Advancing In Silico Methods and Future Opportunities for Understanding Impact of Compositional Differences on Performance

Fiscal Year (FY) 2025 Generic Drug Science and Research Initiatives Public Workshop

June 3, 2025

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Compositional Differences of Non-Orally Administered Drug Products

- Non-orally administered drug products include buccal, injectables, intrauterine, nasal, orally inhaled, ophthalmic, otic, rectal, applied to the skin, and vaginal.
- What triggers qualitative (Q1) and quantitative (Q2) sameness:
  - Regulation (i.e., injectable, ophthalmic, and otic drug products)
  - Non-conventional bioequivalence (BE) approaches (e.g., in vitro totality of evidence approach or in vitro/in vivo combination approach)
- Potential benefits to develop a non-Q1/Q2 formulation
  - Patent protections
  - Complex formulations
  - Supply issues

Mechanistic Modeling for Understanding the Impact of Compositional Differences

- Mechanistic models may facilitate drug development and/or approval for non-Q1/Q2 formulations via providing effective tools to better understand the potential impact of compositional differences on product performance.
- Methods
  - Physiologically based pharmacokinetics (PBPK): predicts local and systemic pharmacokinetics (PK) using compartmental approach
  - Computational fluid dynamics (CFD): predicts fluid and particle transport and has been primarily used pharmacology to predict inhaled medicinal aerosol deposition
- Potential effects of Q1, Q2, or differences in formulation physicochemical characteristics (Q3) on drug delivery that models for drug products applied to the skin or orally inhaled drug products may need to account for
  - Evaporation and condensation
  - Spray formation
  - Changes in permeation and dissolution due to excipients

Metamorphosis of Topical Products on the Skin

Background

Establishing equivalent performance,[1,2] conventionally via:

- Comparative clinical endpoint (CCEP) in vivo BE studies
- Pharmacodynamic (PD) endpoint (e.g., vasoconstrictor [VC] studies)

Based on cutting-edge research, the FDA is streamlining more efficient BE approaches:

- In vitro characterization and performance tests

Problem

Topical drug products with compositional differences compared to the reference standard can result in differences in thermodynamic activity of the active pharmaceutical ingredient (API) in a topical product, which may in turn influence bioavailability (BA).

Potential Solution

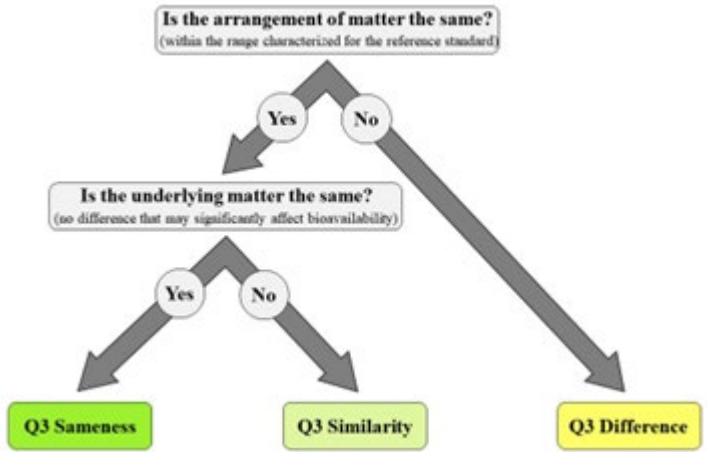
FDA is investigating alternative methodologies that include in vitro approaches coupled with in silico tools to support the assessment of BE for topical drug products that have compositional differences compared to the reference standard.

Mechanistic PBPK models that capture:

1. metamorphosis phenomena post product application and
2. impact of inactive ingredients on API thermodynamic activity and BA

may be utilized to support decision making in drug product development and efficient BE approaches for topical products with compositional differences.

