Research on the Administrative Rules of APIs, Pharmaceutical Excipients and Auxiliary Materials Master File

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Translation version

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The necessity and purpose of establishing a master file system

A comparison between domestic and foreign regulation modes

- Typical foreign regulation mode for APIs, pharmaceutical excipients and auxiliary materials
  - A more mature system is in place;
  - No administrative registration & approval system is implemented;
  - A DMF system is adopted;

* The technical secrets of PRAMs can be kept secret from pharmaceutical businesses;
* Repeated declarations are minimized;
* Implementation is not on a mandatory basis;
* U.S. and European drug regulatory authorities recommend that both the PRAMs and the resultant pharmaceutical preparations be declared together;
* Links to preparations: reviews, production, etc.;

A comparison between domestic and foreign regulation modes

➧ Domestic regulation mode for APIs, pharmaceutical excipients and auxiliary materials

➔ An administrative registration & approval system is adopted in most cases;

* Without exception, all active pharmaceutical ingredients (APIs) and packing materials first get registered for further examination and approval, and when approved, are then given a numbered approval document;

- Provisions 102 and 52 of the Drug Administration Law of the People‘s Republic of China

* Without exception, all herbal extracts and auxiliary materials first get registered for further examination and approval, and when approved, are then given a numbered approval document;

- Provision 11 of the Drug Administration Law of the People's Republic of China

A comparison between domestic and foreign regulation modes

- Domestic regulation mode for APIs, pharmaceutical excipients and auxiliary materials
- Existing defects

* Pharmaceutical preparation producers lack the awareness as the top-tier entities in the accountability system to hold themselves accountable for any problems with their products, which in turn leads to a weak initiative among them to audit the quality of the APIs, pharmaceutical excipients and auxiliary materials;
* Drug supervision & administration authorities lack necessary support in terms of data and information and any supervision and inspections they conduct are poor in traceability and regulatory efficiency;
* The scopes of responsibility are not clearly defined for drug supervision & administration authorities, pharmaceutical preparation producers, and PRAM producers, and as a result, drug supervision & administration authorities shoulder some of the responsibility that should otherwise be undertaken by enterprises;

The meaning and importance of establishing a master file system

- Conduct full demonstration to explore the right regulation mode. Learn from advanced foreign regulation modes and experience, and define regulatory requirements that are consistent with China‘s actual situation, with a view to solving the existing defects of the current regulation mode;
- Clearly define the scope of responsibility for every entity involved, and inform each business of its responsibility. Make efforts to enhance the awareness of pharmaceutical preparation producers as the top-tier entities in the accountability system to hold themselves accountable for any problems with their products;
- Provide enough information to ensure sound traceability and extend regulatory reach. Provide data and information required for drug production and postmarket surveillance, so as to ensure good traceability in regulation and improve regulation efficiency;
- Improve review and approval efficiency. Improve review and approval efficiency by linking drug registration to review and approval;

The main guidelines

★ Stick to a scientific regulatory philosophy, analyze and learn from others' experience, and by taking the actual facts into account, formulate a highly operable master file system that bears unique Chinese characteristics;

★ Stick to regulation by the law, comply with laws like the Drug Administration Law of the People's Republic of China, and adopt a system in which an administrative registration & approval system exists in tandem with a master file system (a dual system);

★ Stick to the rule by which pilot sites are made to take the lead in the implementation, an approach featuring choosing several points at first for an implementation later on a full scale as well as gradual, step-by-step progress, so as to ensure work quality;

★ Stick to proper upgrading of the information system as well as matching it with other systems, so as to truly realize a regulatory system that is supported by data and information systems, enable sharing of resources and enhance regulatory efficiency;

The process of drafting the "The Administrative Rules of APIs, pharmaceutical excipients and auxiliary materials Master File"

