Emerging Concepts and New Technologies for Bioequivalence of Orally Inhaled Drug Products

ATS 2024 Session MD29. GENERIC DRUG DEVELOPMENT FOR RESPIRATORY PRODUCTS, US FOOD AND DRUG ADMINISTRATION UPDATE

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Andrew Clerman, MD, PhD
Senior Physician
Division of Therapeutic Performance I, Office of Research and Standards
Office of Generic Drugs| CDER | U.S. FDA

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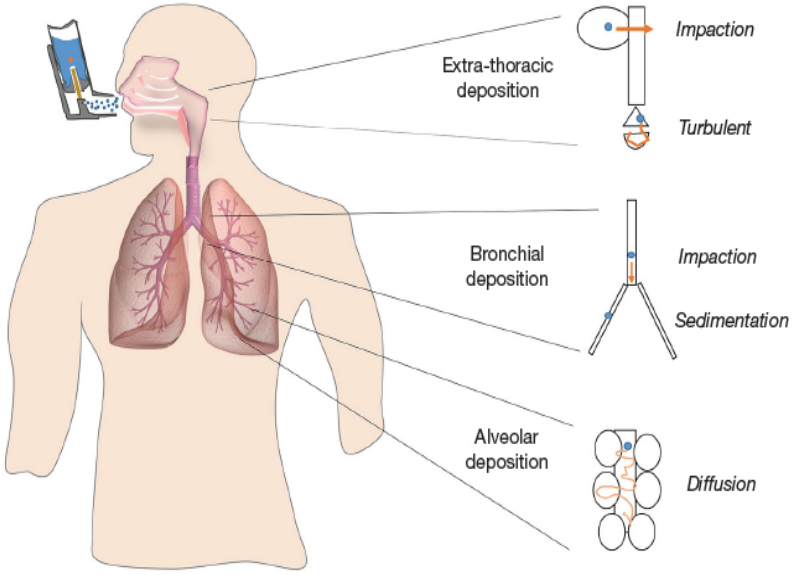
Bioequivalence

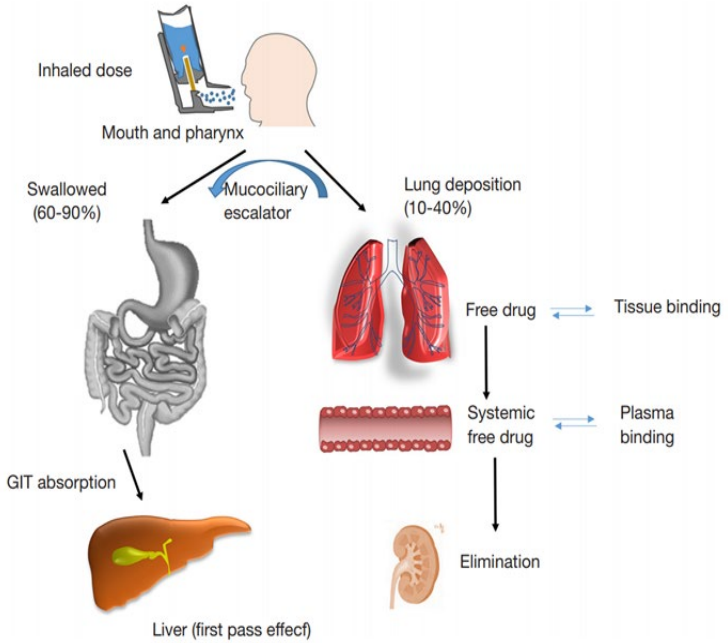
- 21 CFR 314.3: Bioequivalence (BE) is the **absence of a significant difference in the rate and extent** to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives **becomes available at the site of drug action** when administered at the same molar dose under similar conditions in an appropriately designed study.

