
# Session 1
# Insights to Product-Specific Guidance for Complex Products: From Research to Standards

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# Insights to Product-Specific Guidance for Complex Products: From Research to Standard

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Advancing Generic Drug Development Workshop: Translating Science to Approval
October 7-8, 2025

# Overview

- Product-Specific Guidance (PSG) Program for Complex Product
- SME Triage Team Program to Proactively Identify Research Needs for Complex Products
- Roflumilast Topical Cream - A Case Study

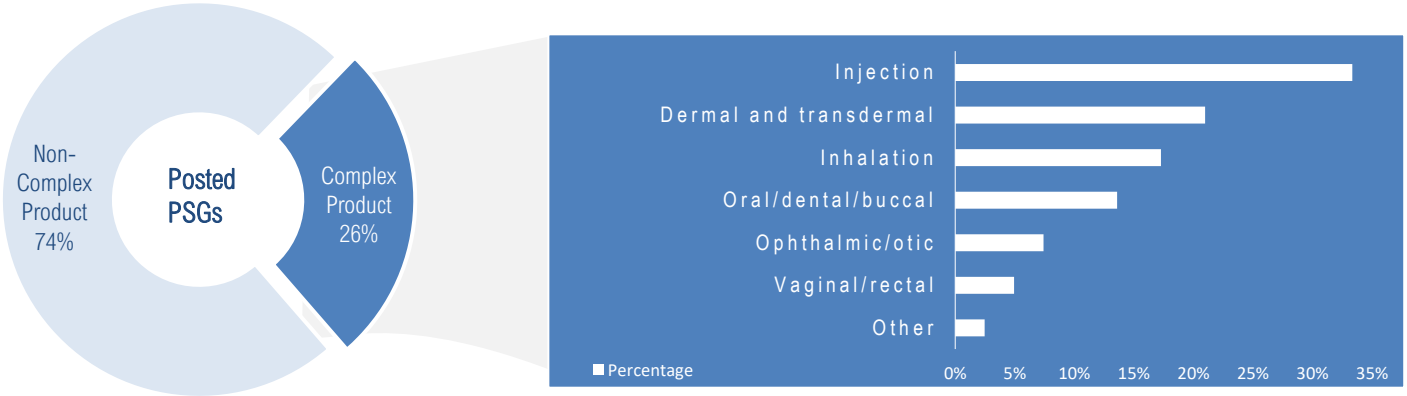
# Product-Specific Guidance (PSG) Program for complex Product

# Product-Specific Guidance (PSG)

- Started in 2007, PSGs outline FDA's current product-specific thinking on the type of studies and information to support the development and approval of a safe, effective, and high-quality generic drug product.
- PSGs are drug-specific recommendations for demonstrating *therapeutic equivalence* of a generic product to the Reference Listed Drug (RLD) product.
  - PSGs are posted on a quarterly basis to FDA's PSG website.
  - As of September 2025, there are over 2288 posted PSGs.
- FDA develops and posts PSGs to:
  - Enhance transparent expectations and conversation between the Agency and the generic industry
  - Reduce industry inquiries by providing a general framework for generic product development
  - Improves the quality of submitted ANDAs

# NDA Approval and PSG Development

Approximately 30% of approved NDA are complex products. Majority of the >500 complex products with a posted PSG have a complex dosage form. These products include different routes of administration and can meet more than one definition of complexity (e.g., complex active ingredient, complex device, locally acting, complex dosage form, etc.).



# PSG for Complex Product and GDUFA III

GDUFA III Commitment Letter: https://www.fda.gov/media/153631/download

## Section III.C Product-Specific Guidance

1. FDA will continue to issue PSG identifying the methodology for generating evidence needed to support ANDA approval.
2. FDA will issue PSGs consistent with the following goals:
   a. **For Complex Products approved in new drug applications (NDAs) on or after October 1, 2022, a PSG will be issued for 50 percent of such NDA products within 2 years after the date of approval, and for 75 percent of such NDA products within 3 years after the date of approval.**
   b. FDA will continue to develop PSGs for Complex Products approved prior to October 1, 2022, for which no PSG has been published.
   c. For non-complex drug products approved in NDAs on or after October 1, 2022, that contain a new chemical entity (NCE) (as described in section 505(j)(5)(F)(ii) of the FD&C Act), a PSG will be issued within 2 years after the date of approval for 90 percent of such products.

To meet this new goal, FDA needed to identify and address any potential complexities and research needs for PSG development soon after NDA approval.

# SME Triage Team (STT) Program: Identify Research Needs for Complex Products

Since July 2021

# SME Triage Team Program

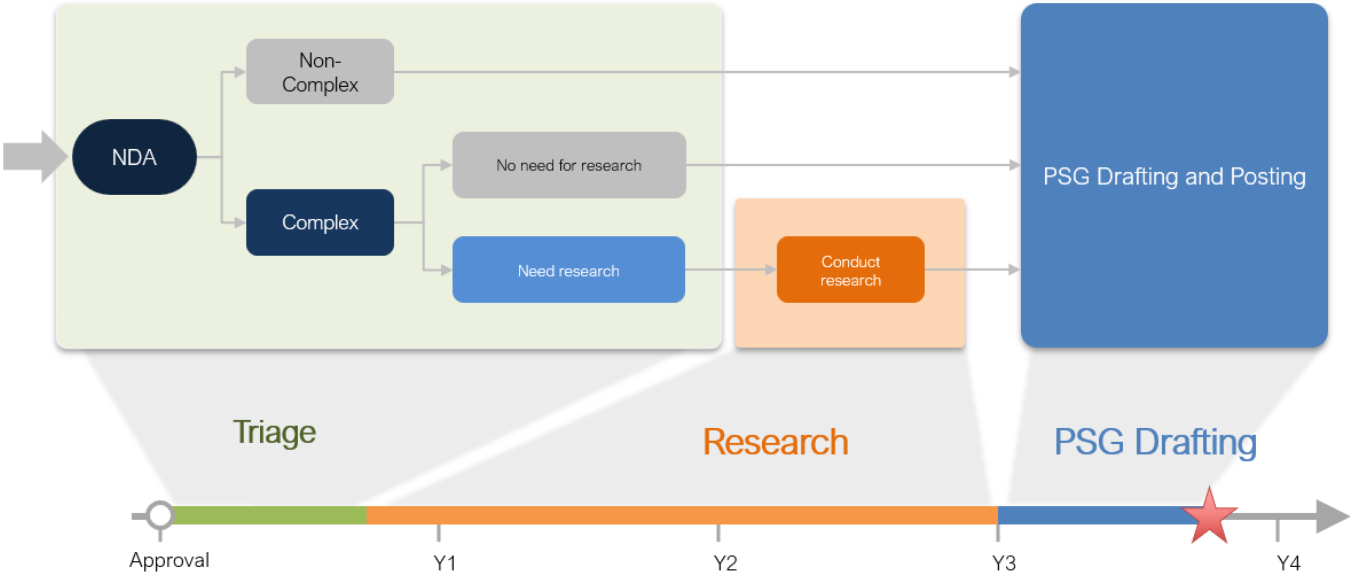
- Established a cross-office program (SME Triage Team, STT) to support complex PSG development. The STT program:
  - Clarifies relevant CDER offices of roles and responsibilities in the development process of complex product PSGs.
  - Successfully connects research and review assessment with PSG development, achieving early identification of knowledge gaps and timely addressing technical challenges.
  - Contains its own SME team for each complex area with membership comprises of experts from research, review, and policy.
  - SME team make key decisions like: Identify area of complexity; Determine if the complexity needs new research; Decide the research objectives.
  - Enables cross-disciplinary collaboration for effective knowledge management to maximize efficient use of Center resources.
  - Started as a pilot in 2021 and become fully operational in October 2022.

# STT Program

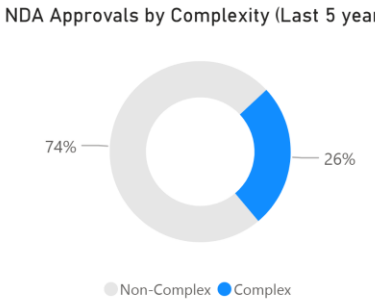
- An internal program to identify and direct research to support PSG development of complex generics
- Comprises 10 complex areas
- Subject Matter Experts across 9 CDER Offices
- Conducted 96 STT meetings of newly approved NDAs since 2021, with 11 ongoing research projects

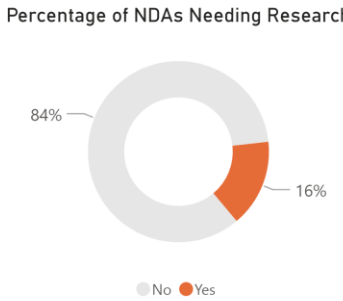
| | |
|---|---|
| 96 | • NDA Triaged |
| 15 | • Research Projects Identified |
| 65 | • PSGs Published |

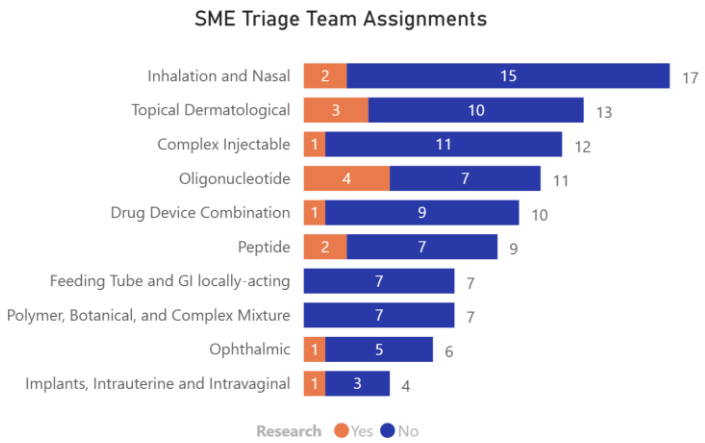
# Complex Product PSG Timeline



# STT Program Highlight




# Roflumilast Topical Cream (NDA 215985): A Case Study

# Roflumilast Topical Cream: A Case Study

A multidisciplinary team of scientists discussed the complexities, challenges, and knowledge gaps associated with this product for PSG development and found that there were:

- Challenges with clinical end point-based bioequivalence (BE) approach
- Challenges with in vitro characterization based BE approach

# Roflumilast Topical Cream: A Case Study

- The research was conducted to:
  - Investigate the permeability testing of roflumilast across human cadaver skin and to assess if IVPT can be a component of characterization-based in vitro BE approach for complex generic products referencing ZORYVE cream (NDA 215985)
  - Identify and characterize the observed crystals, analyze root causes of crystal formation, and assess the drug product's thermodynamic stability


Phoenix diffusion cells

Keyence VHX-7000 Digital Optical Microscope

Malvern Morphologi 4-ID Morphologically Directed Raman Spectroscopy (MDRS)

# Roflumilast Topical Cream: A Case Study

- The research successfully addressed critical knowledge gaps supporting both PSG development and regulatory decision-making by:
  - resolving key scientific uncertainties through comprehensive FDA research,
  - establishing validated IVPT methodology, and
  - correcting crystal identification misconceptions.
- The research enabled efficient regulatory actions by:
  - providing essential scientific foundation from research findings for drafting the PSG, and
  - directly supporting the review of multiple pre-ANDA applications, advancing GDUFA objectives through streamlined, science-based regulatory processes.

