Latest Progression of Chinese Drug Registration Management

Zhang Wei, Department of Drug Registration
I. Revision and update progression of Drug Registration Laws and Regulations

II. About drug registration approval

III. Reform progression of drug registration management system mechanism

IV. Progression of drug research supervision and management

V. Thinking of the 12th Five-year plan for drug registration management

VI. International exchange and cooperation
Revision and Update Progression of Drug Registration Laws and Regulations
Further Improvement in Construction of Drug Registration Legal System

1. Study and formulate “Measures for Drug Research Supervision and Management”

2. Complete the formulation of “Rules for Drug Standard Management”

3. Formulate and release “Management Rules for Registration and Filing of Pharmaceutical Raw and Auxiliary Materials” and its related supporting documents
Revision and Update Progression of Drug Registration Laws and Regulations

- DMF——Management Rules for Registration and Filing of Pharmaceutical Raw and Auxiliary Materials
- Rules for Drug Standard Management
- Technical Guideline of Natural Drug Registration
- Measures for Drug Research Supervision and Management and serial supporting normative documents
- GRP
- Electronic Submission and Common Technical Documentation (CTD)
## Goals of Establishing Chinese DMF System

<table>
<thead>
<tr>
<th>Serve the Technical Review</th>
<th>Serve the Dynamic Audit and Inspection</th>
<th>Serve the Preparation Enterprises</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Benefit the enterprises’ application of real technical documents, and improve the reliability of review</td>
<td>• Provide technical data for site inspection</td>
<td>• Improve the applicability of raw and auxiliary materials used in the scientific research of preparation enterprises depending on their decisions</td>
</tr>
<tr>
<td>• Directly cite DMF in the preparation technical documents to improve the efficacy of review</td>
<td>• Provide technical data for dynamic GMP inspection</td>
<td>• Implement the preparation enterprises to be the first person in charge, and improve the auditing of supply chains</td>
</tr>
<tr>
<td>• The application of the electronic documents with CTD format promotes the electronic review and improve the level of review</td>
<td>• Improve the category-centered inspection level</td>
<td>• Clear responsibility, improve the process control and quality assurance level of pharmaceutical raw and auxiliary material manufacturers</td>
</tr>
<tr>
<td></td>
<td>• Improve the controllability of production process and the traceability of supply chains</td>
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</tr>
</tbody>
</table>


Features of Chinese DMF System

- Chinese DMF mainly promotes the implementation of the first responsible person of drug manufacturers, which benefits the trace of supply chains, and the improvement of supervision and management efficacy and review efficacy.
- The coexisting ways of implementation of registration and filing for some pharmaceutical raw and auxiliary materials of Chinese DMF.
- Filing information system management of pharmaceutical raw and auxiliary materials; synchronous implementation of the application of electronic technical documents with CTD format.
- Release the text and the filing application guidelines separately.
Progression of Chinese DMF

- Text of management provisions to be released recently
- Release the supporting guidelines in succession
- Give a longer transition period
Rules for Drug Standard Management

- Draft for Comment of “Measures for Drug Standard Management”
- 65 articles in 7 chapters in total
- Standardize the work responsibility and division, formulation and release, revision and abolishment, management and publication, implementation and supervision of pharmacopeia standards and registration standard management
Study and Formulate the Policies for Promoting the Development of Traditional Chinese Ethnic Drugs

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Study and draft the opinions on strengthening the management of the traditional Chinese ethnic drugs</td>
</tr>
<tr>
<td>Complete the related management work on the category protection of Chinese medicines</td>
</tr>
</tbody>
</table>
Rules for Drug Research Supervision and Management and Serial Supporting Normative Documents

1. Formulate the Measures for Drug Research Supervision and Management
   • Clarify the legal responsibilities of various participating parties in the clinical trials of drugs
   • Strengthen the management of sponsor, study institutions and ethics committees on clinical trials
   • Enhance the supervision and inspection of the drug supervision and management departments on the clinical trial institutions and processes of drugs

2. Explore the compulsory liability insurance and other relevant remedy systems, independent ethics committee systems and informed consent systems, strengthen the subject protection.