Physicochemical and Structural (Q3) Characterization of Topical Drug Products Submitted in ANDAs Guidance for Industry[3]



Slide prepared by Dr. Eleftheria Tsakalozou

Current Research and Gaps: Metamorphosis of Topical Products on the Skin

Current funded external awards[4]

- Bioequivalence of Topical Products: Elucidating the Thermodynamic and Functional Characteristics of Compositionally Different Topical Formulations (GDUFA Award U01FD006496)
- Bioequivalence of Topical Products: Elucidating the Thermodynamic and Functional Characteristics of Compositionally Different Topical Formulations (GDUFA Award UU01FD006507)
- In Vitro Tests to Support Bioequivalence Determination When Generic Dermatological Formulation has Differences from the Brand Product Formulation (Contract 75F40123C00204)
- Role of Excipients and Excipient Substitution in Topical Semi-Solid Formulations and Their Effect on Product Performance and Quality (Contract 75F40123C00213)
- Development and Validation of a Multi-Functional, Multi-Purpose Quantitative Tool for Dermal PBPK Modeling (GDUFA Award UU01FD007957)
- Formulation Toolbox for Topically Applied Drugs to Account for Physical Parameters, Dynamic Metamorphosis and Influence of Excipients (GDUFA Award UU01FD007954)

Potential Remaining Research Gaps

Build and validate the computational framework

- to predict the simultaneous permeation of the API and inactive ingredient(s) and potential mechanism-based interactions
- to describe vehicle loss (i.e., drying and permeation of inactive ingredients) and its impact on API permeation
- to describe the impact of drug product handling, such as drug product rubbing, on API permeation

Locally Acting Metered Dose Inhalers (MDIs) and Next Generation Propellants (NGPs)

Background

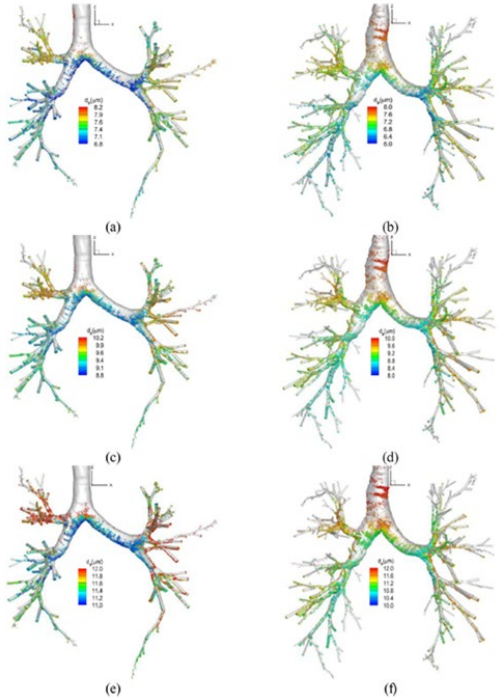
Revised and new product-specific guidances (PSGs) for locally acting MDIs published in February 2024 and after include two options for BE, where Option 2 for non-Q1/Q2 products includes a CCEP or PD BE study.

Problem

Currently approved new and generic locally acting MDIs could be subject to supply shortages in the future due to global phase down from currently used propellants to NGPs.

Potential Solution

- Regional deposition models using either CFD or semi-empirical methods along with PBPK models may potentially be used to support product development to predict the impact of device and formulation changes.
- May provide support for addressing uncertainty from the non-Q1/Q2 MDI, which could facilitate the use of Option 1 (i.e., without a CCEP or PD BE study) instead of Option 2 to support an NGP MDI generic submission.



Predicted deposition locations and droplet sizes for beclomethasone dipropionate inhalation metered aerosol with a) and b) 1%, c) and d) 5%, and e) and f) 20% ethanol in subjects labeled a), c), and e) C3 and b), d), f) C4. (Figure 9 from Rajaraman et al. [2023][5]).

Current Research and Gaps: Locally Acting MDIs and NGPs

Current funded external awards[4]

- Computational Fluid Dynamics (CFD) Models to Aid the Development of Generic Metered Dose Inhalers (Grant 1U01FD007353)
- Research Challenges Related to Environmentally Friendly Propellants in Metered Dose Inhalers (Contract 75F40123C00186)
- ML-CFD-DEM Based Reduced Order Models (ROM) to Quantify Variability in Inhalers, Drugs, and Users for Evaluating Comparability of Generic OIDP Complex Products (Grant 1U01FD008379)
- A Prospective Study to Support Validation of Lung Deposition Models with Nuclear Medicine Imaging Methods (Grant 1U01FD007987)
- A Physiologically Based Pharmacokinetic Model of Human Airway Epithelia (Grant 1U01FD007338)
- Advancing In Vitro and (Patho)physiology-Based Pharmacokinetics Models to Understand and Predict Pulmonary Absorption and Tissue Retention of Inhaled Drugs (Contract 75F40122C00182)

Potential Remaining Research Gaps

- In vivo techniques to provide model validation data for MDIs with multiple active ingredients
- Michaelis-Menten kinetics data for active ingredients that are metabolized in the lung
- Dissolution modeling for PBPK models that better reflects in vivo conditions

Long-Acting Implant and Injectable Formulations

Background

PLGA-based implantable and injectable products require Q1/Q2 assessment of PLGA polymers. The impact of composition of PLGA polymers on product performance is complicated and heavily relies on the properties of PLGA polymers and product manufacturing process.