The Challenge for OIDPs: BE at the Site of Action

- For locally acting orally inhaled drug products (OIDPs), lung tissue is the site of therapeutic effect
- Regional deposition is upstream of local drug action
- Systemic pharmacokinetics (PK) is downstream of local drug activity
- BE approaches for generic OIDPs must account for this complexity

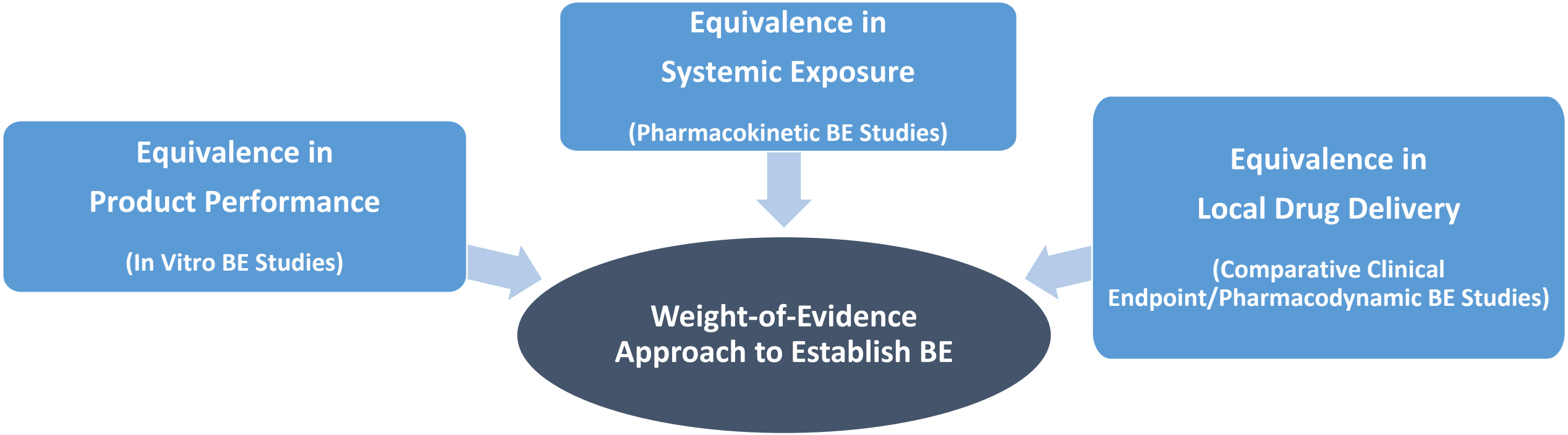


de Pablo et al.[1]



de Pablo et al.[1]

Historical BE Approach for Locally-Acting MDIs and DPIs



Formulation Sameness + Device Similarity

New Tools for OIDP BE Supported by GDUFA Science & Research

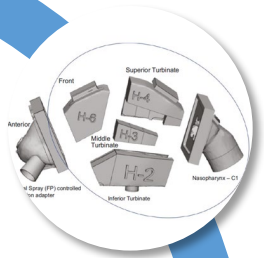
Clinical Endpoint BE Studies

Higher Variability

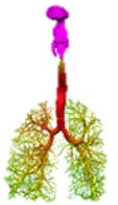
Lower Sensitivity

Time and Cost

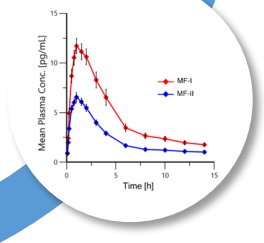
Alternative BE Approaches



In Vitro Methods



In Silico Modeling



Alternative PK studies

Generic Drug User Fee Amendments (GDUFA) Science & Research Program

- Led by OGD's Office of Research and Standards (ORS)
- Annual list of research priorities developed through a public workshop
- Particular focus on complex products, which includes complex active ingredients, formulations, dosage forms, or **routes of administration**, or are a **complex drug-device combination product**
- Overarching goal of providing **new tools to evaluate generic drug equivalence** so that industry can efficiently develop safe and effective generic drugs

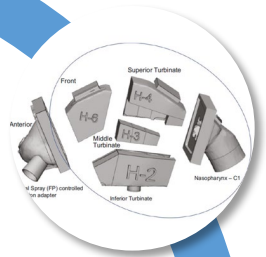
https://www.fda.gov/drugs/generic-drugs/science-research