# Roflumilast Topical Cream: A Case Study

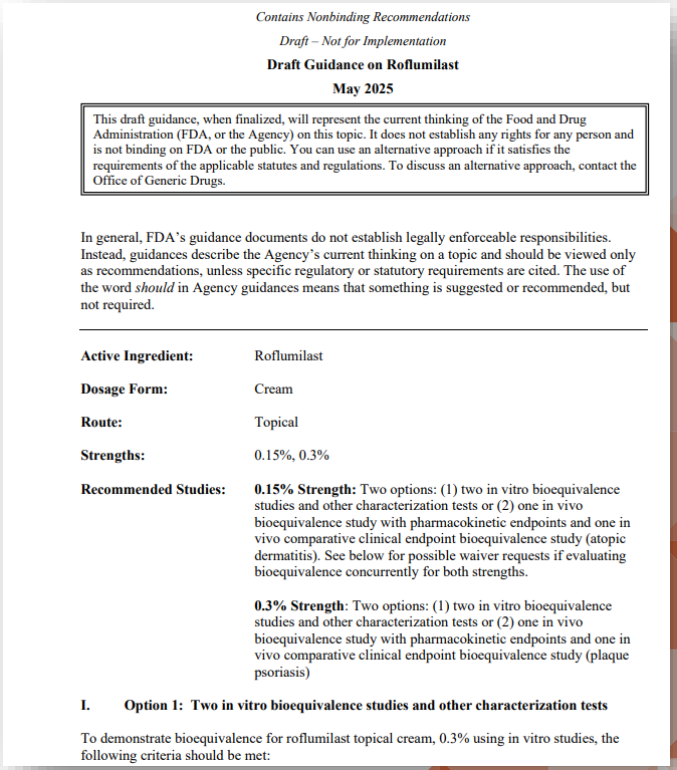
NDA 215985 approved on 7/29/2022

STT Meeting held on 12/2/2022

Research conducted from 9/1/2023-7/2/2025

PSG published on 5/20/2025

NDA approval to guidance development



*Contains Nonbinding Recommendations*

*Draft – Not for Implementation*

**Draft Guidance on Roflumilast**

**May 2025**

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

| | |
|---|---|
| **Active Ingredient:** | Roflumilast |
| **Dosage Form:** | Cream |
| **Route:** | Topical |
| **Strengths:** | 0.15%, 0.3% |
| **Recommended Studies:** | **0.15% Strength:** Two options: (1) two in vitro bioequivalence studies and other characterization tests or (2) one in vivo bioequivalence study with pharmacokinetic endpoints and one in vivo comparative clinical endpoint bioequivalence study (atopic dermatitis). See below for possible waiver requests if evaluating bioequivalence concurrently for both strengths.<br><br>**0.3% Strength**: Two options: (1) two in vitro bioequivalence studies and other characterization tests or (2) one in vivo bioequivalence study with pharmacokinetic endpoints and one in vivo comparative clinical endpoint bioequivalence study (plaque psoriasis) |

**I. Option 1: Two in vitro bioequivalence studies and other characterization tests**

To demonstrate bioequivalence for roflumilast topical cream, 0.3% using in vitro studies, the following criteria should be met:

https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_215985.pdf

# Summary

- FDA's product-specific guidance program provides FDA's current thinking on the type of studies and information to support the development and approval of safe, effective, and high-quality generic drug products
- SME Triage Team program helps to identify and address any potential outstanding knowledge gaps and research needs proactively for PSG development of complex products
- Lifecyle approach towards knowledge generation and information sharing is critical to the timely development of PSG

# Thank you!

# SME Triage Team Case Study, Complex Implant Products – Excipient Sameness: Characterization and Bioequivalence Challenges

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# Outline

- Complex Implant: RLD Overview
- BE Challenges for PSG development
- Research Plan and Results/Findings
- Current thinking on PSG recommendation and Conclusion

# Overview of Xaracoll Collagen Implant-RLD

**Product Details**
- Xaracoll Bupivacaine HCl implant, 100 mg (Innocoll Pharmaceuticals)
- NDA 20911, FDA approved August 28, 2020

**Indication & Dosing**
- Indicated for adults undergoing open inguinal hernia repair
- Single 300 mg dose placed directly into surgical site
- Provides postsurgical analgesia for up to 24 hours

XARACOLL® Bupivacaine HCl 100 mg Implant 10 - McKesson

Dimension: 5 cm x 5 cm x 0.5 cm

**Drug Release Mechanism**
- Locally acting
- Porous lyophilized collagen matrix releases bupivacaine HCl through wetting, dissolution, and diffusion

# Overview of Implant Matrix Composition

**Composition of implant**

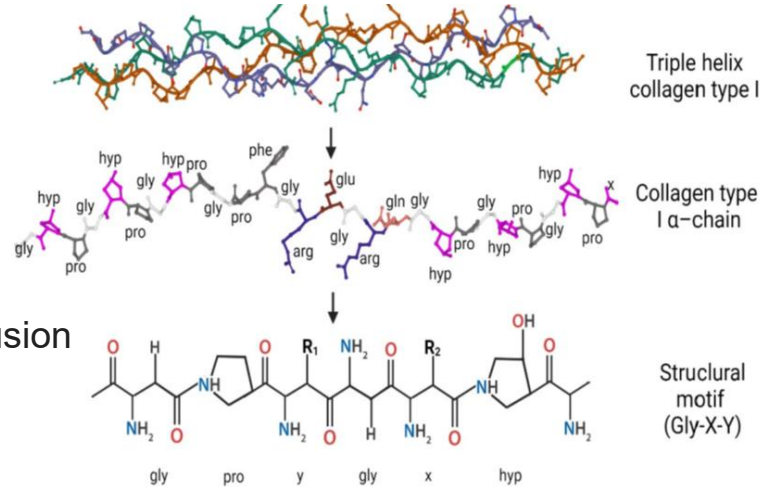
- Composed of purified Type I collagen as the sole inactive ingredient
- Collagen has no USP or Ph. Eur. monograph

**Structural Complexity of collagen**

- Triple helix structure with Gly-X-Y motif (glycine, proline, hydroxyproline)
- Resorbable implant matrix releases drug through diffusion as it dissolves over time

**Source-Dependent Variability of collagen**

- Variations in amino acid ratio can affect cross-linking density, thermal stability, and enzymatic susceptibility
- Variability in collagen directly impacts drug entrapment and drug release kinetics




Structures of type 1 collagen

DOI:10.21608/ijas.2025.378055.1075

# BE Challenges and Knowledge Gaps

**In Vivo BE Challenges**

- BE study in healthy subjects not feasible due to invasive administration and unpredictable variability
- Patient enrollment difficult for clinical studies
- Locally acting product creates surgical site-dependent PK variability

**In Vitro BE Challenges**

- Effect of collagen source & purification process on Q1 sameness complicated
- Limited understanding of critical quality attributes and assessment criteria for characterization of collagen matrix

**Product Quality knowledge gaps** • Effect of manufacturing variables (homogenization speed/time, lyophilization) on product performance (porosity, drug release)

- Lack of characterization data for both the raw collagen and finished product
- In vitro-in vivo correlation (IVIVC) not an option for this type of product

# Research Plan to Address Knowledge gaps

**Characterization of Raw Collagen**

- Define criteria for Q1 sameness for excipient characterization
- Assess impact of collagen source on product performance

**Characterization of collagen dispersion (Intermediate)**

- Characterize properties of collagen dispersion
- Evaluate effect of process parameter (mixing speed, mixing time) on performance of final product

**CQAs of collagen Implants (Finished product)**

- Identify critical formulation attributes for the implant
- Develop comprehensive in vitro characterization and performance testing methods

# Characterization of Raw Collagen

**Collagen Sources**

- **Test Samples**: Purified Type I collagen from three different vendors (A, B, and C)
- **Reference Sample**: Collagen extracted from RLD


**Analytical Methods**

- **Structural Properties:**

Hydroxyproline content, free amino nitrogen, N /Hyp ratio determination and glycine content, collagen solubility assay via colorimetric assays

- **Physical Properties:**

Thermal stability by DSC and moisture content by TGA

- **Chemical Characterization:**

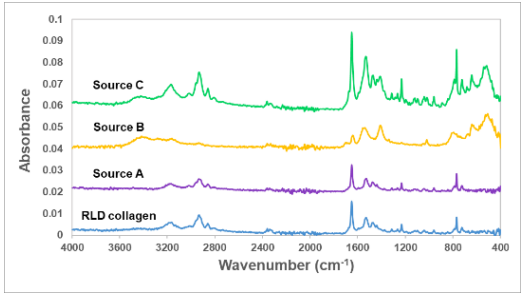
Functional group identification using FTIR spectroscopy

# Evaluation of Raw Collagen Sameness

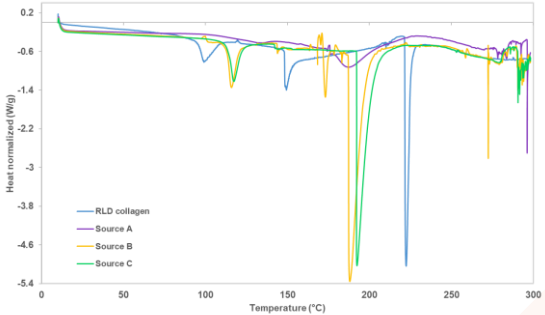
Structural properties of the collagens from various sources (A, B and C) and RLD (mean ±SD, n=6).

| Collagen source | Hydroxyproline content (% wt) | N/Hyp ratio | Free amino nitrogen content (% wt) | Total soluble collagen (% wt) |
|---|---|---|---|---|
| RLD collagen | 11.9 ± 0.27 | 1.51 ± 0.03 | 10.55 ± 0.41 | 0.20 ± 0.11 |
| A | 8.26 ± 0.46 | 2.15 ± 0.12 | 9.69 ± 0.48 | 5.28 ± 0.78 |
| B | 8.62 ± 0.79 | 2.10 ± 0.20 | 10.28 ± 0.22 | 0.19 ± 0.11 |
| C | 9.53 ± 0.35 | 1.89 ± 0.07 | 11.24 ± 0.32 | 0.16 ± 0.001 |

