Regulatory Framework of Biological Products in China and Reform of Drug Review & Approval System

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Outline

I. Regulatory Framework of Biological Products in China
II. Reform of Drug Review & Approval System in China
III. Key Tasks in the Coming Years
I. Regulatory Framework of Biological Products in China

CFDA Organizational Chart

- 17 departments
- 345 "in-staff" working positions
- 19 institutions directly under CFDA
Technical Institutions directly under CFDA

Acceptance Center

National Institutes for Food & Drug Control (NIFDC)

Center for Food and Drug Inspection (CFDI)

Chinese Pharmacopoeia Commission (ChPC)

Information Center

China Center for Food & Drug International Exchange (CCFDIE)

Institute of Executive Development

Center for News Propaganda

China Medical Science Press

Depot of One-Four-Six

China Food and Drug Administration

Center for Drug Evaluation (CDE)

Center for Drug Reevaluation (CDR)

National Committee on the Assessment of the Protected Traditional Chinese Medicinal Products

Chinese Pharmaceutical Association

Center for Medical Device Evaluation (CMDE)

Certification Center for Licensed Pharmacist

China Pharmaceutical News

Southern Medicine Economic Research Institute

Authority Service Center
Department of Drug & Cosmetics Registration

Technical Institutions

- Acceptance Center
- National Institutes for Food and Drug Control (NIFDC)
- Center for Drug Evaluation (CDE)
- Center for Food and Drug Inspection (CFDI)
- Chinese Pharmacopoeia Commission (ChPC)
- China Center for Food & Drug International Exchange (CCFDIE)

Department of Drug and Cosmetics Registration

- Division of General Affairs
- Division of Pharmaceuticals
- Division of Traditional Chinese Medicines
- Division of Biological Products
- Division of Drug Research Supervision
- Division of Cosmetics
Law and Regulation System

Law

- Drug Administration Law of the People's Republic of China (Order of the President of the Peoples Republic of China No. 45, 2001)

Regulation


Department Rule

- Provisions for Drug Registration (SFDA Order No. 28, 2007)
- Provisions for Drug Insert Sheets and Labels (SFDA Decree No.24, 2006)
- Administrative Reconsideration Measures of CFDA (Order of CFDA No. 2, 2013)

Normative Document

- Requirements for On-site Verification for Drug Registration (CFDA annotation〔2008〕No. 255)
- Requirements on Import Drug Re-registration (CFDA annotation〔2009〕No.18)
- Provisions for Registration of Drug Technology Transfer (CFDA annotation〔2009〕No.518)
Scope of Biological Products

◆ Preventive biological products:
   61 products, 41 manufacturers, with an annual output of 1 billion doses

◆ Therapeutic biological products:
   1. Blood derived products: 10 products, 28 manufacturers
   2. Recombinant products: monoclonal antibody, recombinant cytokines, enzymes, hormones, etc.
   3. Others: antitoxin and antisera, biological tissue extraction products, allergen, microecologics, gene therapy, somatic cell therapy, therapeutic vaccines, etc.

◆ In vitro diagnostic reagents:
   1. Blood source screening diagnostic reagents: 8 reagents, 35 manufacturers
   2. Radiolabelled diagnostic reagents: 10 manufacturers
Marketing Authorization Review Process of Imported Drugs

The applicant submits an application

Accepted by Acceptance Center, CFDA

CDE technical evaluation

NIFDC sample inspection and specification verification

CFDA administrative review and approval

Imported Drug License

Not comply with requirement

Notification of nonacceptance

Give feedback (If any)