New Tools for OIDP BE Supported by GDUFA Science & Research

Clinical Endpoint BE Studies

- Higher Variability
- Lower Sensitivity
- Time and Cost

Alternative BE Approaches



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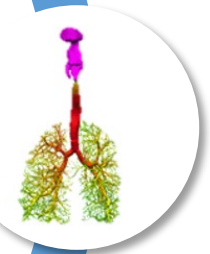

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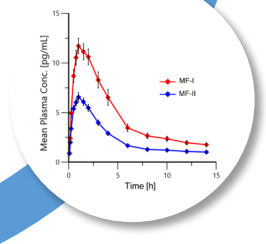
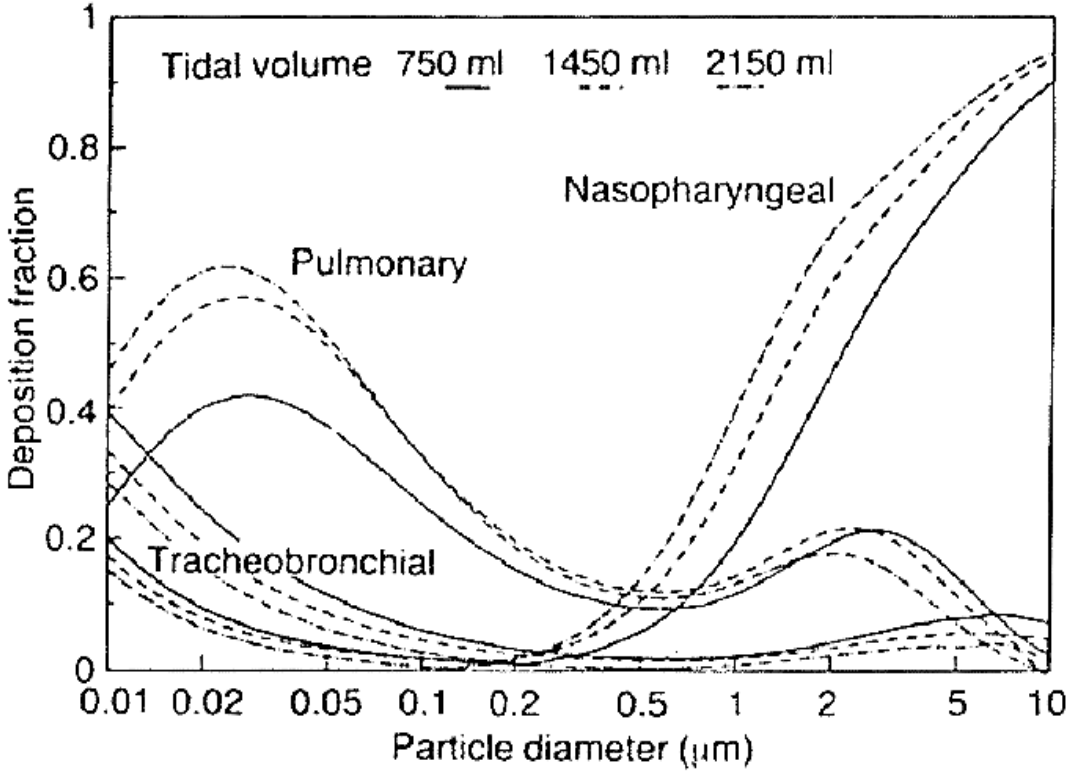


