Regulatory Perspective: Challenges and Opportunities to Enhance Model Sharing upon Regulatory Use

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

Mechanistic Models in ANDAs

- DQMM consulted on ANDAs with mechanistic modeling for bioequivalence (BE) purposes
- DQMM generally consulted for additional assessment of modeling-based BE approaches/justifications
- Types of products involved: oral IR and ER products (40%); topical products (10%); and MDIs (orally inhaled) (50%)
- Types of modeling (from most to least): oral PBPK; inhalation CFD; inhalation "PBPK"; inhalation SERDM; inhalation aerosol evaporation modeling; and dermal PBPK
- When modeling developed: ad-hoc (i.e., integrated into overall BE approach) (50%); post-hoc (i.e., conducted to address Complete Response deficiencies) (50%)

(cont'd on next)

IR = immediate release ER=extended release
MDI = metered dose inhaler PBPK = physiologically based pharmacokinetic [model]
CFD = computational fluid dynamics SERDM = semi-empirical regional deposition model

Mechanistic Models in ANDAs

- Commercial vs. in-house modeling packages:
  - Oral and dermal PBPK and inhalation SERDM - commercial packages
  - Inhalation PBPK or compartmental-based modeling – in-house
  - CFD – commercial and in-house software

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

- Modeling outcome: one example – approval of ANDA 211253 for diclofenac sodium topical gel

Tsakalozou, Eleftheria, Andrew Babiskin, and Liang Zhao. "Physiologically-based pharmacokinetic modeling to support bioequivalence and approval of generic products: A case for diclofenac sodium topical gel, 1%." CPT: Pharmacometrics & Systems Pharmacology (2021).

Mechanistic Modeling in pre-ANDAs

- Purpose: alternative BE approaches for complex generic products in lieu of in vivo PK or CCE BE studies; also address challenges in comparison of in vitro BE study results between test (T) and reference (R) or validate new clinical endpoint

- Pre-ANDA space (including CC) has greater activity in terms of modeling than in ANDA space currently:
  - Dermal (44%)
  - Inhalation DPI, MDI, and spray (40%)
  - Implant (8%)
  - Ocular (4%)
  - Complex injectable (4%)

- Great diversity in inhalation modeling approaches

- We've also seen attempts to model PLGA erosion and rabbit-to-human extrapolation in eye tissue

PDEV = pre-ANDA product development meeting; CC = controlled correspondence
DPI = dry powder inhaler; PLGA = poly(lactic-co-gycolic acid)

Common Assessment Approach

- Quality of data used for model development and V&V activities
- Are justifications scientifically sound? Is parameter selection/optimization appropriate? Have all **A**DME processes been considered?
- For BE purposes, how are T and R defined in the model? Is that appropriate? How are T and R compared, including statistical approach?
- In validation cases, how well is PK data being predicted?
  - Includes platform performance assessment
- Additional model validation – literature search or in-house
- Population – healthy vs. patient?
  - When used for virtual BE
  - When used for model validation

V&V: verification and validation
ADME: absorption, distribution, metabolism & excretion

Common Modeling Challenges

- Lack of clearly defined purpose for the model
- Lack of consideration for how to interpret simulation results
- Inadequate model V&V or lack thereof, for example:
  - Model development only on R or R+T
  - Repurposing of literature/published model
  - Commercial model/platform without clear V&V and/or lack of published case studies
- Lack of cross-talk between in vitro data and model developers – assumptions or model input conflict other parts of ANDA submission

Platform Performance Assessment

Basic Principles

- PBPK Platform: a system of databases and differential equations defining movement of drug through ADME processes defined by anatomy and physiology
- Platform credibility is independent of the proposed implementation of that platform for a specific drug product
- A sufficient number of drug compounds/products ranging in physiochemical and PK properties with observed outcomes predicted with adequate precision
- Should not only include compounds/products used for platform development

Derived from:
Zhao, L., Seo, P., and Lionberger, R. *CPT: pharmacometrics & systems pharmacology* 8.6 (2019): 347
Tsakalozou, E., Alam, K., Babiskin, A., and Zhao, L. CPT (2021), https://doi.org/10.1002/cpt.2356

Platform Performance Assessment

Essential questions during regulatory use

- Who is responsible party? Platform developer, ANDA applicant, FDA
- Independent platform developer:
  - Verify platform for a specific purpose?
  - Only provide modeling framework for other stakeholders to use and verify on their own?
- ANDA applicant:
  - Can a published or commercial model be used directly off-the-shelf?
  - Independent platform performance assessment activities need to be performed?
  - How much confidence does FDA have in use of the platform?
- FDA:
  - Does platform assessment have to be performed for every case?
  - How much internal knowledge should be leveraged?

Hypothetical example

<u>Commercial platform</u> developed for toxicology/safety assessments of orally inhaled compounds; repurposed for comparison of regional deposition

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Why is Model Sharing Beneficial?

- Rule of Parsimony: all parties (regulatory and industry) want to optimize time and resources by minimizing unnecessary or redundant work
- If (1) FDA is already confident in use of a platform for a specific purpose and (2) this has been communicated externally,
  - Does Applicant need to expel resources to “re-verify” a platform?
  - Does Agency have to reconsider platform assessment with every application?
- Even deeper, if model developed for specific compound, does model V&V need to occur again if on same platform for a different ANDA?
- Can commercial developers provide platform verification data directly to the FDA, particularly if the platform development and verification package includes proprietary data not shareable with its users?
- Of upmost importance that everyone using a model (including regulatory decision-makers) have detailed information about development and verification of a modeling platform or model

Challenges with Model Sharing

- Are critical data needed for model/platform development and V&V siloed with specific entities?
- When shared, what elements need to be included for the model to be “reusable”?
- Where can the model be accessed?
- Versioning: managing not only multiple versions of the same model but the implementation of the model in software as the software gets updated

Take Home Message

- Opinions/ideas today are my own from past experiences as a regulatory assessor.
- Science is universal and mechanistic models are reflections on our current knowledge of a specific area.
- Knowledge is not the domain of a single entity – all entities are responsible parties.
- Sharing of knowledge/models will only drive the technology forward faster and see more increased presence in regulatory decision-making on generic drug approval.
- Universal goal is for faster product development time, reduced developmental cost, and reduced clinical testing in human subjects.


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