Regulatory Trends in the Regulations of Biological Products

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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 proteins or peptides with high molecular weights, 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.
Main Features of Biological Products (2)

- Bioanalysis methods, used for product quality control, usually take a longer time, and contain complicated procedures with variability;

- Higher "stability" is required for the raw materials, intermediates, finished products during transportation and storage;

- Vaccines are different from other medicines as they target healthy people, so special considerations on safety and efficacy need to be taken.

- Quality control is implemented by process monitoring of the whole manufacturing processes, and requires a strict and comprehensive quality management system (QMS)..... ,
Special Regulations on Biological Products

- Biological products belong to drugs, the drug regulations generally apply to them
- Biological products have special properties and need specific supervision, especially for different types of variations
  - Article 41, Imported drug testing, "Drug Administration Law"
  - Article 39, lot release, "Regulation for Implementation of Drug Administration Law"
  - Article 52, On-site inspection and sampling for investigational drugs, "Drug Registration Regulation"
  - Article 62, Commercial manufacturing site inspection and sampling, "Drug Registration Regulation"
  - Current divided into 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, transportation, post-marketing surveillance, etc.
  - Appendix on Biological Products and Blood Products in "Good Manufacturing Practice"
Biotech Product: Controlled Similarity production

How much of the Iceberg is visible?

- Release Tests (Specifications)
- Extended
- Characterization (Process & Product)
- Process Control
  - Procedures
  - Materials
  - In-process testing
  - Monitoring
  - Validation
- Unknown
  Learned over time - update control strategy

Compatibility = Safety & Efficacy in Human
Recent Trends in the Regulations of Biological Products
I. Reform Goals

- **To improve review and approval quality**: Establish a more scientific and efficient drug review and approval system
- **To address the review backlog**: Address review backlog before the end of 2015, and achieve the goal of completing review and approval within defined time limit by 2018.
- **To advance the quality of generic drug**: Accelerate the quality consistency evaluation of generics
- **To encourage new drug R&D**: Encourage the clinical-value-oriented drug innovation
- **To promote transparency**: Publish technical requirements, review and approval information to guide the applicants to conduct reasonable R&D activities and applications
II. Reform Measures (12 items)

To promote the quality consistency evaluation of generic drugs

To carry out drug Marketing Authorization Holder (MAH) pilot system

To publish the drug supply-demand and application information timely

To seriously investigate and penalize the falsification of registration application

To reform the review and approval procedures of medical device

To publish review and approval information of medicinal products and medical devices

To improve the criteria for drug review and approval

To accelerate the review and approval procedures for innovative drugs

To implement applicant’s main responsibility for applications

To optimize the approval procedures of drug clinical trial

To simplify the review and approval procedures of drug

To improve quality management system for drug review
III. Accelerate review and approval for innovative drugs

- Implement special review and approval process for innovative drugs.
- Accelerate review and approval for innovative drugs
  - Drugs for prevention and treatment of AIDS, malignant tumor, major infectious diseases and rare diseases, etc.
  - Drugs which are included in State Important Sci-Tech Special Projects and key National Development Plan
  - Innovative drugs and pediatric drugs transferred to local manufacturing in China
  - Innovative drugs using advanced technology, or with innovative treatments or having significant clinical advantages
  - Urgent unmet medical needs and drugs in shortage (listed by HA)
IV. Timely Publish Information on Drug Supply-Demand and Applications

To strictly control approvals and productions of generic drugs with oversupply, low-level duplication and lagged production process.

To encourage development and production of drugs in shortage, and improve drug accessibility.

Regulate the applicants in orderly R&D and restrict low-level duplicate submissions.
V. Optimize Drug Clinical Trial Approval Procedure

- For new drugs which have never been approved in other country, simultaneous clinical trials can be conducted in China once approval.
- Encourage China domestic clinical trial organizations to participate in international multicenter clinical trials, and qualified data from international trials could be used for drug registration in China.
- For clinical trial applications of innovative drugs, the focus is clinical value and human subject protection.
- Strengthen responsibilities of applicants, clinical trial organizations and ethics committees to protect subjects.

Qualified data from international trials could be used in registration of imported drug. Imported innovative drugs transferred to local manufactures will be included in scope of special review, for which priority review will be applied.
VI. Improve Quality Management System for Drug Review

- Establish Good Regulatory Practices by referring to international general guidelines

- Establish professional technical reviewer team, clearly define responsibilities of primary reviewers and reviewers, improve team review mechanism, and strengthen responsibility and time management.

- Establish a re-review expert committee to re-examine controversial conclusions to ensure scientific and fair review results

- Strengthen research on common issues in technical review, the research results to be adopted in the technical standards timely to guide the review, and improve the efficiency of review and approval.
VII. Publish Drug Review and Approval Information

- Publish lists of review items, legal basis, technical requirements, and time limits of drug review and approval procedure.
- Disclose review progress and results to the applicants.
- At time of NDA approval, comprehensive reports, inspection reports and lab testing reports will be published simultaneously for public supervision.

