治区、直辖市人民政府，国务院各部委、各直属机构：

近年来，我国医药产业快速发展，药品医疗器械质量和标准不断提高，较好地满足了公众用药需要。与此同时，药品医疗器械审评审批中存在的问题也日益突出，注册申请资料质量不高，审评过程中需要多次补充完善，严重影响审评审批效率；仿制药重复建设、重复申请，市场恶性竞争，部分仿制药质量与国际先进水平存在较大差距；临床急需新药的上市审批时间过长，药品研发机构和科研人员不能申请药品注册，影响药品创新的积极性。为此，现就改革药品医疗器械审评审批制度提出以下意见：

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**No. 219**

中华人民共和国国务院

国函〔2015〕219号

国务院关于同意建立药品医疗器械
审评审批制度改革部际联席会议制度的批复

食品药品监管总局：

你局《关于建立药品医疗器械审评审批制度改革部际联席会议制度的请示》（食药监〔2015〕262号）收悉。现批复如下：

同意建立药品医疗器械审评审批制度改革部际联席会议制度。联席会议不刻制公章，不正式行文，请按照国务院有关文件精神认真组织开展工作。

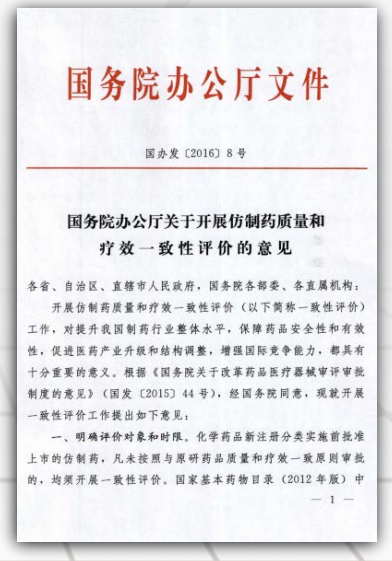
附件：药品医疗器械审评审批制度改革部际联席会议制度

中华人民共和国国务院

2015年12月17日

（此件公开发布）

**No. 8**



国务院办公厅文件

国办发〔2016〕8号

国务院办公厅关于开展仿制药质量和
疗效一致性评价的意见

各省、自治区、直辖市人民政府，国务院各部委、各直属机构：

开展仿制药质量和疗效一致性评价（以下简称一致性评价）工作，对提升我国制药行业整体水平，保障药品安全性和有效性，促进医药产业升级和结构调整，增强国际竞争能力，都具有十分重要的意义。根据《国务院关于改革药品医疗器械审评审批制度的意见》（国发〔2015〕44号），经国务院同意，现就开展一致性评价工作提出如下意见：

一、明确评价对象和时限。化学药品新注册分类实施前批准上市的仿制药，凡未按照与原研药品质量和疗效一致原则审批的，均须开展一致性评价。国家基本药物目录（2012年版）中

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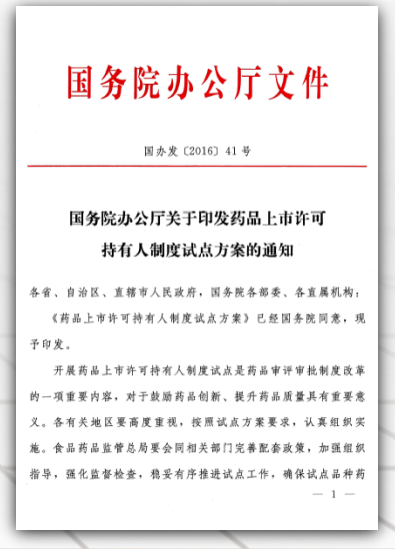
**No. 41**



国务院办公厅文件

国办发〔2016〕41号

国务院办公厅关于印发药品上市许可
持有人制度试点方案的通知

各省、自治区、直辖市人民政府，国务院各部委、各直属机构：

《药品上市许可持有人制度试点方案》已经国务院同意，现予印发。

开展药品上市许可持有人制度试点是药品审评审批制度改革的一项重要内容，对于鼓励药品创新、提升药品质量具有重要意义。各有关地区要高度重视，按照试点方案要求，认真组织实施。食品药品监管总局要会同相关部门完善配套政策，加强组织指导，强化监督检查，稳妥有序推进试点工作，确保试点品种药