Comply

Notification of nonacceptance

Complete clinical trials

90 working days

150 working days

5 working days

20 working days

Approval failed

Approval passed

Not comply with requirement

Provide inspection recommendations based on the review results

Overseas inspection report

CFDI performs overseas production on-site inspection by sampling (since 2011)
<table>
<thead>
<tr>
<th>Date</th>
<th>Issuing Organizations</th>
<th>Policies</th>
<th>Summary of Contents</th>
</tr>
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<tbody>
<tr>
<td>2009</td>
<td>the State Council</td>
<td>Promote the Development of Biological Industry</td>
<td>The biomedicines will be treated as a key area in the development of modern bio-industry, by focusing on support of biomedical manufacturers</td>
</tr>
<tr>
<td>2010</td>
<td>the State Council</td>
<td>Decisions on Speeding up the Cultivation and Development of Strategic Emerging Industries</td>
<td>The biological industry will be listed as the mainstay industry among the seven strategic emerging industries</td>
</tr>
<tr>
<td>2011</td>
<td>Ministry of Science and Technology</td>
<td>Development Programs of Advanced Biological Manufacturing (2011-2015)</td>
<td>Put forward the overall goals, development strategies and guidelines of the &quot;12th Five-year Plan&quot; against the issues of the development of biological manufacturing industry</td>
</tr>
<tr>
<td>2011</td>
<td>the State Council</td>
<td>Schema of the 12th Five-year Plan of the National Economic and Social Development</td>
<td>The biomedicine, biomedical engineering and biological manufacturing are incorporated into the key subdivision industry in China</td>
</tr>
<tr>
<td>2011</td>
<td>Ministry of Science and Technology</td>
<td>Biotechnology Development of &quot;The 12th Five-year Plan&quot;</td>
<td>To promote the rapid development of biotechnology and industry comprehensively, to facilitate the changes of the economic development modes, and to cultivate the strategic emerging industries</td>
</tr>
<tr>
<td>2011</td>
<td>National Development and Reform Commission and other seven ministries</td>
<td>Construction Plan of Vaccine Supply System</td>
<td>To determine the key projects and objectives of the construction of vaccine supply system</td>
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<td>2013</td>
<td>the State Council</td>
<td>Biological Industry Development Plan</td>
<td>To further clarify the key task of biomedical development</td>
</tr>
<tr>
<td>2013</td>
<td>the State Council</td>
<td>Suggestions on promoting the development of health service industry</td>
<td>To cultivate the industries such as TCMs, innovative drugs and the biomedical materials as the key supporting industries of health services</td>
</tr>
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<td>2015</td>
<td>Central Committee of the Communist Party of China</td>
<td>Suggestions on the establishment of 13th Five-year Plan of National Economy and Social Development</td>
<td>To promote the development of biomedical and high-performance medical devices industries</td>
</tr>
<tr>
<td>2016</td>
<td>the State Council</td>
<td>The 13th Five-year Plan for the National Scientific and Technological Progress</td>
<td>To develop the advanced and efficient biotechnology</td>
</tr>
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</table>
Investment on the R & D of Biological Products (RMB 100 million)

- Private capital/ business investment

+28% Compound Annual Growth Rate

<table>
<thead>
<tr>
<th>Year</th>
<th>Private Capital/Business Investment</th>
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</thead>
<tbody>
<tr>
<td>2011</td>
<td>195</td>
</tr>
<tr>
<td>2012</td>
<td>299</td>
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<tr>
<td>2013</td>
<td>371</td>
</tr>
<tr>
<td>2014</td>
<td>439</td>
</tr>
<tr>
<td>2015</td>
<td>531</td>
</tr>
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</table>
Registration applications accepted in last five years

- **Chemical Drugs + TCMs**
  - 2012: 6463
  - 2013: 7529
  - 2014: 8324
  - 2015: 7559
  - 2016: 3369

- **Biological Drugs**
  - 2012: 6919
  - 2013: 7003
  - 2014: 8778
  - 2015: 8120
  - 2016: 3779
State Council issued the Opinions on Reforming Review & Approval System for Drugs & Medical Devices on Aug 13th, 2015, thus opening the reform curtain.

**The key objectives of the reform are:**
- To improve the quality of drugs,
- To achieve the goal of efficacy, safety and quality controllability of marketed drugs through the reform
- To make it reach the international advanced level and meet public demand for drugs.