Alternative PK studies

In Silico OIDP Model Categories: Semi-Empirical Regional Deposition

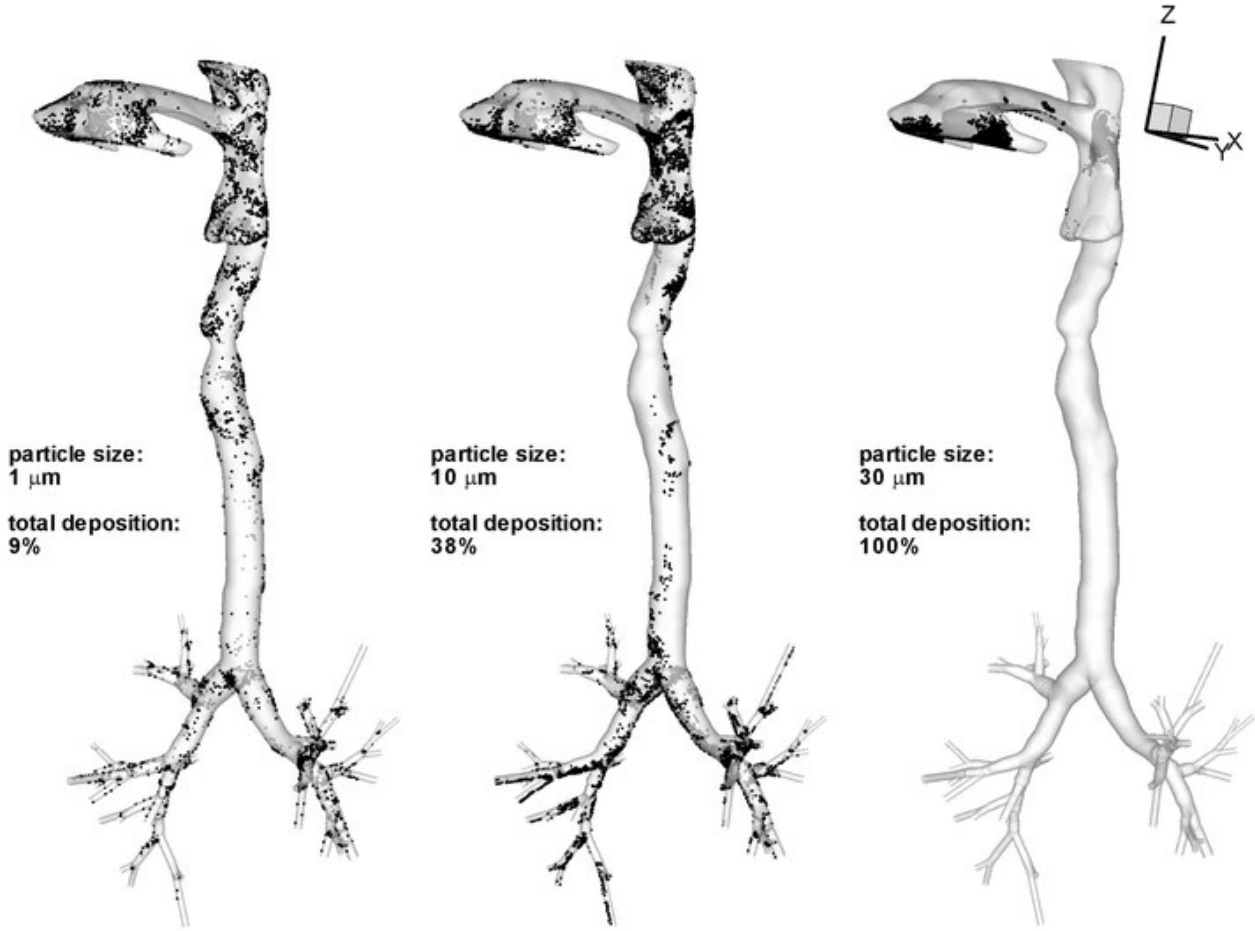
- Algebraic, semi-empirical
- Computationally efficient
- Branch-specific deposition probability that may be summed across branch levels to obtain regional deposition
- Originally developed for toxicology of radioactive particles, not aerosolized drug products



Deposition fraction according to National Council on Radiation Protection and Measurements (NCRP) model (Figure from Phalen et al.[2])

In Silico OIDP Model Categories: Computational Fluid Dynamics (CFD)

- Intended to predict fluid and particle transport
- Can examine the influence of device performance and individual patient characteristics on regional deposition
  - Plume geometry
  - Spray pattern
  - Aerodynamic particle size distribution (APSD)
  - Inhalation waveform
  - Realistic mouth-throat geometry
- More computationally intensive than the semi-empirical model



CFD predictions of lung deposition for varying particle sizes (Figure 3 from Ma and Lutchen[3])

In Silico OIDP Model Categories: Physiologically Based Pharmacokinetics (PBPK)

- Regional deposition may reflect local drug delivery but is not necessarily a surrogate for local drug PK
- PBPK modeling can be used to predict the impact of dissolution, permeation, and metabolism, and clearance on local and systemic PK

