Quantitative Medicine Innovations in the Generic Drug Program

Robert Lionberger
Director, Office of Research and Standards
Office of Generic Drugs
April 25, 2024

FDA Virtual Workshop entitled Streamlining Drug Development and Improving Public Health through Quantitative Medicine: An Introduction to the CDER Quantitative Medicine Center of Excellence

History of Modeling & Simulation in the Generic Drug Program

- Modeling and simulation critical to advances in bioequivalence (BE) science for systemically acting drugs (2003-2013)
  - Partial AUC, narrow therapeutic index drugs, highly variable drugs
- In 2014, OGD includes a Division of Quantitative Methods and Modeling (DQMM) in its reorganization

Core DQMM Teams

- Locally Acting Physiologically Based Pharmacokinetic (PBPK) Team
  - Mechanistic models for Topical, Inhalation, Nasal, Ophthalmic, Implantable routes
- Quantitative Clinical Pharmacology Team
  - Pharmacometrics models for bioequivalence studies
  - PK/PD and exposure response analysis for generic drug applications
- Oral Absorption Modeling Team
  - Models of the GI tract and drug absorption for systemic and locally acting drugs
- Data Science and Machine Learning Team
  - Machine learning and large language models focused on making the generic drug program more efficient by leveraging large data sets

Innovation driven by QM

- Local PBPK
  - FDA grant programs have supported the development and availability of PBPK models for local routes of actions
  - Critical to access to generic versions of inhalation, topical, ophthalmic and nasal products
  - Many generics of complex products are now approved without in vivo BE studies
- CFD (Computational Fluid Dynamics)
  - Mechanistic models for lung deposition and airflow in inhalation delivery devices
  - Physics based models used extensively in CDRH device evaluation
  - Innovative use in drug product development and review

Innovation driven by QM

- Machine Learning
  - Prediction of future ANDA submissions
  - Natural language tools for drug labels
  - More efficient model development (ML based QCP model selection)
- ICH M13 revisions
  - Models for food effect and fed bioequivalence
  - Supported significantly more efficient, globally harmonized BE study recommendations

Regulatory Impact Stories

- ANDA for topical gel approved without a clinical study because of a PBPK model for dermal absorption
- Model of drug delivery to the site of action was critical to support the acceptability of the applicants alternative BE approach

Tsakalozou, E., Babiskin, A. and Zhao, L. (2021), Physiologically-based pharmacokinetic modeling to support bioequivalence and approval of generic products: A case for diclofenac sodium topical gel, 1%. CPT Pharmacometrics Syst. Pharmacol., 10: 399-411. https://doi.org/10.1002/psp4.12600

- In FY23 20 topical ANDAs approved via in vitro only approaches
- In FY23, 2 topical ANDAs approved based on clinical endpoint BE

Innovation

- These innovations were developed to aid access to generic version of pharmaceutical products
- However, they are more broadly useful
- Through the CoE, more access across CDER programs to these type of innovations

In the Pipeline

- Model Informed Evidence (MIE) Meeting Pilot
  - For novel bioequivalence approaches that are more efficient because they combine a pre-specified model with data from in vivo or in vitro studies

- MIE Industry Meeting Pilot – General Principles, Sept. 12, 2023
  - https://www.fda.gov/media/172028/download?attachment

MIE for Long-Acting Injectables

- Consider a drug with three-month dosing interval for continuous use
  - Not safe for healthy subjects
  - Patients can't be washed out between T and R
  - Old thinking: Steady State BE
- MIE thinking
  - Switch before steady state with model-based correction for previous exposure

In the Pipeline

- Model Master File
  - Reusable
    - Efficient product development and application assessment
  - Scalable
    - More model submission in the future
  - Support an “Eco-system” for model development
    - Models are not just for applicants with “in-house” expertise
- May 2-3, 2024: Workshop: Considerations and Potential Regulatory Applications for a Model Master File
  - Register at https://www.complexgenerics.org/education-training/considerations-and-potential-regulatory-applications-for-a-model-master-file/

Summary

- The experience of the generic drug program is that Quantitative Medicine (modeling and simulation) supports innovation and access to equivalent product without unneeded clinical studies


FDA
U.S. FOOD & DRUG
ADMINISTRATION