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# Encouraging Drug Innovation

**Focusing on innovation on drug and medical device, in May 2017, CFDA issued a portfolio of reform approaches, the draft *Policy on Encouraging in Drug and medical device innovation and accelerating review and approval of new drug and medical device*, draft *Policy on Encouraging Innovation and Reformation on Clinical Trial Management for Drugs and Medical Devices*, draft *Policy on Encouraging Drug and Medical Device Innovation and Implementing Life-cycle Management of Drug and Medical Device*, and draft *Policy on Encouraging Innovation on Drugs and Medical Devices and Protecting Innovators' Rights* for *comments* collection.**




*Opinion on Deepening the Reform of the Review and Approval System and Encouraging the Innovation of Drugs and Medical Devices*

# Encouraging Drug Innovation --------- Opnions on Deeping the Review and Approval System Reform and Encouring the Drug and Medical Device Innovation

中共中央办公厅

厅字〔2017〕42号

中共中央办公厅　国务院办公厅
印发《关于深化审评审批制度改革
鼓励药品医疗器械创新的意见》的通知

各省、自治区、直辖市党委和人民政府，中央和国家机关各部委，解放军各大单位、中央军委机关各部门，各人民团体：

《关于深化审评审批制度改革鼓励药品医疗器械创新的意见》已经中央领导同志同意，现印发给你们，请结合实际认真贯彻落实。

中共中央办公厅
国务院办公厅
2017年10月1日

（此件公开发布）

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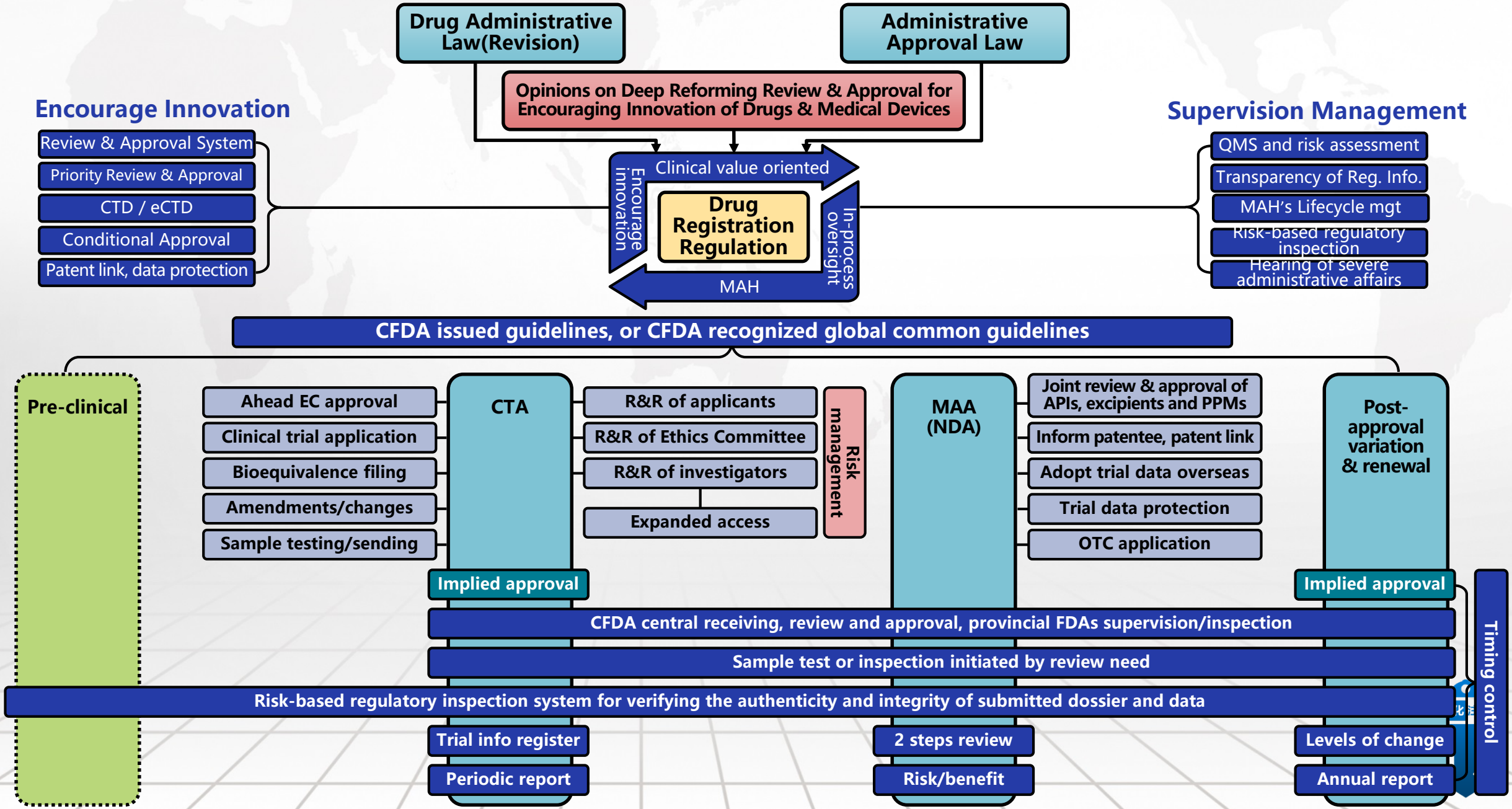
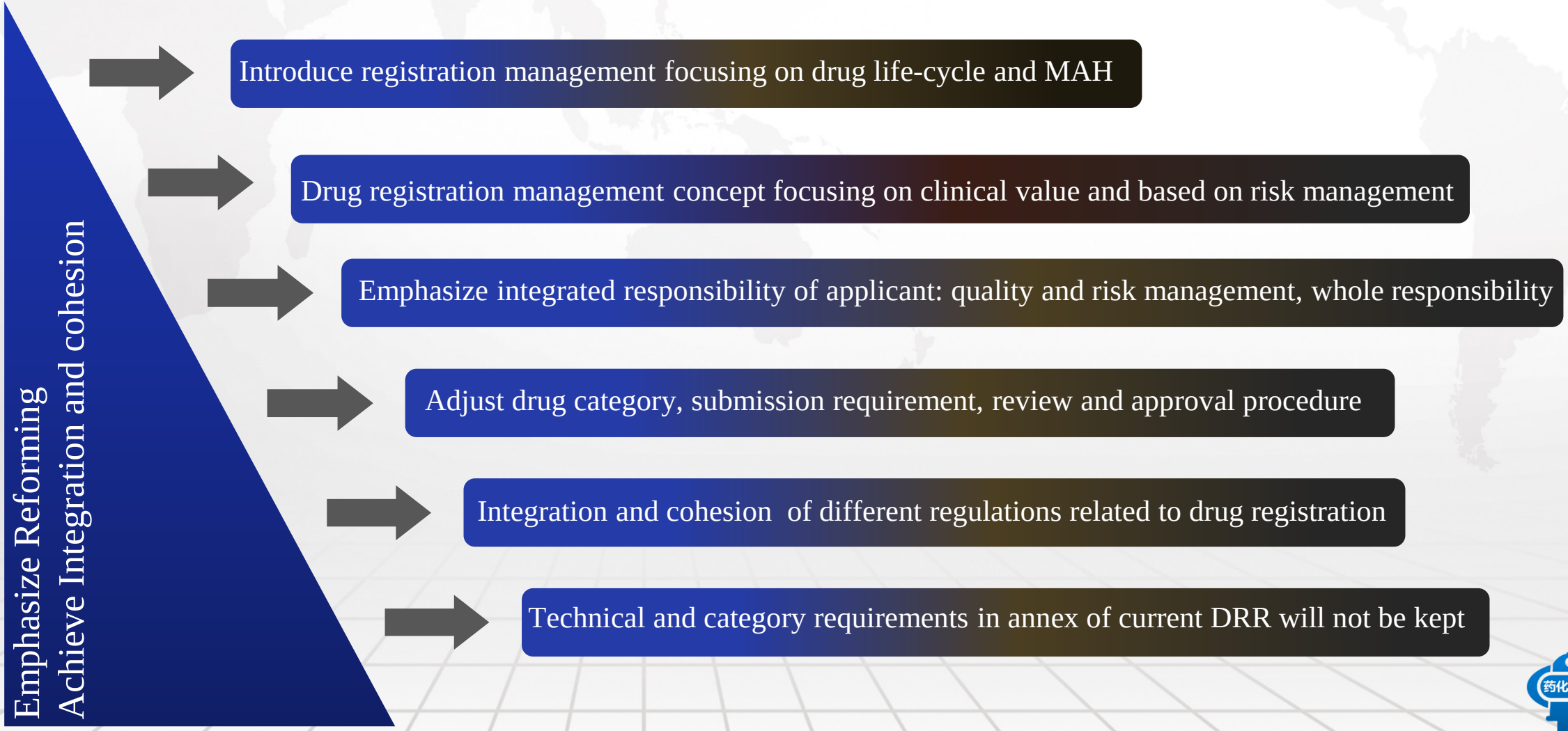
Promulgated by the General Office of Central Committee of CPC and the General Office of the State Council