**The goals for review timeline are:**
- To finish its backlog of drug applications by end of 2016
- To follow strictly its statutory review and approval timeline beginning in 2018

I. Reform of Drug Review & Approval System in China
Purpose of the Reform

(I) Improving Quality

(II) Improving Efficiency

(III) Encouraging Innovation

(IV) Increasing Openness & Transparency
Improving the quality of drugs is the core of reform of drug review and approval system. CFDA will take it as a starting point of improving the drug approval criteria and performing the equivalence evaluation for generic drugs.
New drug

The new classification delivers a signal: Encouraging Innovation!

- To modify the registration classification of chemical drugs
- Improving Quality - To ensure that the quality and efficacy of newly approved generic drugs are equivalent to innovator drugs.

1. Innovative Drugs
   - Creativity and novelty of new drug substance

2. Modified new drug

3. Generic drugs
   - The drugs have not been marketed in China
   - The drugs have not been marketed in and out of China
   - To copy the drugs with the national specification
   - To copy the innovator drug with the equivalent quality and efficacy

By end of Nov 2016, 929 applications under the new chemical drug classification were submitted
Guidelines for drug technical evaluation equivalent to international standard have been issued through modifying, drafting, or transforming over 150 guidelines.
All oral solid preparations of chemical generic drugs in the National Essential Drug List approved before Oct. 1, 2007 should be completed the equivalence evaluation by the end of 2018, involving a total of 289 products, 17636 domestic approval license numbers and 104 imported drug licenses, and 1817 domestic drug manufacturers and 42 foreign drug manufacturers.

1. Increase the pharmaceutical industry development level, and ensure the safety and efficacy of public medication

2. Reduce the medical costs, and promote the industrial restructuring

3. Strengthen the international competitiveness, and encourage the domestic drugs going abroad
A series of specific measures have been carried out to improve efficiency

(II) Improving Efficiency

- Improve the review system
  - Establish the clinical-driven review system
  - Implement the project manager review system
  - Establish the expert advisory committee system

- Establish communication mechanism
  - Establish the communication system between applicants & HA with detailed procedures and requirements

- Implement a BE notification system
  - Simplify the approval process for BE study of generic drugs

- Streamline review & approval procedure
  - Combine review and approval of packaging materials & excipients with the review and approval of drug application

- Build a strong reviewer team
  - Recruit more reviewers with the aim to hire 1000 reviewers
There were only 120 reviewers in CDE in 2014, however the number has reached 400 this year. CDE has issued the recruitment notice to the public intensively from last year. However, the number of reviewers is not enough, and CDE will continue to increase its efforts to recruit more reviewers.
(III) Encouraging Innovation

A series of specific measures have been carried out to encourage innovation

Implement Pilot Plan for Drug Marketing Authorization Holder System

- The pilot plan launched for 10 provinces.

Implement Priority Review & Approval Procedure

- 1241 applications submitted for priority review, and 155 products were granted by Dec 9th, 2016
- The shortest review timeline is 15 days and the longest is no more than 90 days

Implement Inspection of Clinical Trial Data

- 1885 applications conducted self-inspection and 1193 withdrew, accounting for 83% of the total self-inspections by Jun 2016
- 117 applications performed inspection and 30 rejected due to authenticity issue, accounting for 2% of the total self-inspections & inspections by Sep 2016
CFDA synchronized the release of review report and package inserts for marketing applications of new drugs online from October 2016.

Encourage the innovation in research and development, and guide the manufacturers conducting R&D.

Standardize and optimize the submission method. CFDA will promote the submission of registration dossier in the format of CTD (Common Technical Document) and eCTD by referring to ICH (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use).

(IV) Increasing Openness & Transparency
Total of 8868 review tasks have been finished from January to September this year only, which is 2-fold higher than that in the same period last year.

The highest peak in 2015
1) To accelerate the process of the Reform of Drug Review & Approval System

2) To revise and improve the law and regulation system of drug registration

3) To promote implementation of the drug safety body corporate responsibility
Thanks for your attention!