- The drafting initially started in 2008 and public comments were solicited from October 15 through October 30, 2010;
- The drafting group consists of people from the following entities under the State Food and Drug Administration (SFDA): Department of Policy & Regulations, Department of Drug Registration, Department of Drug Safety & Inspection, Center for Drug Evaluation, National Institute for the Control of Pharmaceutical and Biological Products, Chinese Pharmacopoeia Commission;
- Several symposiums were held for people from pharmaceutical producers, R&D institutions, industry associations, provincial offices, etc., including representatives of foreign enterprises and RDPACD member companies;
- Onsite investigations were carried out in Jiangsu, Shandong, Zhejiang and other regions;
- The status quo of the regulation of APIs, pharmaceutical excipients and auxiliary materials in China was understood;
- The necessity and possibility of establishing a master file system for APIs, pharmaceutical excipients and auxiliary materials in China was demonstrated;
- The mode of and the requirements for the regulation of master file were analyzed and evaluated;
- A draft for comments was created;

Proposed arrangements under the current regulatory framework

Main contents

- 6 chapters, 32 provisions
- General
- Basic requirements
- Submission and alteration of the material intended for putting on record in the master file system
- Utilization of on-record information
- Management of on-record information
- Supplementary provisions

Description of the process of putting APIs, pharmaceutical excipients and auxiliary materials on record

It is a process in which, through a platform set up by drug administration authorities for putting APIs, pharmaceutical excipients and auxiliary materials-related information on record, a producer of any APIs, pharmaceutical excipients and auxiliary materials that is used either in the registration of a pharmaceutical preparation or in the manufacture of a pharmaceutical preparation already approved for release to market, submits required information about that APIs, pharmaceutical excipients and auxiliary materials according to relevant requirements.

Materials to put on record

- API
- Herbal extracts
- Pharmaceutical excipients
- Packaging materials and containers that come in direct contact with the drug

Scenarios demanding an initiation of the master file procedure

- APIs, pharmaceutical excipients and auxiliary materials used in the registration of a pharmaceutical preparation
- APIs, pharmaceutical excipients and auxiliary materials used in the manufacture of a pharmaceutical preparation already approved for release to market

Parties supposed to initiate the master file procedure

- Producers
- Domestic
  * Legitimate APIs, pharmaceutical excipients and auxiliary materials producers
- Overseas
  * Chinese offices of legitimate overseas businesses
  * Chinese agencies authorized to act on behalf of legitimate overseas businesses

Method of master file

- Submitting through the master file platform

Information to put on record

- Basic information: Company name, etc.
- The production process and quality control-related information
  - Starting materials, intermediates
  - Manufacturing process
  - Quality specification
  - Test Method, etc.

The master file system is not implemented as a mandatory or an approval system

- It is not intended as a mandatory system;

→ A APIs, pharmaceutical excipients and auxiliary materials producer can elect to put its APIs, pharmaceutical excipients and auxiliary materials on record at will;

- It is not intended as an approval system either;

Drug supervision and management authorities do not separately audit on-record information submitted by the information platform for master file of APIs, pharmaceutical excipients and auxiliary materials;

Master file of APIs, pharmaceutical excipients and auxiliary materials is correlated with the submission of pharmaceutical preparations for approval

- The declaration, registration and production of a preparation

★ Submit declarations in accordance with relevant provisions;

★ Submit the record status and on-record numbers of APIs, pharmaceutical excipients and auxiliary materials;

★ A preparation will not be accepted should its APIs, pharmaceutical excipients and auxiliary materials have not been put on record;

★ APIs, pharmaceutical excipients and auxiliary materials used in the production of pharmaceutical preparations shall always be consistent with their original on-record information;

★ Should a pharmaceutical preparation producer find in auditing a APIs, pharmaceutical excipients and auxiliary materials that the actual situation does not match with the on-record information, it should take the initiative to stop using that PRAM when filing its registration applications for pharmaceutical preparations or using it in production;

★ The registration application and production of pharmaceutical preparations must refrain from using PRAMs whose records have been revoked;

Master file of APIs, pharmaceutical excipients and auxiliary materials is correlated with the declaration of pharmaceutical preparations