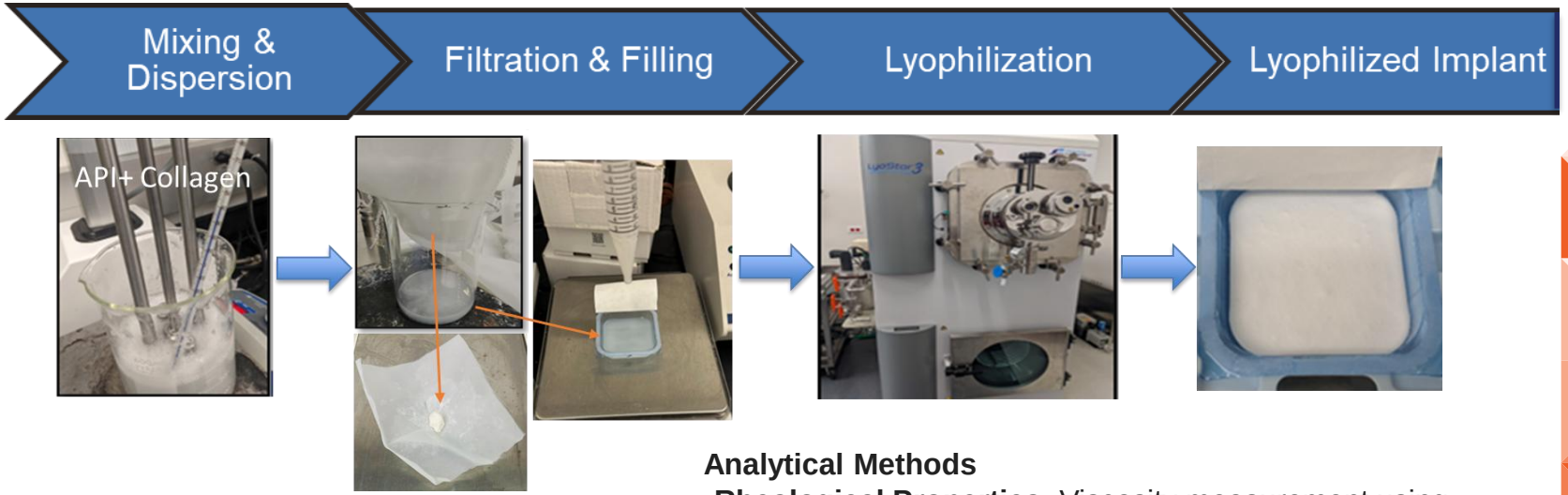
FTIR




DSC



# Understanding Process & Characterizations of Dispersion (intermediate)



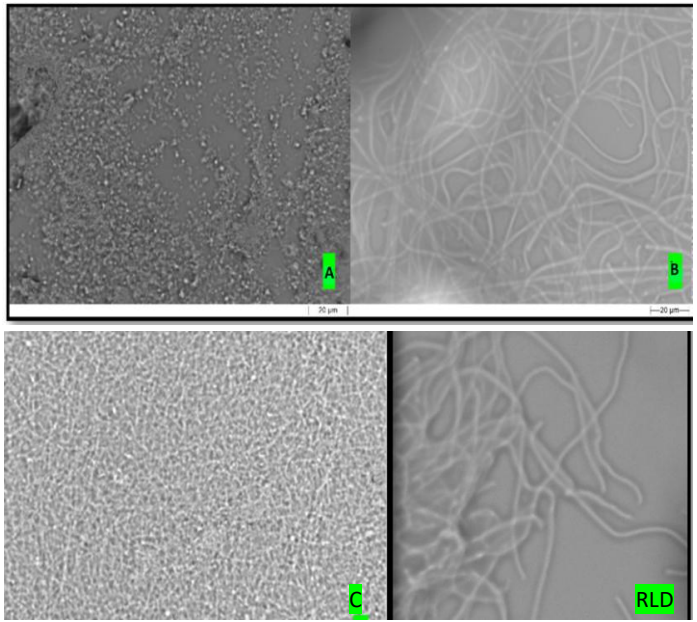

**Process Variables optimizations**

- **Mixing:** Speed and time
- **Filtration:** Pore size selection for filter bag
- **Lyophilization:** Temperature and residence time

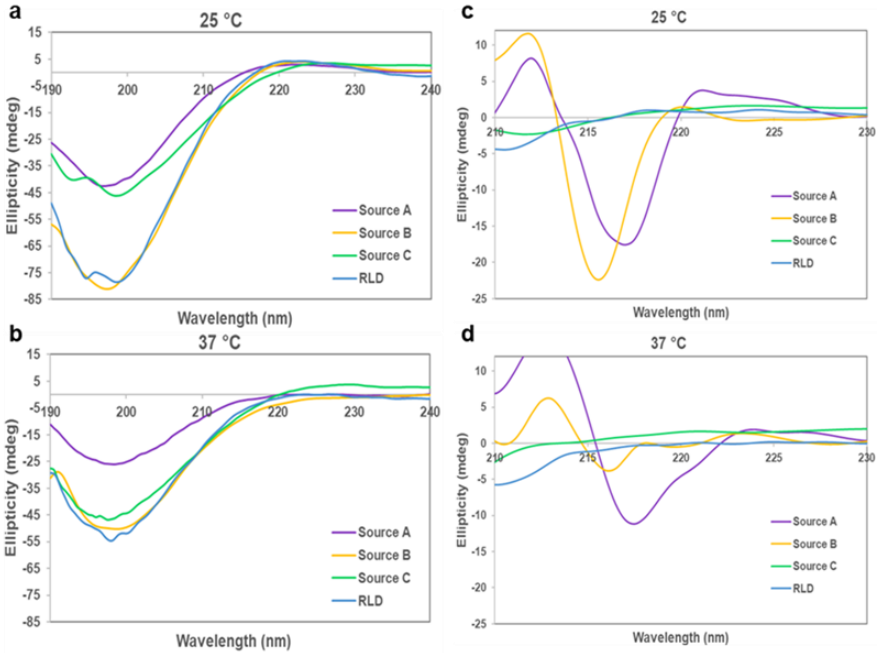
**Analytical Methods**

- **Rheological Properties:** Viscosity measurement using dynamic hybrid rheometer
- **Structural Analysis:** Morphology via morphologically directed Raman spectroscopy and microfibrillar structure through light microscopy
- **Molecular Characterization:** Collagen helicity assessment using circular dichroism spectroscopy

# Results of Dispersion Characterization




Morphological Directed Raman Spectroscopy images of collagen dispersions prepared from source A, B, C and RLD at 25 °C.

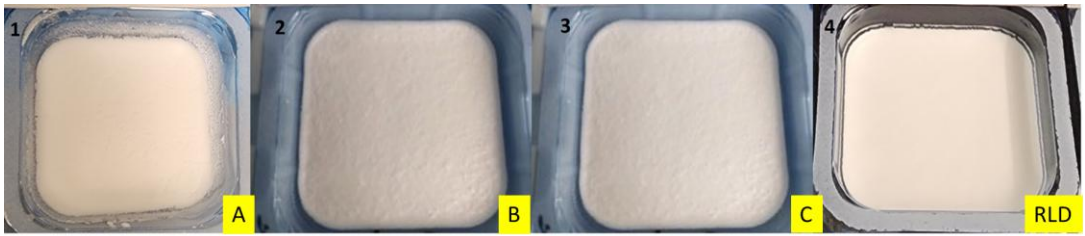



The CD spectra collected for collagen dispersions without API (a, b) and with API (c, d) from source A, B, C and RLD at 25 and 37 °C, respectively.

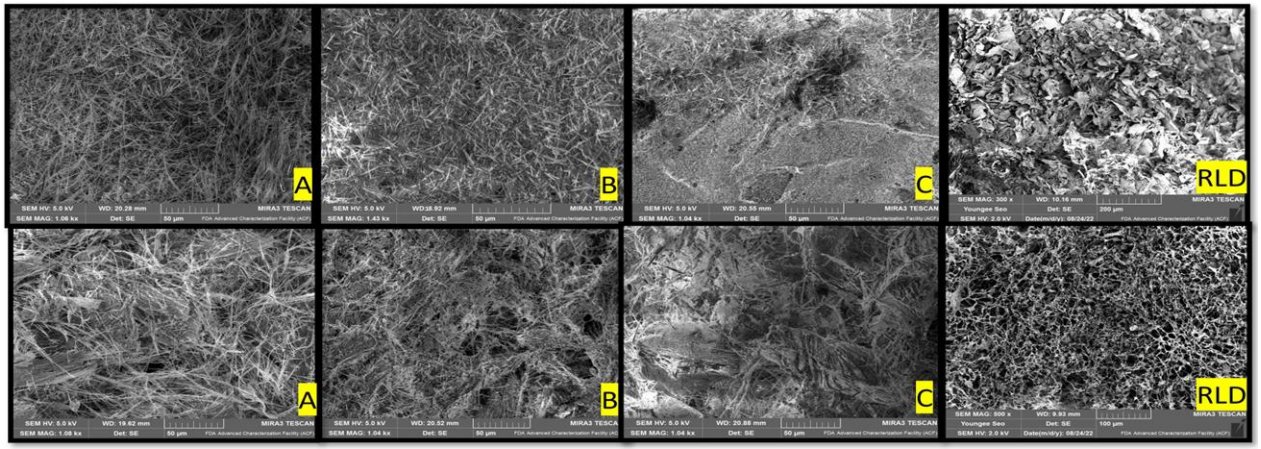
# Characterization of Implants

- Formation of implants
- Structural properties (SEM/Micro-CT)
- Solid state of API (XRD,DSC)
- Moisture content (TGA)
- Drug assay (HPLC)
- Content uniformity (HPLC)
- Porosity (XRM/AI analysis)
- API distribution (AI analysis/HPLC)
- Mechanical properties (Texture Analysis)
- Swelling Test
- Enzyme Degradation Assay
- In vitro drug release testing (USP apparatus)

# Microstructure of Implants: Appearance



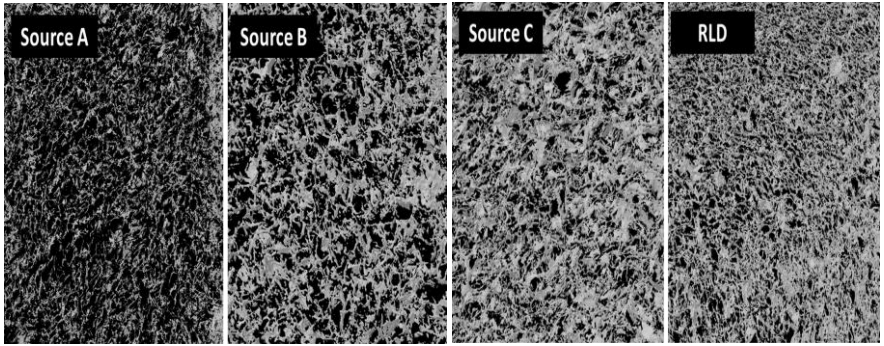

Appearance



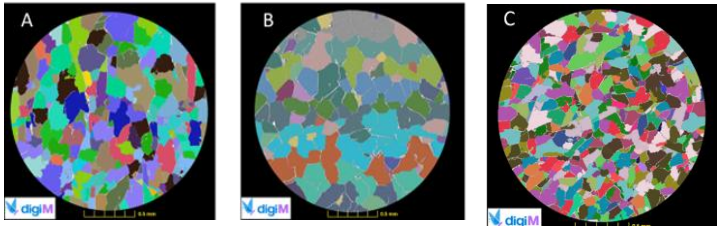

SEM surface morphology (upper tier) and cross sectional (lower tier).

# Microstructure of Implants: Porosity

Micro-CT

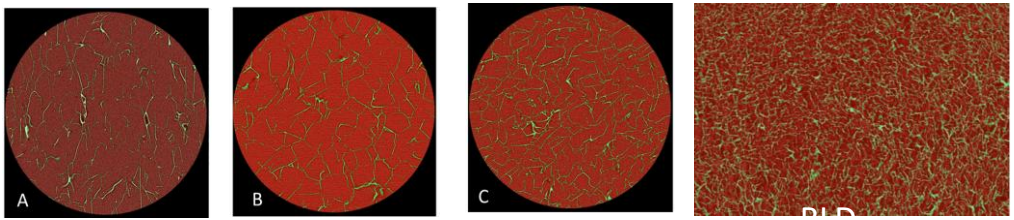



AI Pore size distribution




| Unit (µm) | $D_{10}$ | $D_{50}$ | $D_{90}$ |
|---|---|---|---|
| Source A | 120.8 | **192.1** | 265.1 |
| Source B | 128.1 | **191.4** | 255.5 |
| Source C | 90.5 | **135.2** | 185.4 |
| RLD | 49.4 | **75.2** | 104.9 |

AI assisted image Analysis and Segmentation for Porosity




Pores | Solid

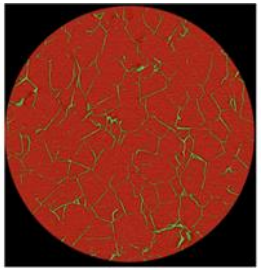
| Overview | | Source A | Source B | Source C | RLD |
|---|---|---|---|---|---|
| Volume Fractions (%) | Porosity | 93.2 | 93.7 | 89.9 | 80.9 |
| | Solid | 6.8 | 6.3 | 10.1 | 19.1 |