# Revision of Regulatory Documents Relevant to Opinions of Reform



# Drug Registration Regulation ( revised version) – main points




# Conception of Drug Registration Category

| | New Drug | | | |
|---|---|---|---|---|
| Chemical product category | Innovative drug | Improved new drug | Generics | |
| Biologics category | New biologics | Improved biologics | Bio-similar | |
| Chinese traditional medicine and natural drug category | Innovative drug | Improved new drug | Analogous drug with same formulation | Ancient classiccal formulation |

- Based on the originality and novelty of the ingredients, new drug was classified as Innovative drug and Improved new drug. Definition of Generics was change from “imitative drug with a national specification” to “imitative drug with consistent quality and efficacy of originator”. Drug registration category is adjusted based on above principles.
- Up to 25 Nov 2017, more than 1500 comments was received .

# More Expectations

- Publish legal basis, approval requirements, technical standards and time limits of drug review and approval procedure.
- Disclose review progress to the applicants.
- Arrange communication in sufficient fair orderly way.
- Accept re-evaluation and reconsideration.
- Improve expert consultation procedure.
- Dispute handling procedure.
- Publish product registration result and accept public supervision.
- At the same time, improve management procedure, define operation requirement, sufficiently protect the technical secret in the dossier.

# Promote Drug Innovation and Generics Development

## Set up Marketed Drug List

New drug approved or generics passed Generics Consistency Evaluation shall be included into China Marketed Drug List, indicating attributions of innovative drug, improved new drug or generics with consistent quality and efficacy as originator , and active ingredient, dosage form, strength, marketing authorization holder, patent, data protection, etc..

## Exploring and establishing a drug patent linkage system

Explore and establish a drug review and approval and drug patent linkage system.

## Launching pilot programs with respect to drug patent term compensation system

Certain new drugs shall be selected to implement the pilot programs, appropriate compensation for a patent term will be granted for when marketing was delayed by clinical trials and review & approval procedures.

## Support the clinical application of new drug

Set up and Improve the dynamic adjustment mechanism

Support the new drugs to be included into the payment scope of basic medical insurance promptly by applicable provisions

incorporate the new drugs into the scope of centralized procurement of drugs for public hospitals promptly.

## Improving and implementing the drug-related trial data protection system

With respect to innovative drugs, therapeutic drugs for rare diseases, specialized drugs for children, innovative therapeutic biologics and drugs that have successfully challenged relevant patents, certain data protection period will be granted. During the data protection period, marketing applications for the same type of drugs submitted by any other applicant will not be approved