- Putting APIs, pharmaceutical excipients and auxiliary materials on record
  - master file only applies to APIs, pharmaceutical excipients and auxiliary materials used in the registration of preparations or in the manufacture of pharmaceutical preparations already approved for release to market;
  - APIs, pharmaceutical excipients and auxiliary materials for the manufacture of pharmaceutical preparations already approved for release to market can be filed within the time specified, and information about use of such materials shall be provided during the filing;
  - APIs, pharmaceutical excipients and auxiliary materials that are to be used for the first time for a pharmaceutical preparation can be filed within 20 days after an application has been submitted for the registration of that preparation;

The division of duty and responsibility among various parties

- General principles

→ The purpose of implementing a master file system for APIs, pharmaceutical excipients and auxiliary materials is by no means to impair the regulation of APIs, pharmaceutical excipients and auxiliary materials;

→ The implementation serves to more clearly clarify the relationships between drug administration authorities, pharmaceutical producers and APIs, pharmaceutical excipients and auxiliary materials producers and their respective responsibilities, so as to form a sound cycle;

The division of duty and responsibility among various parties

- APIs, pharmaceutical excipients and auxiliary materials producers

★ Submit required information to be put on record;

★ Hold themselves responsible for the authenticity of the data to be put on record;

★ Implement quality control over the starting materials, intermediates, the production process , and other aspects;

★ Audit all starting materials and intermediates purchased from external sources, and submit an audit report as part of the full set of information to be submitted for putting on record;

★ Enter into contracts with pharmaceutical preparation producers and accept audits by such producers under such contracts;

★ Should alterations occur, conduct necessary research and demonstration, change the on-record information and promptly notify the affected pharmaceutical preparation producers;

★ Accept supervision and inspections by drug administration authorities;

The division of duty and responsibility among various parties

- Pharmaceutical preparation producers that use APIs, pharmaceutical excipients and auxiliary materials
  - Perform full research and demonstration on the selected APIs, pharmaceutical excipients and auxiliary materials;
  - In applying for the registration of the preparation, submit related information on related APIs, pharmaceutical excipients and auxiliary materials (via Web links);
  - Keep abreast of changes that occurred to the APIs, pharmaceutical excipients and auxiliary materials, and carry out research on and a demonstration of the drug preparation before applying for its alteration;
  - Sign contracts with APIs, pharmaceutical excipients and auxiliary materials producers;
  - Audit PRAMs used for registration and production (with related starting materials and intermediates included if necessary);
  - Should problems occur in an audit, take the initiative to stop using the affected PRAMs in the application for registration of the preparation and in the production of that preparation;
  - Accept supervision and inspections by drug administration authorities;

The division of duty and responsibility among various parties

- **Evaluation process**
  - **Information on the APIs, pharmaceutical excipients and auxiliary materials intended for putting on record shall be submitted, as inseparable part of the full set of information to be submitted for the registration of the related preparation, for a joint review;**

The division of duty and responsibility among various parties

- Drug administration authorities

→ **In supervising and inspecting pharmaceutical preparations already approved for release to market, drug supervision & administration authorities shall carry out inspections, based on the on-record information, such that the APIs, pharmaceutical excipients and auxiliary materials used can be traced to their sources;**

Regulation of intermediates

- Incorporate it into the regulation of APIs, pharmaceutical excipients and auxiliary materials;

★ Make sure that information on intermediates is incorporated into a larger collection of information, to be submitted for declaration purposes, that also includes the on-record information on the APIs involved;

- Quality auditing

★ Applicants for use of APIs, pharmaceutical excipients and auxiliary materials shall audit related intermediates;

★ If necessary, pharmaceutical preparation producers shall also audit any intermediates involved;

Building an information platform

- SFDA is to build a platform;
- SFDA and its branches at the provincial level are to implement hierarchical regulation;
- The Center for Drug Evaluation is responsible for maintaining the information platform;

Making public the on-record information

- Release basic information to the public so that people can make queries through the Internet;
- Technical information should be categorized and made public
  - APIs, pharmaceutical excipients and auxiliary materials producers authorize related preparation producers to publicize relevant information;
  - Available content for query shall be determined, in a case-by-case manner, according to the principle of local control over locally defined content, and based on the level of the queried authority and its position in the surveillance hierarchy;