Data acquired and analyzed by digiM

# Distribution of API in Implants

Solid wall Thickness distribution by AI

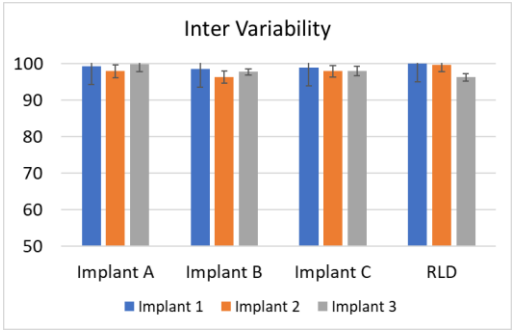
| Unit (µm) | $T_{10}$ | $T_{50}$ | $T_{90}$ | Avg. ± Std. Dev. |
|---|---|---|---|---|
| Source A | 0.6 | **2.7** | 4.4 | 3.9 ± 1.3 |
| Source B | 0.9 | **3.3** | 5.0 | 4.5 ± 1.5 |
| Source C | 0.6 | **2.7** | 4.5 | 3.9 ± 1.3 |
| RLD | 0.7 | 3.9 | 7.7 | 5.7 ± 2.3 |

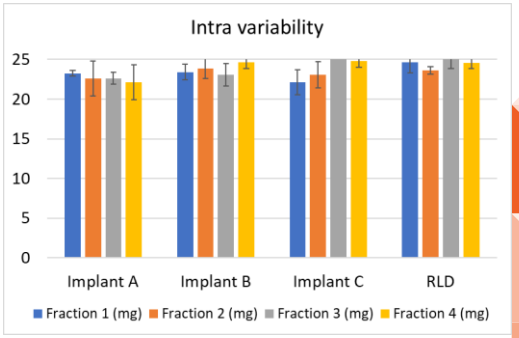


Pores | Solid

Solid wall= API+ collagen

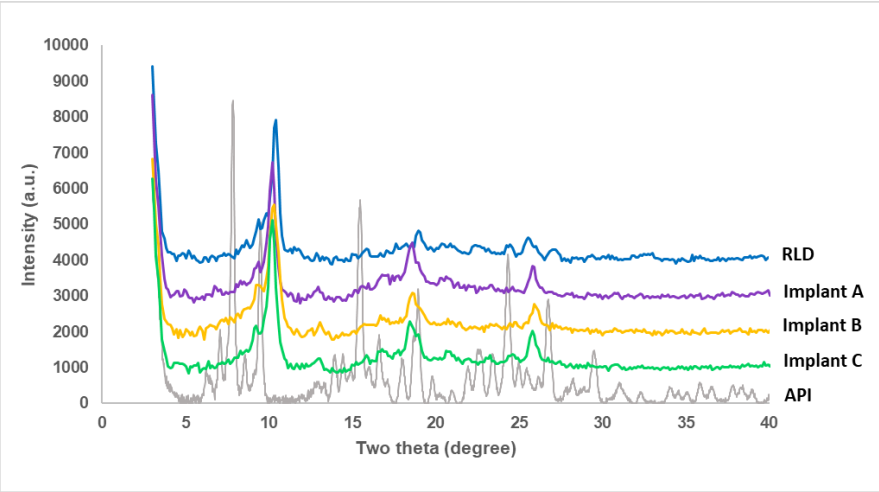
Drug distribution in the implants by HPLC




# Solid State of API in Implants

XRD

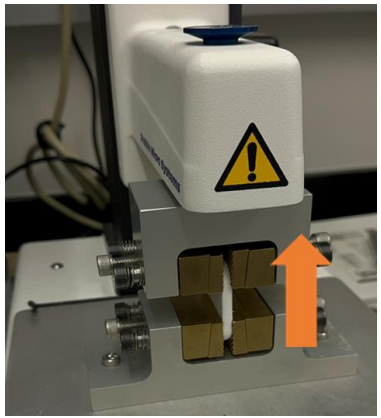



| Implant | % crystallinity |
|---|---|
| RLD | 79.8 |
| A | 62.1 |
| B | 65.4 |
| C | 71.8 |
| API | 93.3 |

% crystallinity: RLD > C > B > A ($p<0.05$)

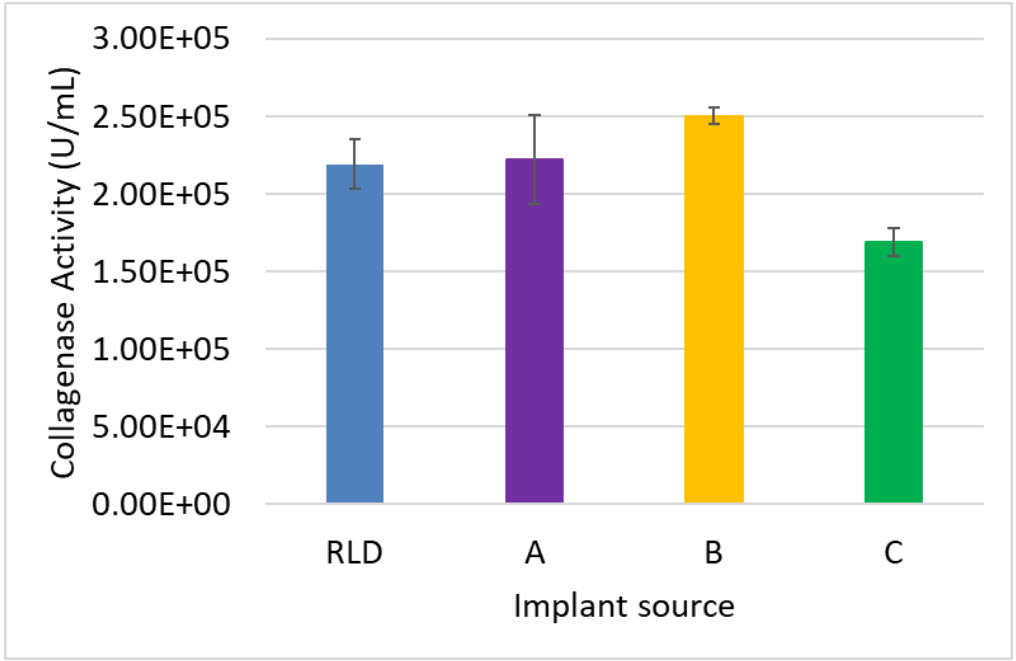
# Mechanical Strength of Implants

| Implant source | Maximum force (N) required for breakage of implants |
|---|---|
| RLD | 11.66 ± 1.75 |
| Implant A | 0.14 ± 0.04 |
| Implant B | 7.54 ± 0.55 |
| Implant C | 5.83 ± 0.92 |



Rigidity: RLD > B > C > A ($p<0.05$)

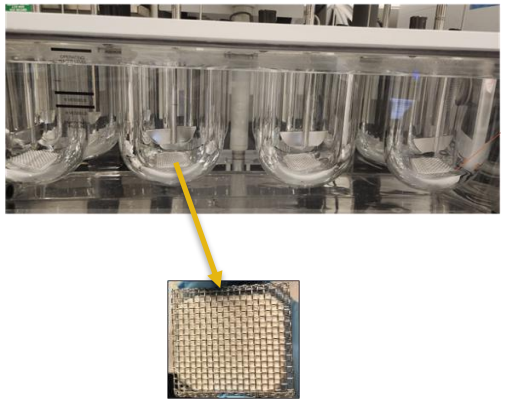
# Enzymatic Degradation of Implants



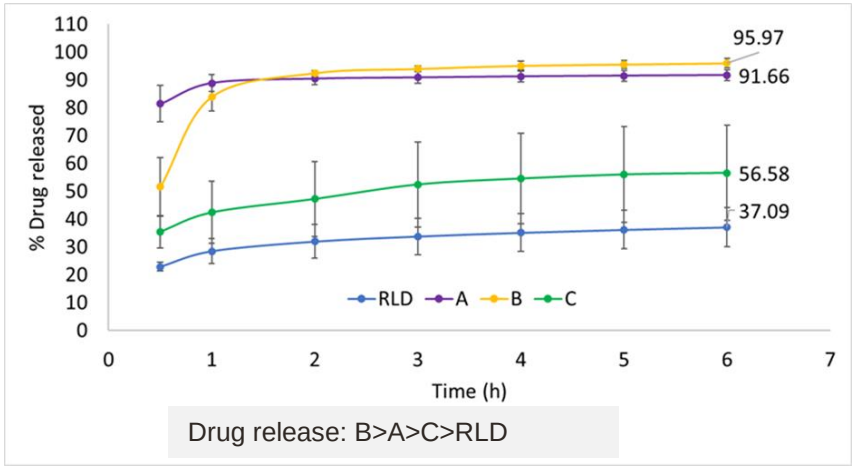

Collagenase Activity: B > A > RLD > C (p>0.05)

# In Vitro Drug Release from Implants

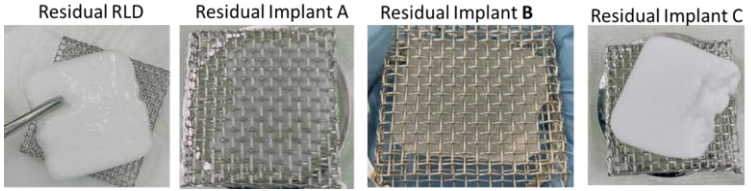
| | |
|---|---|
| **Apparatus** | USP II |
| **Rotation speed** | **50 rpm** (or 100 rpm) |
| **Medium** | Phosphate buffer pH 6.8 |
| **Medium volume** | 500 mL |
| **Temperature** | 37 ± 0.5 °C |
| **Sampling time** | 0.5,1,2,3,4,5, 6 hrs |
| **Sinker** | Custom made, **10 x 10** (or 5 x 5) stainless steel mesh |



Custom-made sinkers




Drug release: B>A>C>RLD




Porosity: B>A>C>RLD

% crystallinity: RLD > C > B > A ($p<0.05$)

# Current Thinking for PSG

**To demonstrate In vitro BE:**

- Use of type I collagen & of the same specie as RLD for generic development.

- Comparative characterization of collagen to demonstrate sameness to that of RLD (e.g., Hyp content, Gly content, nitrogen assay, N/Hyp ratio, soluble content, thermal properties, functional group)

- Comparative physicochemical characterization of test and RLD (appearance, solid state of API, microstructure analysis, mechanical properties, implant uniformity)

- Comparative in vitro drug release testing

# Conclusions

- Collagen source critically impacts the in vitro performance of implants

- Sameness of excipient and in vitro BE challenges for complex collagen implants can be demonstrated by comprehensive characterization

- Findings will be disseminated through peer-reviewed manuscripts to facilitate science-based generic product development

- This research provides scientific evidence that informed FDA's draft recommendations for PSG for in vitro BE assessment of collagen implant.