3. Formulate and issue the normative documents to guide the development of clinical trials of drugs
   • Formulate the supervision and inspection guideline to guide the supervision
Organize the translation of FDA and EU’s GRP
Set a special GRP research group
Preliminarily establish the basic principles of Chinese GRP: Principles of science, transparency, conformity, and efficacy
Establish the basic framework of Chinese GRP: Good Registration Practice for Pharmaceuticals + Standard Operation Manuals for each department
Basic Information of Electronic Submission and Approval of Chinese Drug Registration

On-going:

Electronic Instruction Label Submission System, will connect to the review system in the future, and realize the disclosure of the approved instruction label information.

Electronic Drug Standard Submission and Approval System, in the future, the drug executive standard can be opened to the specific groups according to the different limits of authority.

Electronic Submission of Application Data with CTD Format is studying, CTD application data of generic drugs are submitted electronically and the submission contents include some contents of Module 2 and 3.
Progression in Common Technical Documentation for Chinese Drug Registration

- On May 5th, 2010, “Letter of Opinions on Declared Data with CTD Format” was released (SFDA [2010]86)
- Propose the specific requirements for the CTD application data of generic drugs
- Including the requirements for application data with CTD format (Pharmacy part and Bioequivalence part)
- Summary of main study data (Pharmacy part and Bioequivalence part)
Progression in Common Technical Documentation for Chinese Drug Registration

- The relevant work team starting to participate since July 2010 is responsible for translation and arrangement work of EU and FDA’s guidelines on electronic submission.
- The CTD format after seeking for suggestions is used firstly during the generic drug category application and directly realizes the electronic submission.
Significance of Promoting CTD Electronic Submission on Chinese Drug Registration

Higher technical requirements

• --CTD is not only a simple requirement for document format, but also a higher technical requirement for study contents and level in general

Higher review quality and efficacy

• The electronization of CTD application will greatly accelerate the electronic review work strength and resolve the conflict that the review strength mismatches the application strength

Practice significance of generic drug review

• The pilot implementation in the category application of generic drugs benefits the horizontal comparison of the quality between the same category of generic drugs, improves the generic drug review level, generic drug research level and quality assurance capacity.
Future Development Direction in China

- CTD submission and electronic submission of registration materials
- Electronization of all drug registration materials including CTD
- High-end application of electronic materials, including the full-field and multi-department supervision and management application in R&D, production, circulation and use links of drug products
About Drug Registration Approval
## Analysis of Drug Registration Work Data

### Reception situation of drug registration

<table>
<thead>
<tr>
<th></th>
<th>Domestic application reception</th>
<th>Foreign application reception</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chemical drug</td>
<td>Chinese medicine</td>
</tr>
<tr>
<td>Quantity</td>
<td>1528</td>
<td>105</td>
</tr>
<tr>
<td></td>
<td>69</td>
<td>2433</td>
</tr>
<tr>
<td></td>
<td>2433</td>
<td>599</td>
</tr>
<tr>
<td>Sum</td>
<td>4135</td>
<td>2433</td>
</tr>
<tr>
<td></td>
<td></td>
<td>599</td>
</tr>
<tr>
<td>Total</td>
<td>4734</td>
<td></td>
</tr>
</tbody>
</table>
Analysis of Drug Registration Work Data

Reception situation of drug registration

Reception amount of various chemical drugs
- New drugs: 54%
- Generic drugs: 39%
- Changed drugs: 7%

Registration reception of various Chinese medicines
- New drugs: 69%
- Generic drugs: 20%
- Changed drugs: 11%
Analysis of Drug Registration Work Data

Review Timing Analysis

<table>
<thead>
<tr>
<th></th>
<th>Number of over-timing categories</th>
<th>Proportion (%)</th>
<th>Over-timing median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chinese medicines</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Chemical drugs</td>
<td>305</td>
<td>20.3</td>
<td>13</td>
</tr>
<tr>
<td>Biologics</td>
<td>25</td>
<td>25</td>
<td>35</td>
</tr>
</tbody>
</table>
# Analysis of Drug Registration Work Data