Cancellation of on-record information

- In case drug administration authorities find in their supervision and inspection any misconduct in connection with APIs, pharmaceutical excipients and auxiliary materials, the on-record information about the affected APIs, pharmaceutical excipients and auxiliary materials as well as its on-record number shall be revoked such that any attempt by the enterprise to put its APIs, pharmaceutical excipients and auxiliary materials on record will be rejected within 5 years;
- In case the on-record information on any APIs, pharmaceutical excipients and auxiliary materials has no links to any preparation, it shall be written off accordingly;

Steps taken to ensure step-by-step, steady implementation

Steps taken to ensure step-by-step, steady implementation

- The Text and the related Guides to master file are to be published separately;
- Launch pilot work at selected regions;
- Launch publicity and training work;

Publishing the Text and Guides to master file separately

- It is planned that the Text will be published singly, with the declaration requirements for various types of APIs, pharmaceutical excipients and auxiliary materials treated as no attachments to the Text and excluded from the publication;
- After the Text is published, declaration requirements for APIs, packaging materials, auxiliary materials, herbal extracts and drug intermediates will be published one by one as Guides to master file;

Launching pilot work

- Launch pilot work at selected regions according to the types of APIs, pharmaceutical excipients and auxiliary materials;
- Launch pilot work at selected regions where a relatively large number of APIs, pharmaceutical excipients and auxiliary materials producers exist;

Publishing the Text and Guides to master file separately

- Rationale
  - master file depends on information systems and needs to be properly designed and constantly fine-tuned;
  - Different types of APIs, pharmaceutical excipients and auxiliary materials present different requirements, which makes it feasible to publish requirements for APIs, pharmaceutical excipients and auxiliary materials on a one-by-one basis;
  - This approach will be beneficial to the carrying out of the pilot work at selected sites;
  - It will be beneficial to the continuous accumulation of experience and help gain more room for continued improvement;

CTD-format application material for chemical drugs

- Released on September 25, 2010
- **To improve the quality and the level of excellence in our country's drug research and development and as a result catch up with international standards gradually, SFDA organized the development of the "Compilation Requirements for the Application Material in CTD Format for Chemical Drugs," on the basis of the Common Technical Document (CTD) of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceutical for Human Use, and by taking into consideration the actual situation of China's drug research and development.**

CTD-format application material for chemical drugs

- With respect to the pharmaceutics portion of the declaration material, which is governed by Annexes 2 (regarding the classification of chemical drug registration), 3, 4, 5 and 6 (regarding production, registration, application) to the “Provisions for Drug Registration,” preparation and submission shall be carried out by referring to the CTF format released in print, and an electronic version of that portion also needs to be submitted at the same time. The pharmaceutical information in applications for clinical trials shall not be submitted in CTD format for the time being.

CTD-format application material for chemical drugs

- The clinical trial application and registration production application for chemicals in 1 and 2 Classification of Annex 2 to the Provisions for Drug Registration shall not be submitted in CTD format for the time being.

CTD-format application material for chemical drugs

- To encourage the submission of application data in CTD format and steadily push forward this work, the following ways are to be taken now.
- The application material for registration and production, which is submitted in conformity to the requirements of Annex 2 to the “Provisions for Drug Registration,” will still be received.
- Technology review departments will evaluate the application material for registration and production submitted in CTD format separately in sequence.

Actively launch training and publicity work

- The discussion of the new models of drug administration, which are different from the approval system, is absolutely necessary to the pre-implementation publicity, and the training during the implementation process ;
- Pharmaceutical preparation producers, APIs, pharmaceutical excipients and auxiliary materials producers, and drug administration authorities shall fulfill their respective duties and work together to achieve the desired objectives;

Differentiated timing in implementation

- APIs, pharmaceutical excipients and auxiliary materials used in the registration of a pharmaceutical preparation;
- APIs, pharmaceutical excipients and auxiliary materials used in the manufacture of a pharmaceutical preparation already approved for release to market;

It is feasible to initiate the master file procedure within the specified time, and in putting a APIs, pharmaceutical excipients and auxiliary materials on record, it is necessary to provide information about the use of pharmaceutical preparations that use that APIs, pharmaceutical excipients and auxiliary materials.

Thank you!