# Acknowledgments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  - –ORS: Qiangnan Zhang, Yan Wang, Qi Li , Bin Qin
  - –DiGiM: AI image analysis and segmentation
- **SMEs involved in the STT meeting**
  - –OPQR: Nahid Kamal, Xin Feng, Xiaoming Xu, Rangeeta Kumari
  - –OGD: Yan Wang, Satish Sharan, Bing Li, Qiangnan Zhang, Darby Kozak, Bin Qin
  - –OLDP: Bhagwant Rege, Robert Berendt
  - –ONDP: Dorota Matecka, Mark Seggel, Qi Zhang
  - –OPPQ: Kimberly Peters
- **STT meeting chairs:** Wenlei Jiang, Xiaoming Xu, Darby Kozak (previous chair)

# Questions?

**Nahid S. Kamal, Ph.D.**
Pharmacologist
OPQ/OPQR/DPQR-V
CDER | US FDA

# FDA's Option-Based BE Approach Recommendations for Locally Acting Metered Dose Inhalers and Dry Powder Inhalers

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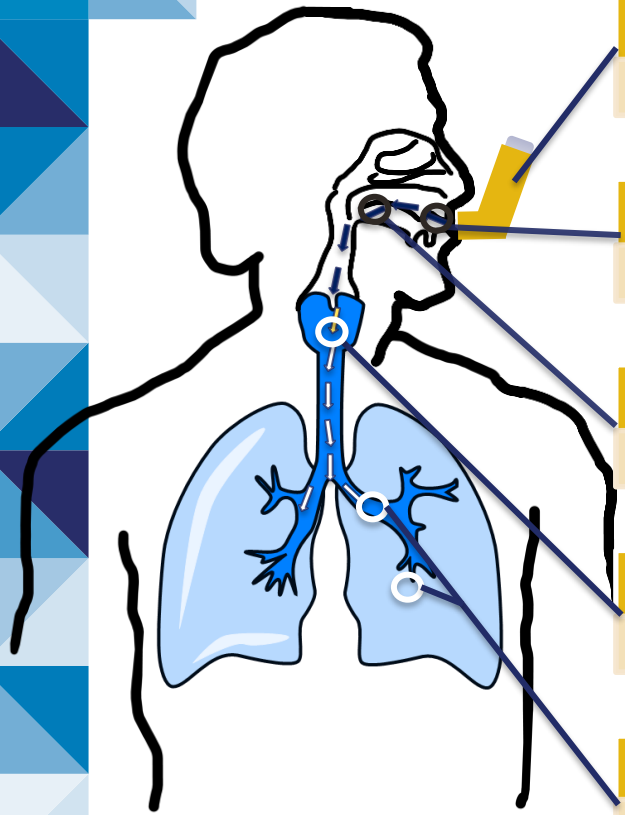
Office of Generic Drugs| CDER | U.S. FDA

Advancing Generic Drug Development Workshop: Translating Science to Approval
Session 1, October 7, 2025

# Outline

- Exploring the available **tools**, **supportive FDA research**, and **external input** for developing ***alternative BE approaches.***
- An overview of the ***option-based BE approach*** for **OIDPs.**
- Study design considerations for ***formulation sameness*** determination, ***realistic aerodynamic particle size distribution (rAPSD)***, ***dissolution***, ***particle morphology of the emitted dose***, ***charcoal block pharmacokinetic (PK) BE studies***, and ***computational modeling***.
- **Challenges** and **future directions** for ***OIDP BE approaches***.
- Conclusions.

# Potential Methods for Assessing Contributing Factors to Local Drug Delivery to the Lungs



**Step 1**
Formulation/Device Characteristics

**Step 2**
Actuation and Aerosolization

**Step 3**
Formulation Post-Actuation

**Step 4**
Airway Transit

**Step 5**
Deposition, Dissolution, Absorption

## IN VITRO STUDY METHODS

- Realistic Aerodynamic Particle Size Distribution
- Dissolution
- Optical Suspension Characterization
- Droplet Size Distribution by Laser Diffraction
- Morphology-assisted Raman Spectroscopy (MDRS)
- Scanning Electron Microscopy (SEM)
- X-ray Tomography
- Shadowgraphic imaging/shadow motion analysis
- Phase Doppler Interferometry/Anemometry
- Particle Imagine Velocimetry
- Optical Photothermal Infrared Microscopy
- Atomic Force Microscopy – Infrared Microscopy
- Cell Permeability Assays

## IN VIVO STUDY METHODS

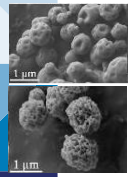
- Charcoal Block Pharmacokinetic (PK) Study
- Imaging – based Study (e.g., Scintigraphy)

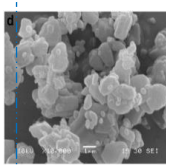
## IN SILICO STUDY METHODS

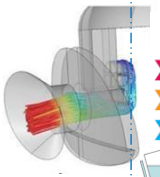
- Computational Fluid Dynamics
- Regional Deposition Modeling
- Physiologically-based PK modeling
- Population PK Modeling

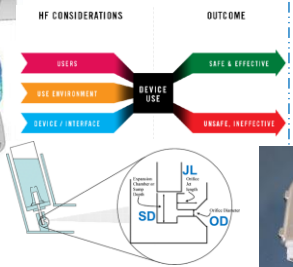
# ORS Research Activities for OIDPs

Formulation → Device → User Interface → Regional Deposition → Dissolution → Absorption





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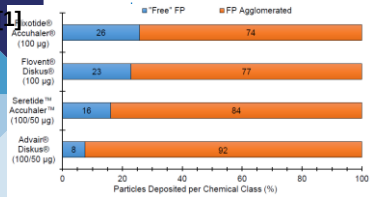


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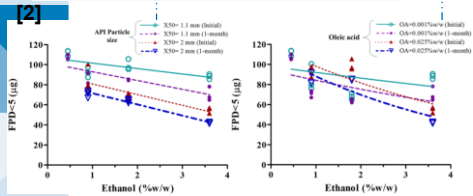


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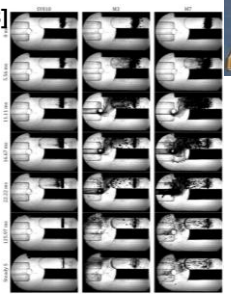

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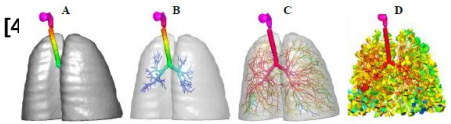


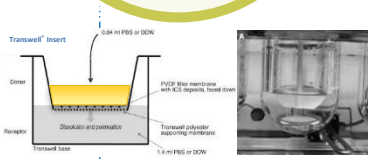




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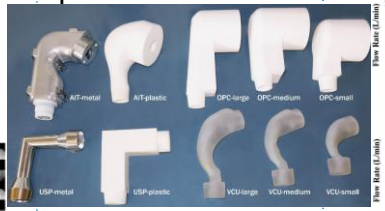


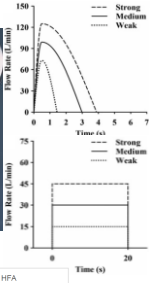


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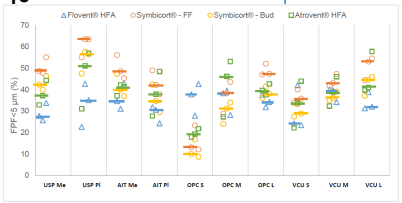


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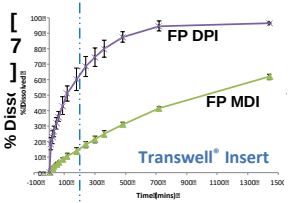


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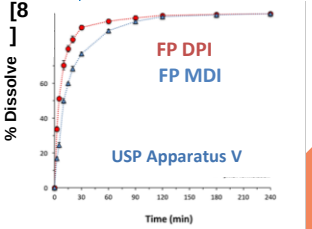


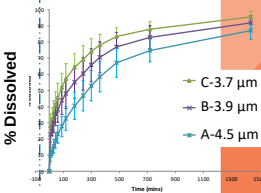


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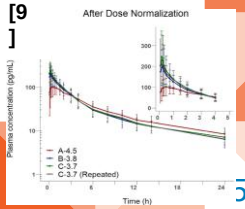
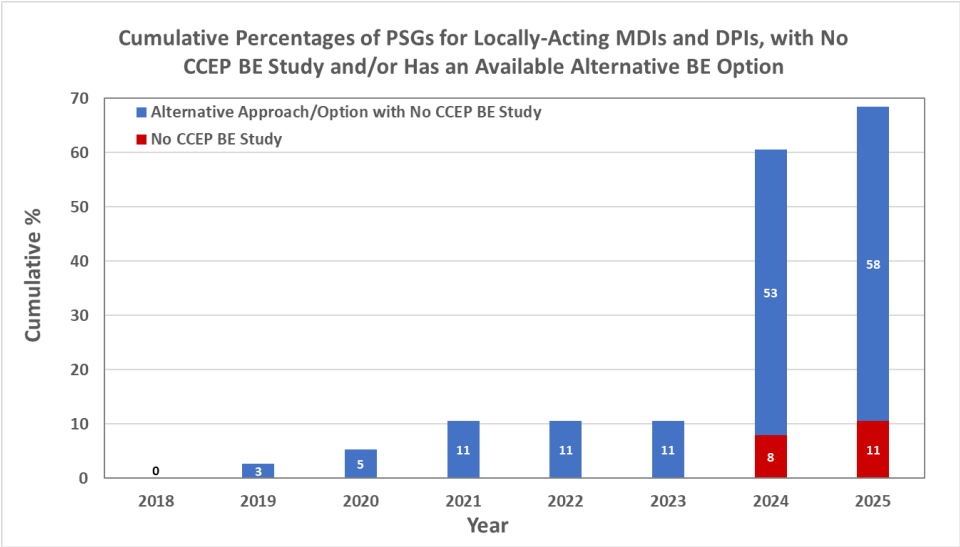


# Updates to PSGs of Locally Acting MDIs and DPIs

- Since 2018, FDA has **increased the percentage of available PSGs** for locally acting MDIs and DPIs.
  - Recommend ***alternative approaches*** to CCEP BE studies.
  - An ***option-based*** BE approach (no CCEP/PD BE study in Option 1)
  - ***Do not recommend*** the CCEP BE study.

- **2018**:
  - **0%** of available PSGs had alternative BE approaches to a CCEP BE study (i.e., a CCEP BE study recommended in every case).
- **2019**:
  - **First alternative BE approach/option** available.
- **2025**:
  - **11%** - PSGs with no recommended CCEP BE study.
  - **58%** - alternative approach/option available.
  - Total → **69%**



# Recommendations to Demonstrate BE: MDIs and DPIs

## Option 1^

**Formulation Sameness**
- No difference in formulation (e.g., Q1/Q2 sameness to RS)

**In Vitro Studies**
- SAC, APSD, Spray Pattern, Plume Geometry, Priming/Repriming, rAPSD, Dissolution*

*When BA of API is dissolution limited*

**Comparative Characterization Studies**
- Particle Morphology of the Emitted Dose**

**When formulations are more complex*

**In Vivo Studies**
- PK BE Study, PK BE Study With Charcoal Block***

***When GI absorption of API affects systemic BA*

**Additional Information**
- Optional Computational Modeling Study(ies)
- Device Similarity (in design and user interface) to the RLD

## Option 2 ^

**Formulation Sameness**
- None (e.g., Q1/Q2 or non-Q1/Q2 the same to the RS)

**In Vitro Studies**
- SAC, APSD, Spray Pattern, Plume Geometry, Priming/Repriming

**Comparative Characterization Studies**
- Particle Morphology of the Emitted Dose**

**When formulations are more complex*

**In Vivo Studies**
- PK BE Study, PD/CCEP BE Study

**Additional Information**
- Optional Computational Modeling Study(ies)
- Device Similarity (in design and user interface) to the RLD

^ *Refer to the product-specific guidance (PSG) on the MDI or DPI of interest for the specific recommended BE studies.*

# Option 1 BE Formulation Recommendations for MDIs and DPIs

## Option 1

**Formulation Sameness**

- The test (T) product should contain no difference in inactive ingredients or other aspects of the formulation relative to the RS that may significantly affect local or systemic availability of the active ingredient (e.g., Q1/Q2 sameness to RS).

