Overview of Regulatory Trends in Biological Products

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Table of Contents

Main Features of biological products
Supervision of biological products
Progress of regulatory reform
Future expectation
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

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

- 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

Risks
Benefits

Drug Registration

Enterprises

Gov

Intl Demands

The People

Safety
Accessibility
Affordability
Risk controllability, efficacy expectability
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-accessment in July 2014.
Release Tests (Specifications)

Extended Process Control Characterization (Process & Product)

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

Unknown
Learned over time-
update control strategy

Consistency
Equivalence
Comparability

In-Process Controls
Finished-Product management

Who is the steersman – the applicants are actually the Key person for quality of products
Progress in Reform of Review & Approval Mechanism
Evolution of Biological Product Registration Regulations

**Initial Stage**
- 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)
- Regulation of Biological Product Administration (1993, Ministry of Health)
- ……

**Improvement Stage**
- 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
- 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
- ……
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.

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Reform of Drug Review and Approval – Policy setting
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.
Encouraging Drug Innovation -------- Opinions on Deeping the Review and Approval System Reform and Encouring the Drug and Medical Device Innovation

1. Reform clinical trial management
2. Accelerate marketing review and approval
3. Promote drug innovation and generic development
4. Strengthen life-cycle management of drug and device
5. Improve technical supportive ability
6. Strengthen implementation

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

Encourage Innovation
- Review & Approval System
- Priority Review & Approval
- CTD / eCTD
- Conditional Approval
- Patent link, data protection

Opinions on Deep Reforming Review & Approval for Encouraging Innovation of Drugs & Medical Devices

Clinical value oriented

Drug Registration Regulation

MAH

Drug Administrative Law (Revision)

Administrative Approval Law

Pre-clinical
- Ahead EC approval
- Clinical trial application
- Bioequivalence filing
- Amendments/changes
- Sample testing/sending

CTA
- Implied approval
- CFDA central receiving, review and approval, provincial FDAs supervision/inspection
- Sample test or inspection initiated by review need
- Risk-based regulatory inspection system for verifying the authenticity and integrity of submitted dossier and data
- Risk/benefit

Trial info register
- Periodic report

MAA (NDA)
- Joint review & approval of APIs, excipients and PPMs
- Inform patentee, patent link
- Adopt trial data overseas
- Trial data protection
- OTC application

Post-approval variation & renewal
- Implied approval
- Levels of change
- Annual report

Levels of change
- Timing control

CFDA issued guidelines, or CFDA recognized global common guidelines
Drug Registration Regulation (revised version) – main points

- Introduce registration management focusing on drug life-cycle and MAH
- Drug registration management concept focusing on clinical value and based on risk management
- Emphasize integrated responsibility of applicant: quality and risk management, whole responsibility
- Adjust drug category, submission requirement, review and approval procedure
- Integration and cohesion of different regulations related to drug registration
- Technical and category requirements in annex of current DRR will not be kept
Conception of Drug Registration Category

<table>
<thead>
<tr>
<th>Chemical product category</th>
<th>Innovative drug</th>
<th>Improved new drug</th>
<th>Generics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biologics category</td>
<td>New biologics</td>
<td>Improved biologics</td>
<td>Bio-similar</td>
</tr>
<tr>
<td>Chinese traditional medicine</td>
<td>Innovative drug</td>
<td>Improved new drug</td>
<td>Analogous drug with same formulation</td>
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<td>and natural drug category</td>
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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.

To simultaneously release while product marketing approved:
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.

**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.

**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.

**Supporting 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.

**Exploring and establishing a drug patent linkage system**
Explore and establish a drug review and approval and drug patent linkage system.

**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

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.

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

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

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

Form an organic supervision entirety and set up rapid, effective issue handling mechanism.
Meet Clinical Urgent Needs

Science Integrity

Innovation & Availability

Execution

Risk Controllability

Integration of power and responsibility

Honest and Trustworthy

Justice of procedure

High efficiency and convenience to people

Administration Rationality

Legality of administration
THANKS!

THE END