To Establish A DMF System In China – A Proposal By RDPAC

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On Behalf of

RDPAC DMF Task Force

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Outline

- DMF Development in China
  - RDPAC's Efforts to Support Establishing a DMF System
  - SFDA's Draft DMF Regulation
    - Key Points of Draft Regulation
- RDPAC Proposal for DMF in China

RDPAC's Efforts to Support DMF

- Discussed DMF systems in US/EU with SFDA (Nov 2008)
- RDPAC formed DMF Task Force
  - Prepared and submitted industry proposals (Dec 2009)
  - Pursued and held a roundtable discussions with SFDA (Mar 2010)
  - Prepared and submitted major concerns to SFDA (Apr 2010)
    - *Potential significant impacts if a filing is required for each of the components in a drug product submission*
  - Submitted comments on the draft DMF regulation to SFDA (Oct 2010)

* RDPAC: R&D-based Pharmaceutical Association Committee

SFDA's Draft DMF Regulation

- SFDA issued an official draft "Regulation for Filing of APIs and Pharmaceutical Auxiliary Materials" for commenting
  - 《药用原辅材料备案管理规定》征求意见稿 Sept 19, 2010
- This proposed filing system would regulate submission, amendment, use and management of information about APIs, TCM extracts, excipients and packaging materials to be used in drug products.
- Requirements for the contents in DMFs of different types of materials will be issued separately

SFDA's Draft DMF Regulation

- This draft regulation is intended to
  - Reinforce the understanding that a drug product manufacturer are responsible for its drug quality;
  - Clarify the responsibilities and obligations between the manufacturers of drug products and the suppliers of APIs and pharmaceutical auxiliary materials;
  - Integrate and enhance the regulatory information of marketed products.
  - Aim to enhance the assurance of drug product quality and traceability of all components in a drug product, in addition to protect proprietary information.

Key Points of Draft Regulation

- DMF has open/closed parts and can use CDT format.
- A number will be assigned to a DMF after its filing is completed.
- Information in the filed DMFs will be kept confidential by the regulatory authorities.
- A filed DMF will not be reviewed until it is linked to a drug product registration application that refers to the DMF.
- For APIs and primary packaging materials, novel excipients and excipients to be used in injection, both registration and filing of DMFs will be required.

Key Points of Draft Regulation

- For APIs and pharmaceutical auxiliary materials used in drug products that are under registration, their DMFs should be filed within 20 days of the submission of the referring drug product applications.
- For APIs and pharmaceutical auxiliary materials used in drug products that are already approved for marketing, their DMFs should be filed within specified time frames.
- For a drug product registration application, DMF filing status and DMF #'s should be provided.
- Drug product manufactures are responsible for auditing suppliers' qualifications and quality systems.

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RDPAC Proposal for DMF in China

- Open/Closed Parts
  - DMF should contain the open and closed parts, both of which are submitted by DMF holders to SFDA
  - DMF holders should provide the open parts to the applicants of new drug, generic drug and imported drug (including international multi-centered clinical trial) applications.
  - The applicants do not need to resubmit the open parts.

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- Optional/Mandatory
  - Optional
  - For those that have been approved and registered with SFDA, they should not be required to switch to DMF
- Approval Status
  - Neither approved nor disapproved
  - After a DMF is found satisfactory upon review, only administrative information should be announced in the CDE website.
    - i.e., DMF #, DMF holder/manufacturer and name of the submission (e.g., API and intermediate chemical names, etc.
  - Information contained in the open parts of a DMF should not be disclosed to the public

RDPAC Proposal for DMF in China

- Multiple Manufacturing Sites/Processes
  - Should allow one DMF to cover
    - multiple manufacturing sites
    - alternative manufacturing processes
  - This will reduce regulatory burden for the industry while save review resources for SFDA
- Multiple Specifications
  - When risks are manageable, it should be acceptable to allow one DMF to contain more than one specifications suitable for different intended uses if appropriate
    - e.g., one API specification with particle size control and another without particle size control)
  - This risk-based approach can reduce the regulatory burden for the industry while save review resources

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- Variation/Supplement/Revision
  - DMF holder to amend the DMF and notify each of the affected new drug, generic drug and imported drug (including international multi-centered clinical trial) applicants, who then submit variation applications to cross-reference to the DMF amendment.
- Maintenance Responsibility
  - A DMF holder should provide annual report to CDE, which describes changes to a DMF and authorized usage of a DMF. CDE may terminate a DMF if its DMF holder fails to provide annual report for two consecutive years.

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- Communication of Deficiencies
  - Specific deficiencies should be communicated between CDE and the DMF holder.
  - Applicants referring to DMFs are informed only with general information regarding deficiencies by CDE.
- Sample Testing
  - Sample testing by SFDA is unnecessary.
    - DMF holders are responsible for their products to meet appropriate quality requirements
    - The applicants referring to DMFs are responsible for ensuring that those products by DMFs are appropriate for their intended uses.

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- Remarks
  - Information about the various components of a drug product may be submitted (optionally) in the format of DMFs to support review, approval and management of the post approval changes of the drug product.
  - DMF system is still under development. Suggest that a DMF system be rolled out in a staged manner for different types of materials, e.g., novel excipient, API and intermediate.

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- Remarks
  - It is important to consider potential practical problems that may be encountered when using DMF to establish an information management system for APIs, intermediate, excipients and packaging materials.
  - It is necessary to use science/risk based approaches when establishing such a system to ensure regulatory oversight of the drug product quality while retaining regulatory flexibility when associated risks are manageable, for example, excipients.

RDPAC DMF Task Force

- Bayer
- BMS
- GSK
- Novartis
- Pfizer
- Xian-Janssen

Thank You!

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- Back Up Slides

Submission Trigger

- There should be no restriction for filing a DMF. DMF including new chemical entity (NCE) can be filed independent of a drug product application for new drug, generic drug or imported drug (including international multi-centered clinical trial).

Submission Status

- To protect proprietary information contained in a DMF, only administrative information, i.e., DMF #, DMF holder/manufacturer and name of the submission (APIs and intermediate chemical names, etc.) should be listed on SFDA website (or the website of an organization designated by SFDA, e.g., CDE) after a DMF is accepted.
- Open part information is shared only among DMF holder, DMF user and SFDA (or an organization designated by SFDA, e.g., CDE), and should not be disclosed to the public.

Review Trigger

- Submission of an application for new drug, generic drug or imported drug (including international multi-centered clinical trial), which has a letter of authorization for referring to a DMF.
- A DMF already reviewed will not be reviewed again for a new cross- reference unless it is scientifically warranted for its application in a referenced application for new drug, generic drug, or imported drug (including international multi-centered clinical trial).

Single Submission/Cross-references

- Single DMF submission is sufficient.
  - May be referenced by multiple applications for new drug, generic drug, and imported drug (including international multi-centered clinical trial) by applicants if authorized.

Reference to Multiple DMFs

- Should allow an application for new drug, generic drug or imported drug (including international multi-centered clinical trial) to reference to multiple DMFs for a single item (e.g., an API).

Confidentiality

- For the entire DMF, between the DMF holder and CDE.
- For the open parts of a DMF, between the DMF holder and the new drug, generic drug or imported drug (including international multi-centered clinical trial) applicant.
  - Open parts should not be disclosed to the public.