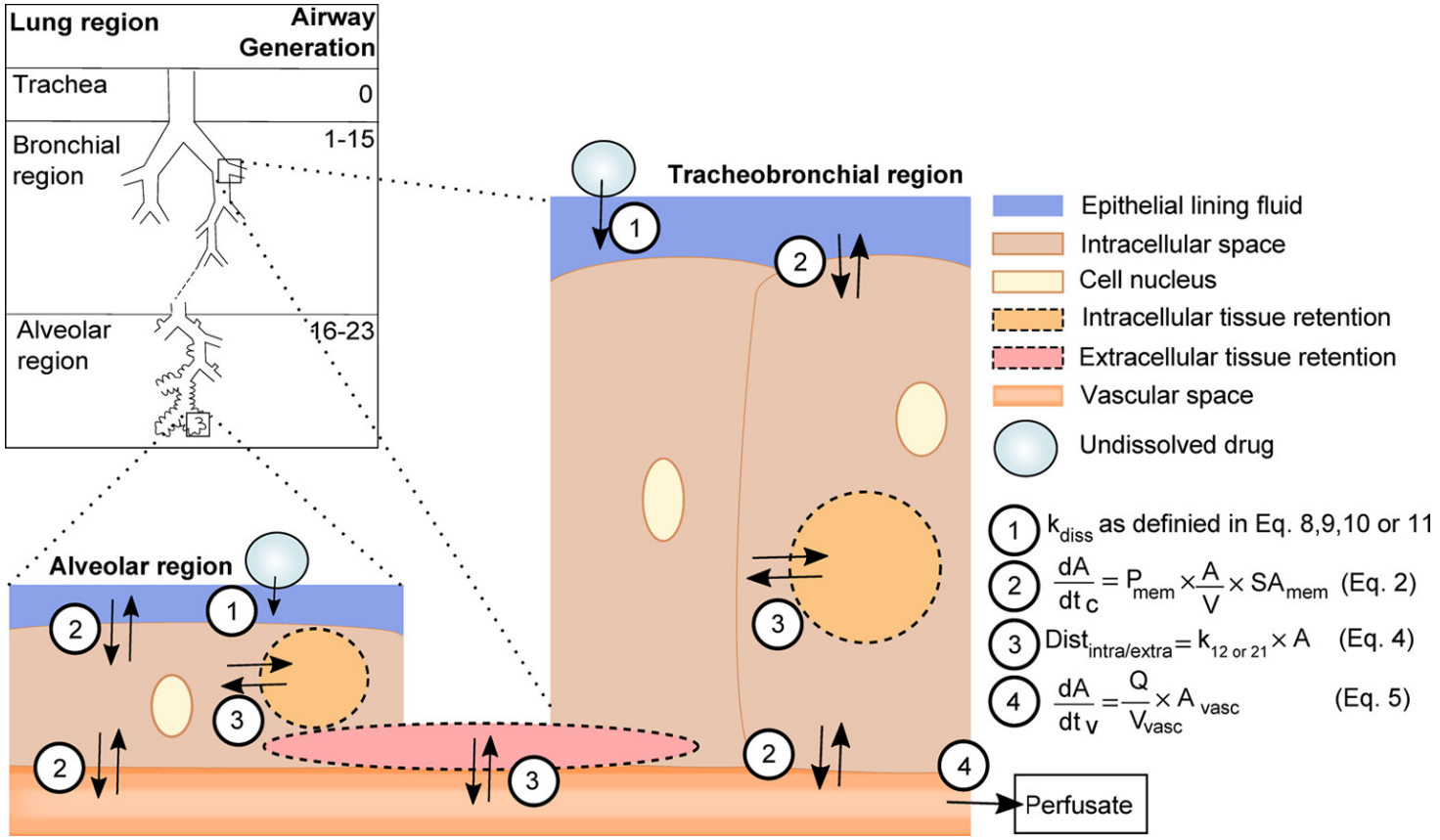


Figure 2 from Eriksson et al.[4]