## Data of Approved Drugs in 2010

<table>
<thead>
<tr>
<th>Category</th>
<th>Quantity (calculated by the reception number)</th>
<th>Number of involved drug categories</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical drugs</td>
<td>794</td>
<td>369</td>
</tr>
<tr>
<td>Chinese medicines</td>
<td>80</td>
<td>72</td>
</tr>
<tr>
<td>Biologics</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>886</td>
<td>451</td>
</tr>
</tbody>
</table>
## Analysis of Drug Registration Work Data

### Data of Approved Drugs in 2010

<table>
<thead>
<tr>
<th></th>
<th>Chemical drugs</th>
<th>Chinese medicines</th>
<th>Biologics</th>
</tr>
</thead>
<tbody>
<tr>
<td>New drug</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Form-changed drug</td>
<td>103</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Generic drug</td>
<td>51</td>
<td>59</td>
<td>9</td>
</tr>
<tr>
<td>New drug</td>
<td>640</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Form-changed drug</td>
<td>12</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Generics drug</td>
<td>794</td>
<td>80</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>886</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Analysis of Drug Registration Work Data

Comparison of Approved Quantity between Different Registered Categories of Chemical Drugs in 2010
Analysis of Drug Registration Work Data

Comparison of Approved Quantity between Different Registered Categories of Chinese Medicines in 2010

<table>
<thead>
<tr>
<th>Category V Chinese medicine</th>
<th>Category VI Chinese medicine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quantity</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>10</td>
</tr>
</tbody>
</table>
The increasing proportion of new drug application suggests the legislation idea of encouraging innovation and promoting generic drugs is practiced.

By continuously completing the drug review and approval systems, enhancing the site inspection of drug registration and strictly implementing the drug review and approval standards, the falsification phenomenon has been restricted effectively, which purifies the drug registration environment to a certain degree.

The number and structure of drug registration applications gradually return back to the normal state, the review and approval are basically completed within the timing, and the satisfaction on drug registration management is gradually increasing in all circles of the society.
The summary of drugs approved to enter the clinical study in 2009 is shown in the table below:

<table>
<thead>
<tr>
<th>Registration category</th>
<th>Domestic application</th>
<th></th>
<th></th>
<th>Foreign application</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chemical drug</td>
<td>Chinese medicine</td>
<td>Biologic</td>
<td></td>
</tr>
<tr>
<td>Reception No.</td>
<td>658 (20 of class1.1)</td>
<td>101</td>
<td>26</td>
<td>320 (132 international multi-center clinical study)</td>
</tr>
<tr>
<td>Compound or prescription</td>
<td>267</td>
<td>91</td>
<td>/</td>
<td>171</td>
</tr>
<tr>
<td>Total (Reception No.)</td>
<td></td>
<td></td>
<td></td>
<td>1105</td>
</tr>
</tbody>
</table>
About International, Multi-center Clinical Trials

- The participation degree of China in the synchronic research of global new drug research and development is increasing year by year.
- In 320 clinical trials from foreign applicants that was approved in 2009, 132 are the international, multi-center clinical trials, significantly increasing compared with the last years. The approval summary of the application for international, multi-center clinical trials in the past 5 years is seen in Fig. 1

![Fig. 1 Number of International, Multi-center Clinical Trials Approved during 2005-2009](chart.png)
1. As there is rapid social and economic development in China, the distribution of disease types is wide, the clinical resources are rich, and the R&D costs are relatively cheap, China becomes one of optional important countries for global research and development.

2. China is continuously completing and improving the construction of legal system, approval system and supervision capacity with the objective of gradually catching up the international standards and specifications and the mutual coordination.

3. Facing the main tendency of globally synchronic research and development, China shall be brave to handle the challenges, grasp the opportunities, further optimize the allocation of review resources, and further improve the review capacity, quality and efficacy.