**Formulation Sameness**

- *Demonstrate Q1/Q2 sameness to RS.*
- *If formulation sameness not met (e.g., an NGP MDI), demonstrate formulation change will not affect local or systemic BA of API.*
  - *Provide justification, which may include, but not limited to formulation characterization data, product development data, comparative characterization studies, and/or scientific literature.*

- *Goal: understand the formulation design space of critical excipients, their ranges, and their potential impact(s) on API bioavailability within the lungs.*
- *Information, data, and/or studies warranted will depend on the formulation changes being proposed.*
- *Ensure formulation difference(s) do not impact desired outcomes in product performance, safety, and efficacy.*
  - *No novel excipients, and consider inactive ingredient maximum daily exposures (MDEs).*

RS: Reference Standard

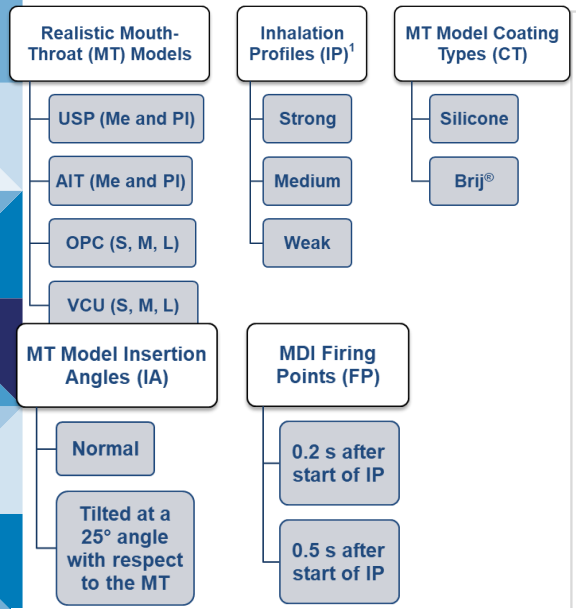
# Realistic APSD

- **Realistic APSD (rAPSD):**
  - Incorporates more ***clinically relevant*** conditions via considering patient factors.
    - **Patient breathing/inhalation profiles (IPs)**
    - Representative ***mouth-throat (MT) models***
  - Understand the ***impact of patient variability*** on aerosol performance.

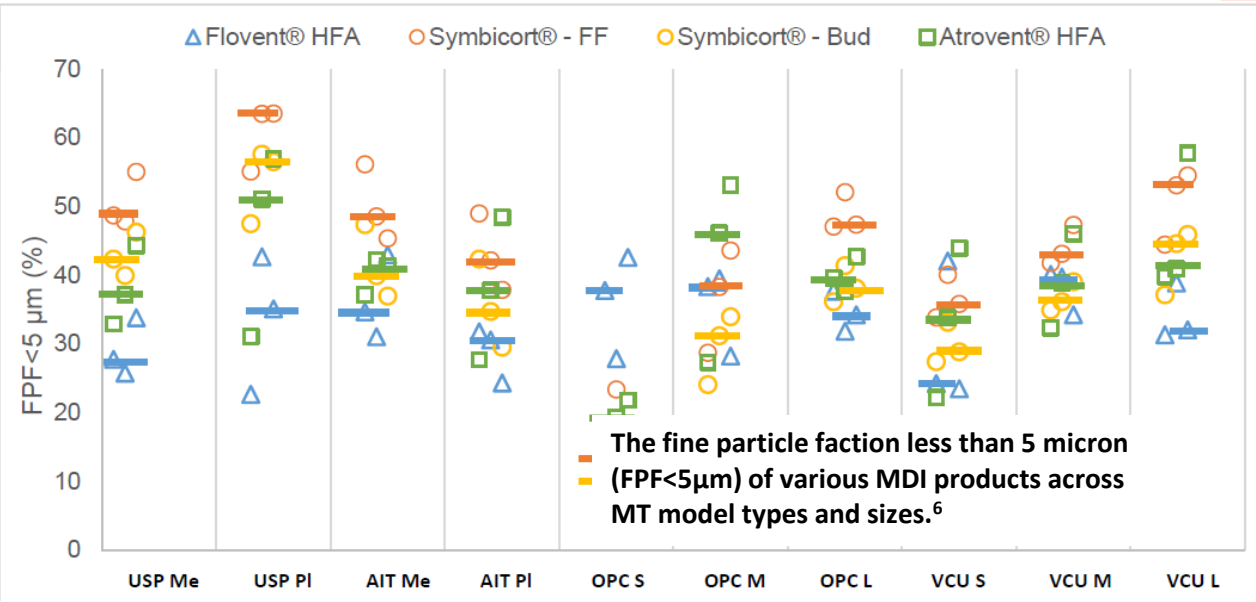

**APSD: aerodynamic particle size distribution;**
**VCU: Virginia Commonwealth University; OPC: Oropharyngeal Consortium**

# Realistic APSD Study Design Considerations

- **GDUFA-Funded Research Outcomes**
  - Response to the various study factors is ***product-specific.***
  - **Method Development:** consider mouth-throat (MT) types and size, inhalation profiles (IPs), and other factors.




Study design factors evaluated for rAPSD with solution and suspension-based MDIs.[6]

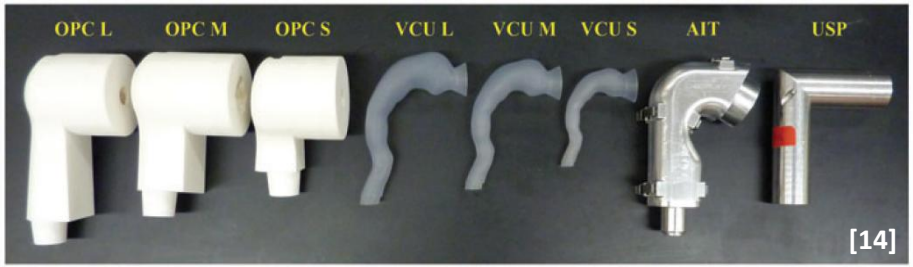



The fine particle faction less than 5 micron (FPF<5µm) of various MDI products across MT model types and sizes.[6]

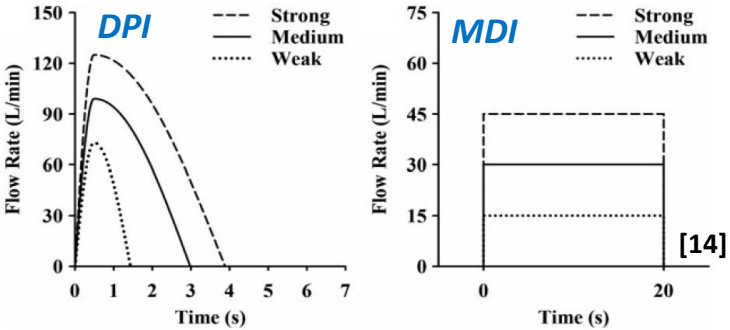
GDUFA: Generic Drug User Fee Amendments; USP: United States Pharmacopeia; AIT: Albert Idealized Throat; OPC: Oropharyngeal Pharmacopeia Consortium; VCU: Virginia Commonwealth University

# Realistic APSD Study Design Considerations

***Realistic mouth-throat (MT) models***



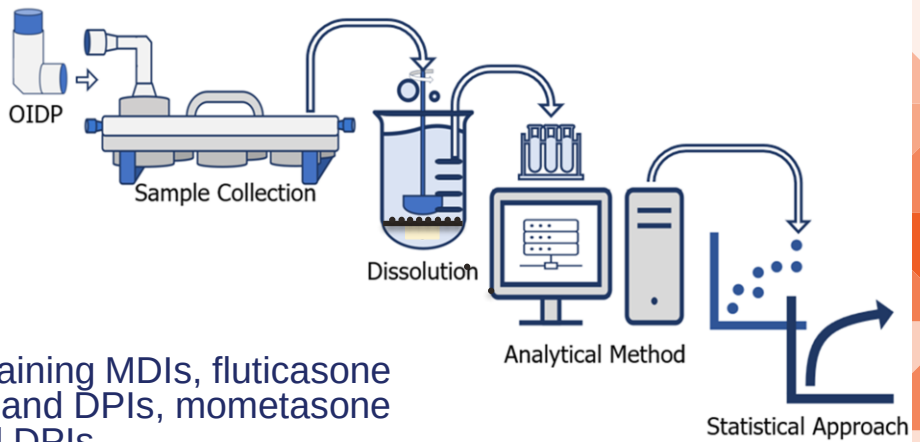

***Inhalation profiles (IPs)***




- **PSG Recommendations:**
  - **Beginning** lifestage.
  - Include different ***MT sizes*** and ***IPs*** that reasonably cover the expected inter-subject variability of the indicated patient population via **bracketing approach.**
    - Example: Small and large MT sizes + weak and strong IPs the cover patient population.
    - Correlate in vitro performance to in vivo lung deposition data, if available.
    - IPs obtained from patients.
  - **BE:** ***population bioequivalence (PBE)*** of ***impactor sized mass (ISM)*** for each MT-IP combination.
    - ***Alternative statistical approaches*** may be used if scientifically justified.
    - Request a ***Pre-ANDA meeting*** to discuss **alternative approaches** to the study design and/or statistical methods.

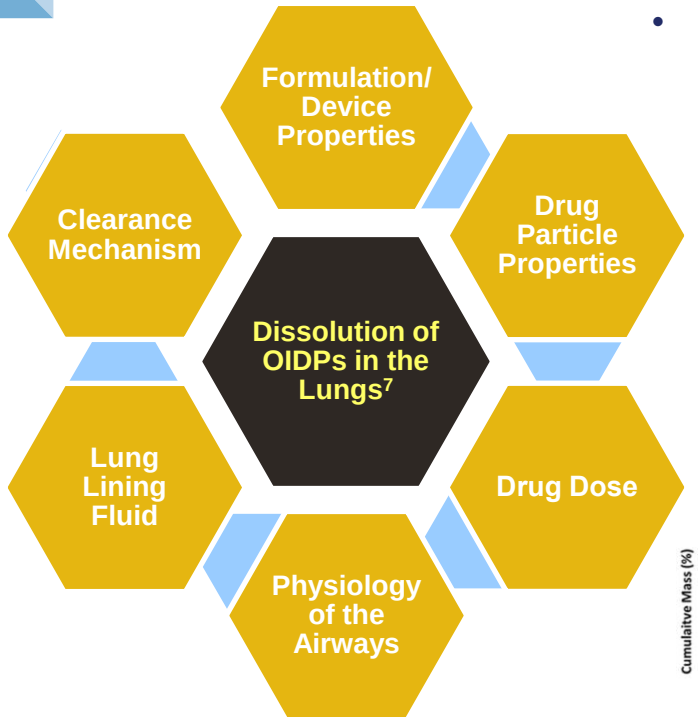
# Dissolution

- **Dissolution** of the active pharmaceutical ingredient (API) from the emitted dose:
  - Helps to understand the ***rate at which the API dissolves.***
  - Is recommended ***only*** for those cases for which:
    - The ***API is dissolution-limited***, i.e., dissolution is the rate-limiting step in absorption in the lungs, or
    - Contains other ***formulation properties*** that ***make dissolution the rate-limiting step*** in absorption in the lungs.



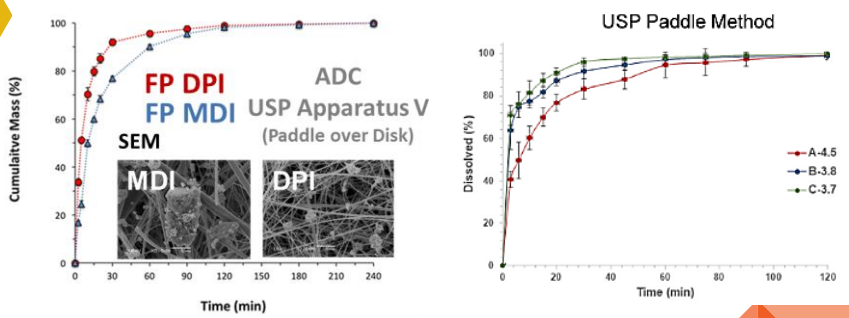

  - Examples: budesonide containing MDIs, fluticasone propionate containing MDIs and DPIs, mometasone furoate containing MDIs and DPIs.