GDUFA Science & Research Program Support for OIDP In Silico Model Development

- Funding (FY2023)
  - Development of a Laser-Based Testing Platform for Generic Dry Powder Inhaler (DPI) Evaluation and In Silico Model Validation (75F40123C00201-University of Sydney)
  - Feasibility of Predicting Regional Lung Exposure from Systemic Pharmacokinetic Data of Generic OIDPs Via Population Pharmacokinetic Modeling and Non-Compartmental Approaches (U01FD007936-University of Florida)
  - A Prospective Study to Support Validation of Lung Deposition Models with Nuclear Medicine Imaging Methods (U01FD007987-Fluidda, Inc.)
- Workshops (in collaboration with the Center for Research on Complex Generics)
  - Regulatory Utility of Mechanistic Modeling to Support Alternative Bioequivalence Approaches (September 2021)
  - Best Practices for Utilizing Modeling Approaches to Support Generic Product Development (October 2022)
  - Considerations for and Alternatives to Comparative Clinical Endpoint and Pharmacodynamic Bioequivalence Studies for Generic Orally Inhaled Drug Products (April 2023)
  - Considerations and Potential Regulatory Applications for a Model Master File (May 2024)
- Publications and presentations
  - https://www.fda.gov/drugs/generic-drugs/science-research
  - https://complexgenerics.org/

Incorporating Modeling into Regulatory Decision Making

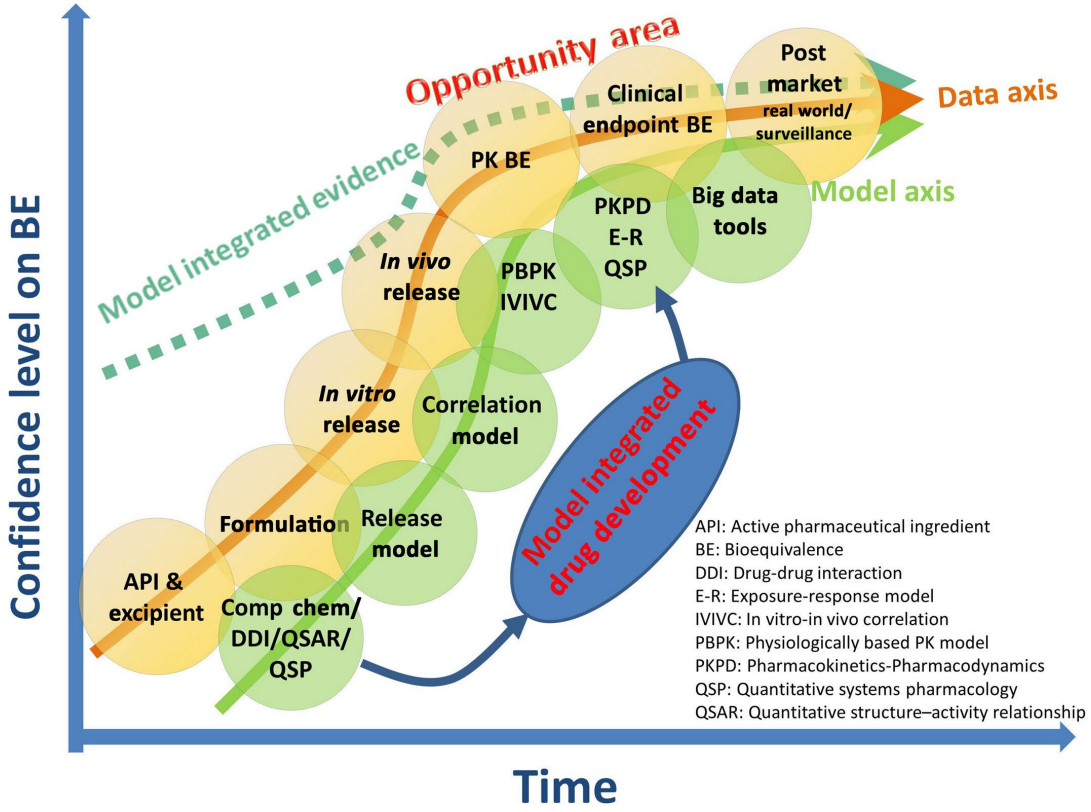


Figure 2 from Zhao et al.[5] – Model-integrated drug development for generic drugs