4. Actively participating in and making a response to global research and development will bring a deeply reform for China in terms of subject protection system, ethics committee setting and clinical trial supervision mode.
Progression of Drug Registration Management System Mechanism Reform
Reform of Review and Approval Systems Mechanism

Several considerations on accelerating the reform promotion of drug review and approval systems

• Targeting to reduce the unnecessary procedures and improve the efficacy, actively explore the scientific division of technical review and administrative approval rights
• Targeting to enhance the risk management and control and improve the predictability of review and approval processes, actively explore the reform of clinical review and production review management modes and the adjustment of the management strategies
• Targeting to establish an uniform, efficient, coordinated and flexible review and approval systems, further optimize the allocation of drug registration review and approval resources (central and local, inside SFDA, management of experts)
• Enhance the running investigation of drug registration system, and timely find out the indicated issues and the difficulties during the implementation of regulations and policies to make an active response and resolve as early as possible
Reform of Review and Approval Systems Mechanism

Several works to optimize the drug review and approval mechanisms

• 1. Explore and establish the drug registration work quality & efficacy assessment mechanism and the administrative performance assessment mechanism
• 2. Accelerate and promote the formulation and implementation of Good Registration Practice for Pharmaceuticals and Good Review Practice for Pharmaceuticals (GRP), and the draft of Chinese GRP has been made primarily
• 3. Explore and establish the drug registration management expert consultation committee
• 4. Further complete the work mechanism of encouraging drug innovation, research and formulate the specific measures to encourage innovations, and practically embody the innovation encouragement.
• 5. Explore and establish the internal and external supervision & restriction mechanism for review and approval work
Reform of Review and Approval Systems Mechanism

Institutional reform of drug review and evaluation centers

- Conduct surrounding the work mechanism, review quality and review efficacy
- Establish the review correction, academic supervision and quality evaluation mechanisms
- Occupational and professional review duty system
- Have published the Rules and Procedures for Technical Review of Drugs
- Communication and exchange—the key of review and decision-making efficacy
Institutional reform of CDE
Progression of Drug Research Supervision and Management
- Establishment of the research supervision and management legal system
- Establishment of the research supervision, management and inspection system
- About the primary practice of electronic supervision and management
Establishment of the Research Supervision and Management Legal System

Formulate the Measures for Drug Research Supervision and Management

- Clarify the legal responsibilities of various participating parties in the clinical trials of drugs
- Strengthen the management of sponsor, study institutions and ethics committees on clinical trials
- Enhance the supervision and inspection of the drug supervision and management departments on the clinical trial institutions and processes of drugs

Strengthen the subject protection

- Explore the compulsory liability insurance and other relevant remedy systems, independent ethics committee systems and informed consent systems

Standardize and enhance the supervision and inspection

- Formulate and issue the normative documents to guide the development of clinical trials of drugs
- Formulate the supervision and inspection guideline to guide the supervision
Establishment of the Research Supervision, Management and Inspection System

Establish an inspector team within the drug supervision and management system

- Complete the selection, assignment, evaluation and management of inspectors and complete the management of the expert team

Site inspection work mechanism and clinical trial supervision & inspection

- Research and establish the scientific clinical trial registration site inspection work mechanism and clinical trial supervision & inspection system with technical review as the core and site inspection as the support

Supervision and inspection requirements and standards

- Detail and complete the supervision and inspection requirements and standards for clinical trials, standardize the site inspection of clinical trials, and enhance the guidance for organization, implementation and management of clinical trial site inspections in various provinces.

“Risk Management” and “Process Supervision”

- Research and establish the uniform and standardized supervision workflow and coordinated and consistent work mechanism based on the information system, with “Risk Management” and “Process Supervision” as the mainline and with the scientific and reasonable responsibility division
About the Primary Practice of Electronic Supervision and Management

- The electronic supervision and management has been realized primarily in Tianjin, and the primary experience has been accumulated.
- Formulate and publish the uniform information construction data standards and management specifications
- Objective: To establish a national, uniform supervision and management information platform for drug clinical trials
Thinking of the “12th Five-year Plan” for Drug Registration Management
## Issues and Challenges of Drug Registration Management

1. The system institution and legislation construction of drug registration management can not be fully adaptable to the demand of the new drug innovative production and industrial development changes in China.

2. The relevant management regulations in the dug R&D field (especially the clinical trial link) are still to be completed, and the complete system still needs to be constructed for technical guidance principles.