# Dissolution Study Design Considerations




Drug dissolution in the lungs can be impacted by multiple factors.[15]

- **GDUFA-funded research**
  - **Many contributing factors** that can affect ***dissolution performance*** and ***study sensitivity.***
  - Currently **no** standardized method; method development is ***product-specific.***
  - Can develop dissolution methods that are **sensitive** and **discriminatory** to meaningful differences in ***formulation*** and/or ***manufacturing process.***
  - The need for dissolution studies is ***API-*** (e.g., high/low solubility) and ***product-specific.***




Dissolution of OIDPs can are sensitive to differences in both dosage form (left) and particle size (right).[8,9]

# Dissolution Study Design Considerations

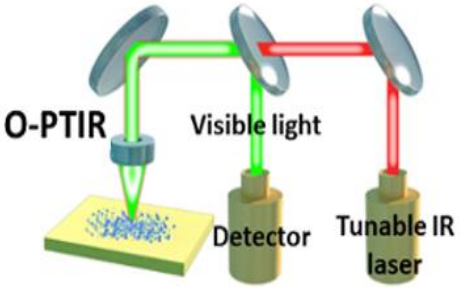
- Sample Collection
- Dissolution Apparatus
- Dissolution Media
- Method Validation
- Assessment

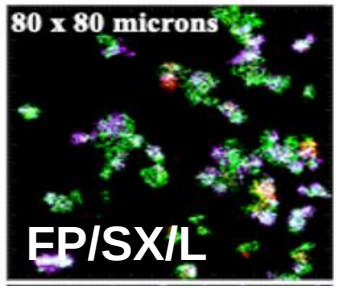
- **PSG Recommendations:**
  - ***Beginning*** Lifestage.
  - Collect **aerosolized dose** of ***similar drug mass*** between T and RS products.
  - **Optimized** and **validated** method (e.g., apparatus, sample collection, dose, media type and volume, stirring/agitation rate, sampling times).
  - **Discriminatory** (e.g., differences in ***deposited drug particle sizes***).
  - **BE:** Comparative analysis of dissolution profiles with an appropriate statistical method (e.g., ***similarity factor [f2]***).

# Comparative Characterization Study: Particle Morphology

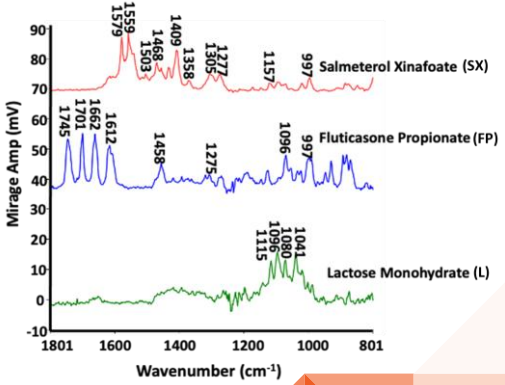
- **Particle Morphology**
  - Particle ***shape***, ***surface roughness***, ***porosity***, ***crystalline/amorphous structure***, etc. of the residual aerosolized dose, once deposited in the lungs, can impact the rate of ***dissolution*** of the API and ***cellular permeability*** and ***uptake*** within the lungs.
  - Compare the residual particle morphology, agglomeration behavior, amorphous/crystalline content, and/or polymorphs and for those cases with ***complex formulation considerations***.

**Analysis of Fluticasone Propionate (FP); Salmeterol Xinafoate DPI by Optical Photothermal Infrared Spectroscopy (O-PTIR).[16]**

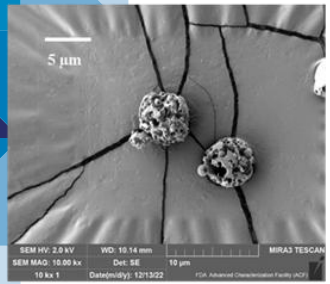


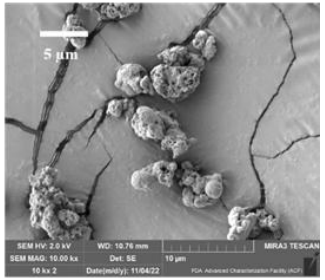




NGI Stage 3



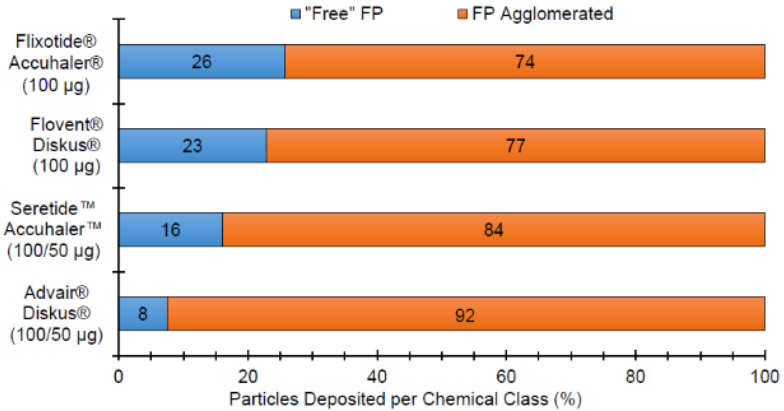
# Particle Morphology of the Emitted Dose Study Considerations

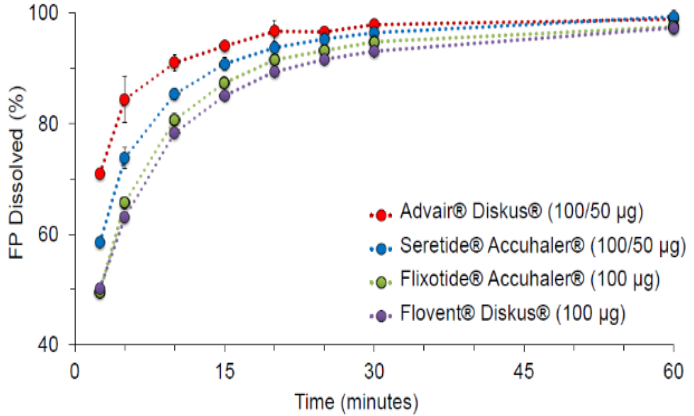



- ***Comparative characterization studies*** provide **supportive evidence** for establishing BE between T and RS OIDPs.
- For example, particle morphology can contribute to the APSD and dissolution performance for certain OIDPs.
- Whether a PSG for an OIDP incorporates comparative characterization studies depends on the specific product.

**Figure 7: SEM images of phospholipid porous particles found in a marketed DPI (left) and MDI (right) [21]**



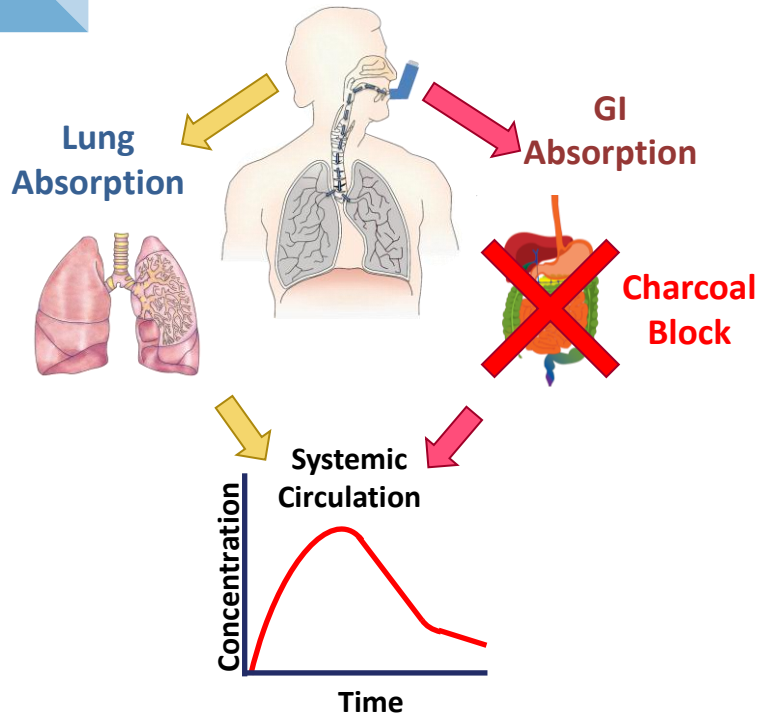




**Microstructural differences in the deposited particle agglomerates (left) may be one potential contributing factor to performance differences, such as with dissolution performance (right).[1]**

# Particle Morphology of the Emitted Dose Study Considerations

- **PSG Recommendations:**
  - A minimum of ***three batches*** of the T and RS product should be testing using the ***beginning lifestage*** of the product.
  - ***Imaging comparisons*** should be conducted on the deposited particles of the **emitted dose.**
  - The ***morphological features*** of the particles, which may include their **agglomeration characteristics**, should be evaluated.
  - A description of the ***sampling collection method*** should be provided.

# In Vivo Charcoal Block PK BE Studies




**Drug absorption into the systemic circulation following dosing with certain OIDPs can occur through both lung absorption as well as gastrointestinal (GI) absorption. Dosing with charcoal can block GI absorption.**

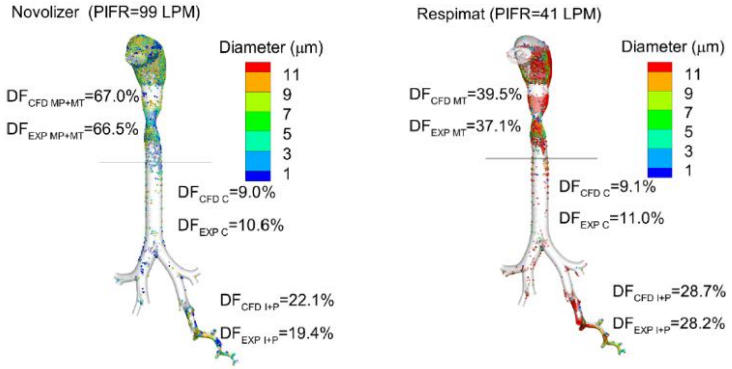
- For OIDPs, a portion of the emitted dose may be swallowed rather than inhaled and end up in the GI tract.
- For drugs with significant gut absorption, systemic levels may be difficult to distinguish between inhaled vs. swallowed portions.
- ***Charcoal block PK studies*** allow for a more direct analysis of the lung dose contribution in systemic circulation by eliminating the GI tract dose contribution.