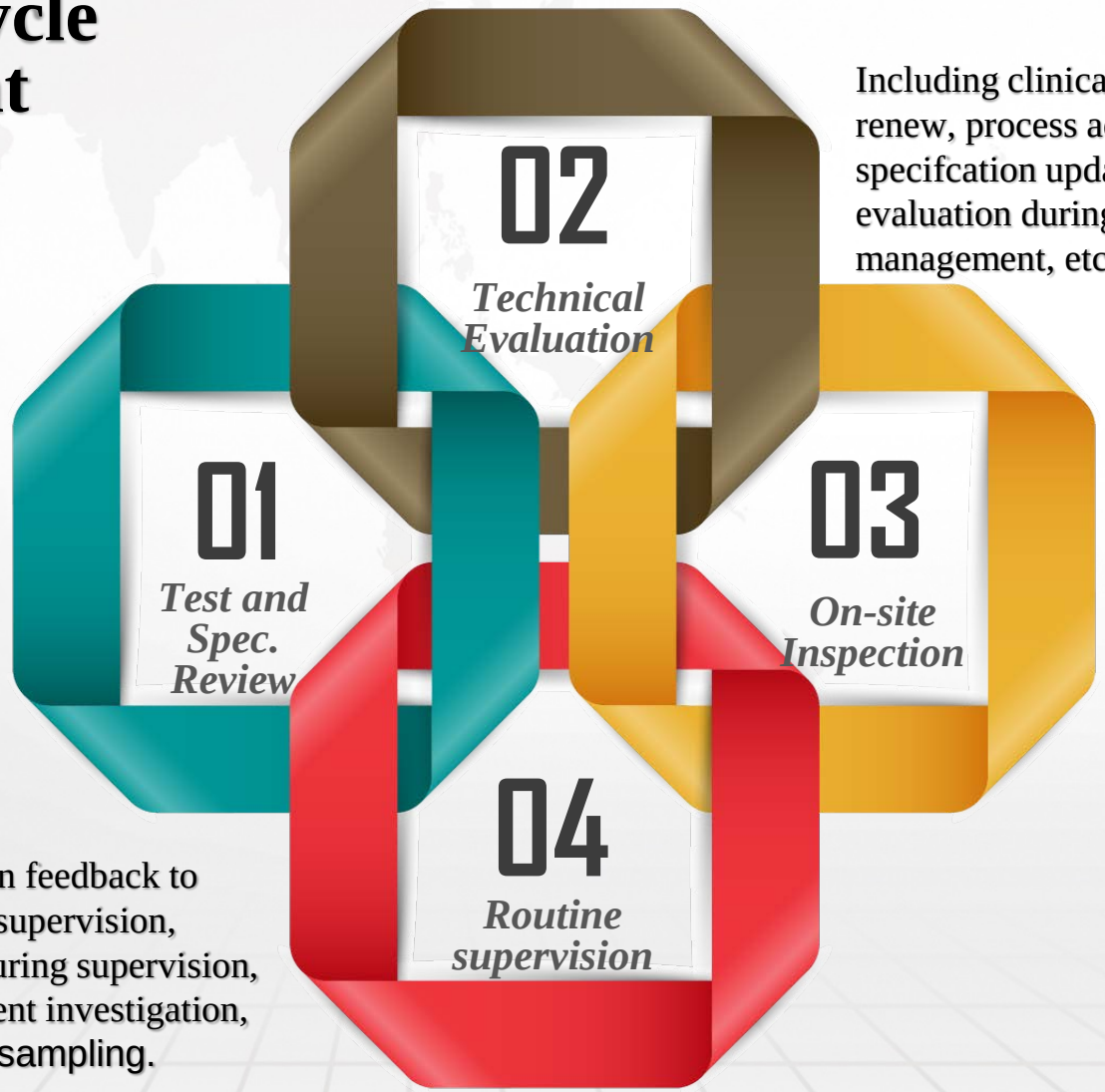
## Promoting the production of generics

Publish the lists of drugs whose patents expired, are terminated or become invalid and where no application for generics has been submitted. Support the development of both biosimilar and drug and medical device combination products with clinical values

## Giving full play to the role of enterprises in innovation

Encourage the drug and medical device company to increase investment in research and development, Allow scientific institutes and scientific researchers to apply for clinical trials on the condition that they shall assume relevant legal responsibilities.

# Extend Life-cycle Management




Including clinical, marketing, renew, process adjusting, specifcation update, re-evaluation during life-cycle management, etc..

Not only dossier review, QC test and trend analysis, but also early step-in for registration specification making, and trend analysis of product overall situation

Routing inspection, for cause inspection, unannounced inspection, to really objectively reflex actual manufacturing situation , and do well on sampling

Do well on feedback to localized supervision, manufacturing supervision, enforcement investigation, National sampling.

*Form an organic supervision entirety and set up rapid, effective issue handling mechanism*

# Future Expectations

Meet Clinical Urgent Needs

Science

Integrity

Innovation & Availability

Execution

Risk Controllability

# THANKS!

## THE END