OGD's Model-Integrated Evidence (MIE) Industry Meeting Pilot

- New meeting opportunity for prospective generic drug applicants to foster early and focused interaction with FDA related to modeling approaches to BE
- Intended for model-based approaches to BE that cannot be addressed under existing meeting types
- Provides a dedicated platform for in-depth scientific and technical discussion regarding model implementation in product development
- Launched October 2023

https://www.fda.gov/drugs/abbreviated-new-drug-application-anda/model-integrated-evidence-mie-industry-meeting-pilot-between-fda-and-generic-drug-applicants

FDA/CDER's Quantitative Medicine (QM) Center of Excellence (CoE)

- Established March 2024
- QM is the use of modeling and simulation approaches derived from nonclinical, clinical, and real-world sources to inform drug development, regulatory decision-making, and patient care
  - Contribute to the totality of understanding of a drug's benefits and risks, which will advance drug development and inform regulatory decision-making
- Lead the development of QM policy and best practices across CDER
- Facilitate outreach to scientific societies, patient advocacy groups, and other stakeholders
- Coordinate QM education and training

https://www.fda.gov/drugs/drug-safety-and-availability/cder-establishes-new-quantitative-medicine-center-excellence

Product-Specific Guidance (PSG) Recommendation

- Optional modeling approach to support BE
- Purpose of model is to either 1) establish biorelevant limits of key in vitro studies (e.g., APSD and plume geometry) or 2) conduct virtual BE simulations
  - Example: CFD or semi-empirical model to predict central and peripheral lung deposition
  - Example: PBPK model if regional deposition may not be considered as a surrogate for regional lung delivery (e.g., slow drug absorption expected)
- Model credibility and validation should be established
- Validation acceptance criteria and statistical analysis methods should be defined prior to testing and justified for virtual BE studies

PSG on *Formoterol Fumarate; Glycopyrrolate Inhalation Aerosol Metered* (NDA 208294)
https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_208294.pdf

Model Master File (MMF) Concept

- Analogous to Drug Master Files (DMFs), MMFs are quantitative models or modeling platforms that have been sufficiently verified and validated to be recognized as sharable intellectual property and are acceptable for regulatory purposes
- Intended to be portable, reusable, generalizable, and sharable
- Goal is to increase the efficiency and consistency of modeling to support generic drug development
- CRCG Workshop: Considerations and Potential Regulatory Applications for a Model Master File (May 2024)

Fang L, Gong Y et al. The Role of Model Master Files for Sharing, Acceptance, and Communication with FDA. AAPS J. 2024;26(2):28. Published 2024 Feb 27.

Conclusions

- Establishing BE of locally-acting OIDPs is complex due to the need to assess regional deposition and local PK
- In silico models, including CFD and PBPK, are promising approaches to evaluate regional deposition and local PK in support of BE determinations of generic OIDPs
- OGD is conducting research and implementing strategies to support the use of in silico modeling across generic drug development, including OIDPs
- CDER's establishment of the QM CoE will facilitate the use of QM in drug development and public health more broadly

References

1. de Pablo E, Fernández-García R, Ballesteros MP, Torrado JJ, Serrano DR. Nebulised antibiotherapy: conventional versus nanotechnology-based approaches, is targeting at a nano scale a difficult subject?. Annals of Translational Medicine. 2017 Nov;5(22).
2. Phalen RF, Cuddihy RG, Fisher GL, Moss OR, Schlesinger RB, Swift DL, Yeh HC. Main features of the proposed NCRP respiratory tract model. Radiation Protection Dosimetry. 1991;38(1-3):179-84.
3. Ma B, Lutchen KR. CFD simulation of aerosol deposition in an anatomically based human large–medium airway model. Annals of biomedical engineering. 2009;37:271-85.
4. Eriksson J, Thörn H, Sjögren E, Holmstén L, Rubin K, Lennernäs H. Pulmonary dissolution of poorly soluble compounds studied in an ex vivo rat lung model. Molecular pharmaceutics. 2019;16(7):3053-64.
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