Problem

The current Q1/Q2 assessment requires comparative physicochemical data (e.g., molecular weight, monomer ratio, and polymer structure) on extracted PLGA polymer from both the test and reference standard products, given that manufacturing may alter PLGA properties. Knowledge is currently developing with respect to the impact of differences in PLGA characteristics on critical formulation attributes, which in turn influence the in vivo release and behavior of the drug product. Moreover, there are challenges associated with conducting in vivo BE studies such as long duration in vivo BE studies, low subject recruitment, high dropout rate, and increased variability with PK metrics as compared to studies with shorter duration.

As a result, there is low availability of generic PLGA implants and injectables in the U.S. market today.

Potential Solution

Mechanistic PBPK models of PLGA-based implants and injectables can describe the in vivo release mechanism when the model is informed with critical formulation attributes. Such models may potentially be utilized to justify why a difference in physicochemical characteristics (e.g., molecular weight/weight distribution, lactide to glycolide ratio, particle size distribution of microspheres) may not impact the in vivo performance of the test drug product. Mechanistic modeling also has the potential to be used in an alternative BE approach such as virtual BE or mechanistic in vitro in vivo correlation (IVIVC) and/or provide scientific justification to support an in vitro-only approach.

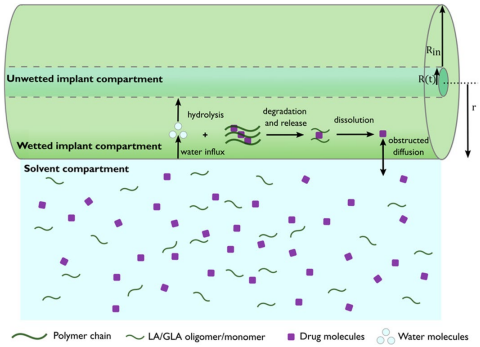


Figure 1 from Mittapelly et al.[6]

Current Research and Gaps for Developing Modeling Tools: PLGA Implants and Injectables

Current funded external awards[4]

- Developing PBPK-Model Based Mechanistic IVIVC for PLGA Implants (Grant 1U01FD008303)
- A State-of-the-Art Virtual Bioequivalence Platform and Case Studies on Complex Formulations, Systemic and Local Concentration-based Bioequivalence (Grant 1U01FD007904)

Potential Remaining Research Gaps

PLGA implants: Developing mechanistic PBPK model that account for critical formulation attributes such as PLGA molar ratio, molecular weight of PLGA, polymer endcap, drug loading, porosity, etc., to describe both in vitro and in vivo drug release process mechanistically.

Conclusions

1. There are instances where a non-Q1/Q2 formulation may be advantageous for a generic non-orally administered drug products.

2. Mechanistic modeling methods such as PBPK and CFD may help facilitate drug development and/or approval for non-Q1/Q2 formulations via providing tools to better understand impact of formulation composition and characteristics on product performance.

3. GDUFA research has been funded to support use of mechanistic modeling for topical, MDI, and PLGA implant and injectable drug products.

4. Potential research gaps were identified that may be important to focus on for future GDUFA-funded research.

Acknowledgements

- FDA/CDER/OGD/ORS
  - Khondoker Alam
  - Elizabeth Bielski
  - Susan Boc
  - Steven Chopski
  - Liangfeng Han
  - Anubhav Kaviratna
  - Jae Ho (Mike) Lee
  - Bora Sul
  - Mingliang Tan
  - Morgan Thomas
  - Bryan Newman
  - Eleftheria Tsakalozou
- FDA/CDER/OGD/ORS
  - Lanyan (Lucy) Fang
  - Andrew Babiskin
  - Markham Luke
  - Yan Wang
  - Lei Zhang
  - Robert Lionberger

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