What Is a Model Master File and How Can It Be Shared?

2021 CRCG PBPK Workshop: Regulatory Utility of Mechanistic Modeling to Support Alternative Bioequivalence Approaches

Day 2, Session 4: Model Acceptance and Model Sharing for Regulatory Use

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Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

The presenter is offering his perspective based upon his experiences during regulatory decision-making

What is Drug Master File (DMF)?

- Provide confidential, detailed information about facilities, processes, or articles used in the manufacturing, packaging, and storing of human drug products. DMFs
  - Allow parties to reference material without disclosing DMF contents to those parties
  - Are not required by statute or regulation
  - Are neither approved nor disapproved. Instead, FDA reviews the technical contents of DMFs in connection with the review of applications that reference them (e.g., NDAs, ANDAs, INDs, BLAs)
- Types of DMFs
  - Type II Drug Substance, Drug Substance Intermediate, and Material Used in Their Preparation; or Drug Product
  - Type III Packaging Material
  - Type IV Excipient, Colorant, Flavor, Essence, or Material Used in Their Preparation
  - Type V FDA-Accepted Reference Information

https://www.fda.gov/drugs/forms-submission-requirements/drug-master-files-dmfs
Draft Guidance for Industry: Drug Master Files (October 2019) https://www.fda.gov/media/131861/download

DMF Characteristics

- DMF holders “can authorize one or more applicants or sponsors to incorporate reference information contained in the DMF without having to disclose that information to the applicants or sponsors”
- DMFs are reviewed “in connection with the review of applications that reference them”
- DMF does not need to be re-reviewed for subsequent applications unless DMF has been modified since last assessment
- A DMF can include the proprietary information about synthetic chemistry process to produce a drug substance and then subsequent purification steps

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Benefits to Formalize Model File Sharing

- Public awareness on
  - Utilities of relevant models
  - Regulatory acceptance on certain models
  - How to sufficiently verify and validate (V&V) a model for regulatory use
- Model recycling for the same purpose and cost saving on model duplication
- Model standardization across different types – model building and model V&V
- Potential data sharing when situation allows
- Advancing model from “master” models
- Knowledge/Platform sharing to overcome common challenges

What Types of Models Need Model Master File?

- Models (1) with challenging-to-get/proprietary information and/or (2) that need large datasets from other sources to verify and validate may benefit from having Master files
  - Physiologically based PK models (PBPK)
  - Systems pharmacology
  - Mechanistic in vitro-in vivo correlation models
  - Other types of mechanistic models
- Models that can be easily duplicated from scientific publications may not necessarily need Master Files
  - Population Pharmacokinetic (PK)
  - Exposure-response analysis
  - Pharmacokinetics-Pharmacodynamics (PK-PD) relationships

Mechanistic Models in ANDAs

- Commercial vs. in-house modeling packages:
  - Oral and dermal PBPK and inhalation SERDM - commercial packages
  - Inhalation PBPK or compartment-based models – in-house
  - Computational Fluid Dynamics – commercial and in-house software

- Modeling purpose:
  - Address aberrations with in vitro, pharmacokinetic (PK), or comparative clinical endpoint (CCE) bioequivalence (BE) studies
  - Waive follow-up study
  - Provide alternative BE approaches in lieu of CCE BE study

- Regulatory use: One example of generic approval – ANDA 211253 for diclofenac sodium topical gel

Characteristics of a Model Master File

- Has explicit regulatory purpose
- Has received regulatory acceptance for the purpose
- Includes all technical details
  - Data/software/platform
  - Scope of use
  - Model building
  - Model V&V
  - Simulated results
- Includes modeling and simulation practices that can be duplicated, cross-referenced, and inter/extrapolated within the scientific scope of use

Announcing and Hosting Model Master Files

- Entities that can potentially play the role:
  - The agency
  - The pharmaceutical industry
  - The consulting firms
  - Academic/professional journals
  - Dedicated function of potential organizations
    - Separate model hosting from model developing roles
- Will there be a fee involved?
  - Open access
  - Pay for service

How to Share a Model Master File?

- Conventional ways
  - Conferences
  - Publications
  - On-line scientific community (User groups and social media)
  - Consulting
- Other potential venues
  - Review documentation/Recognition
  - Agency sponsored website/database?
  - Dedicated journal/journal section?
  - Consortium/organization sponsored database?

Potential Questions

- Can we just share part of the model?
  - What is the part that can be shared?
- How to deal with proprietary information?
- What are the legal implications?
- How to reconcile with Commercial interest?

Need Inputs from the Panel

- What is a model master file (key elements)?
- How to qualify a model master file?
  - What is the process flow?
  - Who have the authority?
- How to share a master file?
- Who to host the master file?


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