Challenges for Industry in Implementing New Computational Methods that Arise from Regulatory Science Initiatives

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FY 2019 Generic Drug Regulatory Science Initiatives Public Workshop

Silver Spring, MD

May 1st, 2019

Disclaimer

- The views and opinions presented here represent those of the speaker and should not be considered to represent advice or guidance on behalf of the U.S. Food and Drug Administration

Examples of New Computational Methods from Research

- In vitro BE methods such as the earth mover distance (EMD) method
- In vivo approaches
  - Dose scale analysis
  - Emax models
- Virtual BE simulations based on
  - Population based PK-PD/exposure-response models
  - Mechanistic models including PBPK models

Case I (Pre-ANDA Meeting): PBPK Analysis to Support an Alternative BE Approach

Product X, metered aerosol

Background: An alternative BE approach was proposed, including the in vitro tests and PK studies, but no comparative clinical endpoint study. The firm provided predictions from computational fluid dynamics (CFD) and PBPK models, along with data from additional in vitro tests to justify their approach.

Question: Is the proposal to eliminate the PD study acceptable, in light of additional PK study and modeling results?

Impact: With sufficient model verification, the PBPK modeling approach can be used as part of the evaluation as to whether the in vitro and PK studies provide evidence of locally delivery equivalence.

Case II (ANDA Review): PBPK Modeling to Support BE Evaluation for a Locally Acting Product

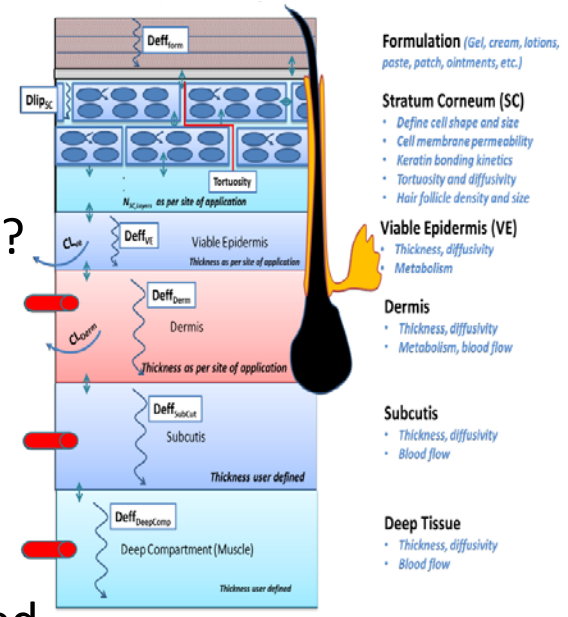
Product Y, Topical Gel for topical treatment

Background: The applicant proposed an alternate approach for the BE evaluation which includes Dermal PBPK as part of support of not conducting a comparative clinical endpoint study with a Q1/Q2 and Q3 similar formulation.

Question: Is the proposed alternate BE approach acceptable?

Impact:

- The PBPK model helped us understand the systemic to local link and supported the proposed alternative approach.
- In vivo PK BE study supported the BE assessment and product approval without conducting a PSG recommended comparative clinical endpoint BE study.



What Can Be Improved in These Submissions

- Proper documentation of the entire model development process
  - A list and justification of model assumptions needs to be provided
- Literature and other data sources utilized for model development and verification need to be properly and accurately cited
- The rationale behind the various decisions made during model development need to be clearly stated and supported by scientific evidence
- Verification standards need to be stated at the initiation of the model verification process and applied throughout
- Incorporation of quality attributes for the drug products of interest is an important component of the model structure
  - when these are not available, the selection of parameter values needs to be justified
- For locally acting products
  - Need to compare model-predicted drug concentrations in the local tissues with experimentally obtained values when available in addition to assessing model performance at the systemic exposure level
  - Incorporation of compounds with local, in addition to systemic, experimental data into the verification plan is desirable

Challenges to Implement Methods in Industry

- Lack of initiative and/or awareness
- Lack of resources, investment, and convention in generic firms
- Inverse relationship between method complexity and standardization
- Underdeveloped eco-system between agency and industry for quantitative methods and modeling development and communication

Features of an Ecosystem

- Initiatives for method development and implementation from both ends
- Timely scientific exchanges
- Multiple sources for software implementation
  - Open source versus commercial implementation
- External expertise available for hire
- Internal industry experts
- Application specific discussion venue
  - GDUFA II Pre-ANDA meeting
- General issue discussion venues
  - Meetings and workshops with FDA participants

Questions for the Panel

- What can FDA do to grow the ecosystem?
  - Publications
  - Guidance on PBPK model verification
  - Conferences/workshops
  - Code sharing
- We are seeking your input on which of these are most critical to address

Acknowledgment

Office of Generic Drugs

- Office of Research and Standards (ORS)
  - Robert Lionberger
  - Lei Zhang
- ORS/ Division of Quantitative Method and Modeling, Office of Research and Standards
  - Myong-Jin Kim
  - Lanyan (Lucy) Fang
  - All Scientists in DQMM
- ORS/Division of Therapeutic Performance
- Office of Bioequivalence

Office of Translational Sciences

- Office of Clinical Pharmacology
  - Shiew-Mei Huang
  - Issam Zineh
- Office of Biostatistics

Office of Product Quality

- Division of Biopharmaceutics, Office of New Drug Products
  - Paul Seo

Office of New Drugs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