To simultaneously release while product marketing approved:

- QC testing Report
- On-site Inspection Report
- Open to the public

Review and Approval List
Legal Basis
Processing Time Limits
Review and Approval Requirements
Technical Review Report
Comparison of registration procedures for biological products
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)
The applicant submits an application

Format check by Provincial FDA

Not conform to the provisions

Conform to the provisions

Preliminary review of dossiers, R&D site verification, take samples for three batches and seal the samples

30 working days

CDE technical review

60 or 90 working days

NIFDC tests samples and verifies specifications

60 or 90 working days

Give feedback if any

Not pass

90 working days

CFDA administrative review and approval

Not approval

20 working days

CFDA administrative review and approval

Notification of non-approval opinion

Clinical Trial Approval

Approval

Non-acceptance notification
Procedures of Clinical Trial Application in New Registration Regulation (Draft)

1. Submission of clinical trial application
2. Centralized acceptance
3. Establish review team and project management
4. Technical Review
5. Review and approval
   - Approval
   - Non-approval
     - Disagreed
     - Approval
8. Non-approval
9. Notification to applicant by letter
10. Disagreement

- **Phase I clinical trials**
  - Assess on clinical trial outcome, submit protocol of the next phase clinical trial and get agreement with CDE on the trial design

- **Phase II clinical trials**

- **Phase III clinical trials**

- Cease the study or carry out a new clinical trial

- New drug marketing authorization application

- Pre-submission Communication

- Project Manager system:
  - whole process communication
  - quality management and supervision

- Compliance with GCP:
  - New or revised protocol
  - Severe Adverse Event Report
  - Annual Report

- Clinical trial registration

- Notification of a notice
Current Marketing Authorization Application Procedure (vaccine)

1. Submit application
2. Format Check by Provincial FDA
   - Yes: Preliminary review of dossiers, R&D site verification,
     - 30 working days: CDE technical review
     - 60 working days: Technical review not passed
   - No: Notification of non-acceptance
3. Notification of on-site inspection to applicant and CFDI
4. The applicant submits application of on-site inspection
   - Within 6 months: CFDI conducts inspection, takes sample from 3 continuous batches
   - Technical review passed: Comprehensive report
   - Technical review not passed: Notification on on-site inspection to applicant and CFDI
5. CFDI on-site inspection of clinical trial
   - Within 6 months: CFDI conducts inspection, takes sample from 3 continuous batches
   - Approval: Comprehensive report
   - Non-Approval: Comprehensive report
6. CFDA administrative review and approval
   - 30 working days: CFDA administrative review and approval
   - 20 working days: Approval
   - 20 working days: Notification of non approval opinion
7. CDE "Three in One"
   - 30 working days: NIFDC tests samples and verifies specifications
   - Within 6 months: Comprehensive report
   - Feedback (if any) feedback (if have)
8. NIFDC tests samples and verifies specifications
   - 90 working days: NIFDC tests samples and verifies specifications
   - 90 working days: Comprehensive report
   - Feedback (if have) feedback (if have)
Marketing Authorization Application Procedures under New Registration Regulation (Draft)

- Pre-submission Communication
- Submit new data or explanation
- Establish review team and project management
- Technical review by review team
- On-site Inspection
- Verification on specification and package insert by applicant
- Expert committee re-evaluation
- Applicant's objections on review conclusion
- Review and approval
- Announcement
- Disagreed
- Agreed
- Marketing authorization approval
- Submit annual report
- Update study data and status of post-marketing risk management
- Post-marketing variation application
- Post-marketing evaluation and supervision, implementation of life cycle management
- Centralized acceptance
- Submit MAA application
- Supplementary notification
- Not accepted
- Notification to applicant by letter
- CFDA consider CDE conclusion vague or questionable
Other Considerations

I  Definition and scope of biological products
  • Biological products include those products for preventive use, therapeutic use and blood screening diagnosis.
  • Clear definition of biological products which is regulated as drug will help improve the efficiency of research and development, application and registration.

II  Registration categorization of biological products
  • In the current Drug Registration Regulation, biological products are separated into two parts: preventive biological products and therapeutic biological products.
  • There are 15 registration categories under each part with lots of crossover among categories.
  • New categorization will be adjusted primarily based on innovation level, life cycle (variation). Special considerations on biosimilar, cell therapy will be taken as well.

III  Registration regulation of biological products
  • Keep pace with the reform plan, encourage innovation and biosimilar development
  • Establish requirements on registration management, procedure, standard and whole process control for biological products based on general requirements of drugs, by combing China regulatory requirements and features of biological products, by referring to WHO, ICH relevant technical guidelines
Future Expectations

Comprehensive Evaluation
High Efficiency
Innovation
Scientific
Execution

Unequivocal Procedures
Public Disclosure
Definite Timeline
High Efficiency
Fair & Authoritative
THANKS!
THE END