3. The whole-process supervision and inspection system of drug registration is not complete, and there is lack of professional and full-time inspection teams, shortage of administrative resources while continuous increase of supervision and management demands.

4. The risk control capacity in the drug R&D and registration process is insufficient, and the capacity to communicate and supervise before, during and after study is still to be improved further. The excessive emphasis on post hoc supervision and management does not resolve the issues in their sprouting period.
Specific Issues Faced by Drug Registration Management

### Process of drug registration

**Study**
- 1. The relevant management regulations are still to be completed, and the complete system still needs to be constructed for technical guidance principles.
- 2. The supervision and inspection system is not complete.
- 3. The excessive emphasis on post hoc supervision and management does not resolve the issues in their sprouting period.

**Submit**
- 1. The current materials submission requirements cannot meet the review requirements increasingly.
- 2. Lack of electronic submission specifications and systems.
- 3. Lack of the channels to communicate with the applicants before submission and the process control.

**Review and Approval**
- 1. Lack of GRP
- 2. Lack of knowledge management systems required by review
- 3. The electronic review system is still to be improved further
- 4. Lack of investigation on the standardization of application data
- 5. Lack of the third party’s validation, re-validation from validity to science
- 6. The review and approval capacities for innovative drugs still need to be further improved.

**Supervision**
- 1. The supervision and inspection mechanism is not flexible, and fails to combine the construction of the integrity mechanism.
- 2. The post hoc supervision and management is emphasized too much and there is no advanced communication and process control capacity.
Strategies and Thinking

Registration submission links

• With the common technical documentation (CTD) of drug registration as the starting point, pay importance to the introduction of international specifications for application materials, improve the science of application materials and promote the increase of the research level.

• Actively explore the electronic submission of CTD application materials, pay importance to the science of materials and improve the submission efficacy, and introduce the energy-saving and environment-friendly work modes at the same time.

• Establish the whole-process (beforehand, in-process and post hoc) communication mechanism for supervisors and applicants, and assist with the corresponding supervision and management process control measures, so as to resolve the issues in their sprouting period.

Future objective: To realize the standardized and efficient electronic submission system
Strategies and Thinking

Review and approval links

- Improve the standardization investigation of application data by combining the promotion of CTD application format
- Promote the formulation and implementation of Good Registration Practice for Pharmaceuticals and Good Review Practice for Pharmaceuticals (GRP)
- Gradually establish the knowledge management system required by high-efficient review while completing the electronic review system
- Further enhance the third party validation methods, validation from improving the validity of materials gradually to the science of data

Future objective: To establish the electronic review system based on the drug review knowledge network system
Strategies and Thinking

Supervision and management links

- Establish the regulations: Formulate the Measures for Drug Research Supervision and Management and its relevant supporting regulations.
- Establish the systems: Research and establish the scientific registration management systems with technical review as the key and audit, inspection, testing and verification as the support.
- Establish the teams: Establish the internationalized, professional and full-time inspector teams.
- Establish the mechanisms: Establish the uniformed, coordinated, flexible, and efficient dynamic audit & inspection mechanisms, and focus on the combination of the audit and inspection with the honesty system.
- Establish the institution: Research, explore and establish the grading and classification management institutions for drug R&D units, drug clinical trial institutions, contracted study organizations, drug registration applicants and their registration commissioners.
- Establish the platforms: Establish the drug research supervision and management information platforms.

Future objective: To establish the scientific, complete electronic registration supervision and management systems
International Exchange and Cooperation
International Exchange and Cooperation

Sino-US
- FDA exchange
- Generic Drug Forum
- Conference under JCCT framework
- BIO Chinese Annual Meeting

Sino-Japan and Korea
- Seoul Conference

Sino-Japan
International Exchange and Cooperation

ICH

- APEC
- ICH Chinese Study Team

WHO Vaccine Pre-authentication

- Vaccine pre-authentication
- System authentication

IRCH  FHH
About the Work of ICH Chinese Study Team

- Formulated work specifications
- Regular work meetings
- Positive advancements:
  - Publication of the translated version of ICH guidelines
  - Expanded study team members
  - Completed logo design of ICH Chinese Study Team
  - Established research achievement online disc
  - 2010 Annual Report