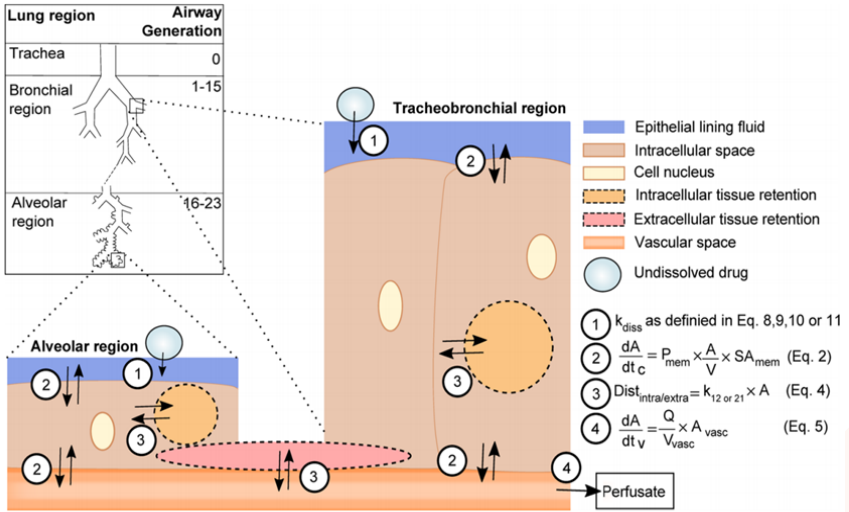
# In Vivo Charcoal Block PK BE Study Considerations

- **PSG Recommendations:**
  - Similar to a PK BE study in many aspects.
    - ***Healthy*** adult male and female subjects.
    - ***Minimum number of inhalations*** to sufficiently characterize the PK profile with a sensitive analytical method.
    - Dose administration should follow the approved labeling instructions.
    - ***Bio-IND*** may be needed if the administered dose is **above the maximum labeled single dose.**
  - **No** standard for the ***charcoal dose***, so the selected dose and how and when its administered should be justified in the abbreviated new drug application (ANDA).
  - **BE:** 90% confidence interval (CI) for the T/R ratios of AUC and $C_{max}$ being between 80 – 125%.
  - **Prospective applicants are encouraged to discuss *other approaches* for assessing BE in local and systemic bioavailability of the active ingredient with FDA via a pre-ANDA meeting request before conducting a charcoal block PK BE study.**

# Optional Computational Model(s) as Supportive Studies

- ***Computational models*** can provide support for a wide array of questions impacting both **drug development** and assessment of **performance.**
- Various in silico models (e.g., ***regional deposition modeling, CFD, PBPK***) are available and can serve **different purposes**.




**Computation fluid dynamic (CFD) models (left) and physiologically based PK (PBPK) models (right) are two samples of computation models that can support BE assessments as well as drug development.[17,18]**

# Optional Computational Model(s) as Supportive Studies

- **PSG Recommendations:**
  - ***Purpose***
    - Impact of product factors on regional drug delivery to establish biorelevant BE limits for BE studies (e.g., rAPSD, plume geometry).
    - Assess regional lung deposition BE via virtual simulations.
  - Model ***purpose*** should be **well stated.**
    - Example: CFD or semiempirical model to predict central and peripheral lung deposition
    - Example: PBPK models useful if drug absorption is not expected to be rapid, such that regional deposition may not be considered as a surrogate for regional lung delivery.
  - Model ***credibility*** and ***validation*** should be established.
  - Model ***verification*** is needed to establish **credibility.**
  - Model ***validation acceptance criteria*** and the ***statistical analysis methods*** for virtual BE studies should be **defined prior to testing** and be **justified.**

**Full Details: PSG on *Formoterol Fumarate; Glycopyrrolate Inhalation Aerosol Metered* (NDA 208294).**[19]

# Current Challenges and Future Directions

- **Need for method standardization.**
  - **rAPSD:** which MT models and IPs to use for bracketing.
  - **Dissolution:** sample collection, dissolution apparatus, dissolution media, etc.
  - **Charcoal PK BE Studies:** standardization of charcoal dosing.
- **Establish validated in silico methods to support BE evaluation of OIDPs.**
- **Find areas to streamline and harmonize BE approaches globally for OIDPs.**
  - Identify key vs. supportive BE studies.
  - Establish in vitro-in vivo relationships.
- **Provide additional guidance and clarity where warranted.**

- FDA continues its efforts to address these challenges.
- Refer to most recent PSGs on MDIs and DPIs which are updated periodically and will reflect the Agency's current scientific thinking.
- Prospective applicants are highly encouraged to discuss their development plans with the Agency to gain feedback on complex and challenging issues, including:
  - Appropriate study designs, analyses and supporting justifications for NGP MDI submissions

# Conclusions

- To address these challenges, FDA has explored ***in vitro, in vivo, and in silico study designs*** through GDUFA-funded research initiatives and workshops to identify ***alternative approaches*** that can be used in lieu of the CCEP BE study for establishing local drug delivery equivalence.
- FDA recently developed ***PSGs for MDIs and DPIs*** that recommend an ***option-based BE approach.***
  - Study recommendations are included for ***rAPSD***, ***dissolution***, ***comparative characterization studies***, ***charcoal block PK BE studies***, and ***computational models.***
- While FDA's option-based BE approaches allow for BE pathways without a CCEP BE study, FDA will continue its efforts to ***clarify***, ***streamline***, and ***harmonize*** its BE approaches for OIDPs.

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# Resources


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# Resources


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# Thank you!

# Streamlining Recommendations for Topical Products Applied to the Skin and Mucosa

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Office of Generic Drugs
CDER | US FDA

Advancing Generic Drug Development Workshop: Translating Science to Approval
October 7-8, 2025

# Disclaimer

This presentation reflects the view of the presenter and should not be construed to represent FDA's views or policies.

# Outline

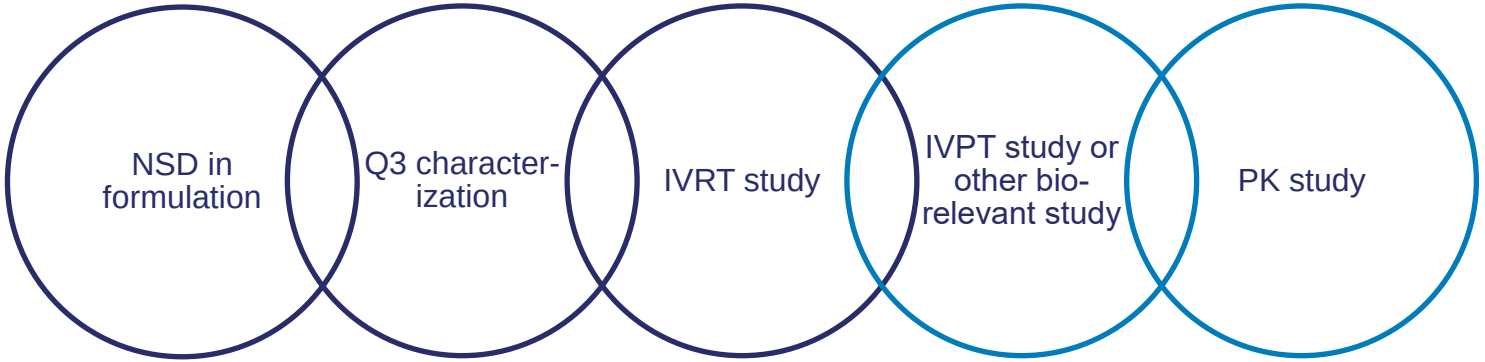
- Topical products applied to the skin and mucosa
  - Efficient BE approaches
  - Waiver of BE studies for an additional strength(s)
  - Practical insights on ANDA submissions

BE: Bioequivalence; ANDA: Abbreviated new drug application

# Efficient BE approaches for topical products applied to the skin and mucosa

# Common BE approaches

## Characterization-based BE approaches




## In vivo BE approaches

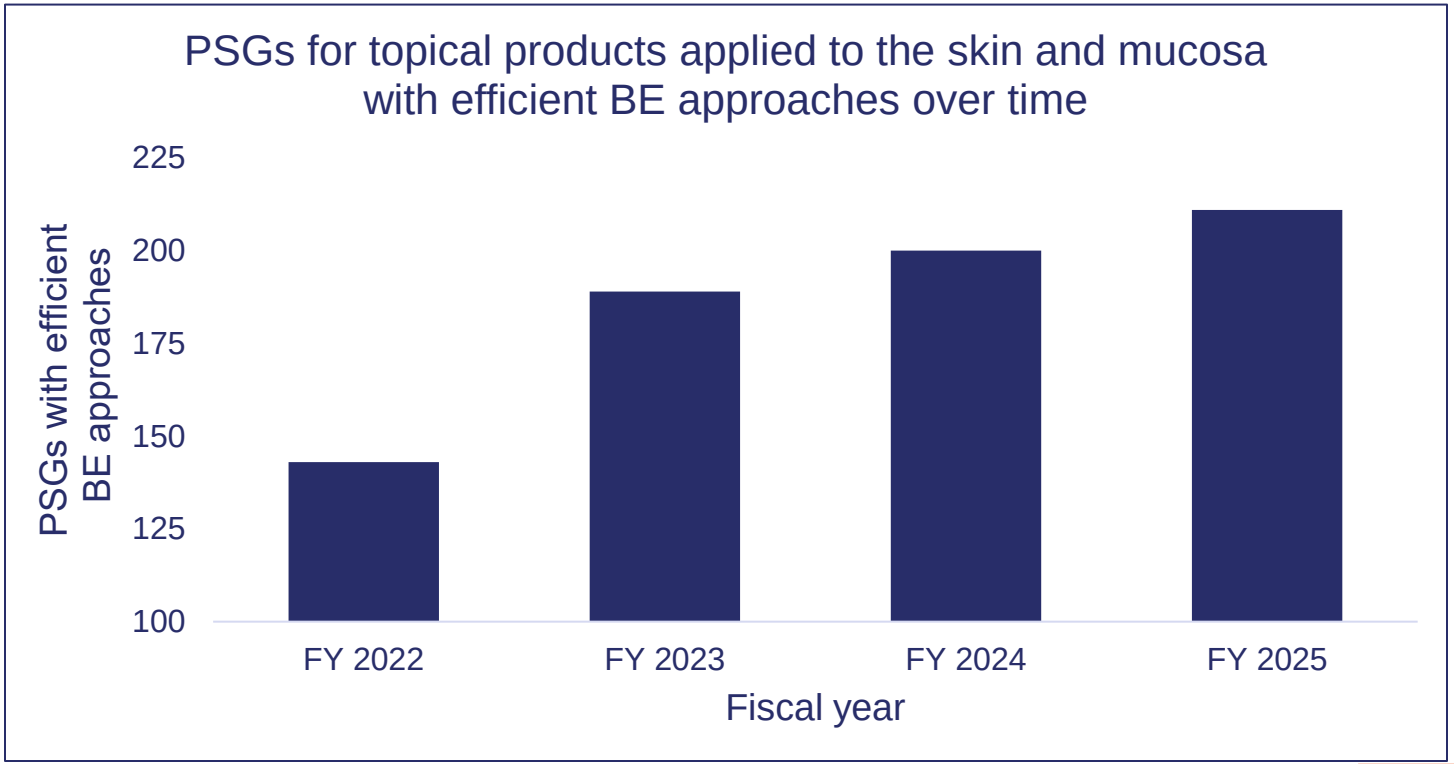
CCEP study

VC study

NSD: No significant difference; Q3: Physicochemical and structural; IVRT: In vitro release test;
IVPT: In vitro permeation test; PK: Pharmacokinetic; CCEP: Comparative clinical endpoint; VC: Vasoconstrictor

"An Overview of the Current Product-Specific Guidances for Topical Products"

# Efficient BE approaches over time




PSG: Product-specific guidance; Data through September 2025

# Revisions to add efficient approaches

## Recommended Aug 2022

| | |
|---|---|
| **Active Ingredient:** | Ruxolitinib phosphate |
| **Dosage Form:** | Cream |
| **Route:** | Topical |
| **Strength:** | EQ 1.5% Base |
| **Recommended Study:** | One comparative clinical endpoint bioequivalence study |

## Revised Nov 2024

| | |
|---|---|
| **Active Ingredient:** | Ruxolitinib phosphate |
| **Dosage Form:** | Cream |
| **Route:** | Topical |
| **Strength:** | EQ 1.5% Base |
| **Recommended Studies:** | Two options: (1) two in vitro bioequivalence studies and other characterization tests or (2) one comparative clinical endpoint bioequivalence study |

## Revised Feb 2019

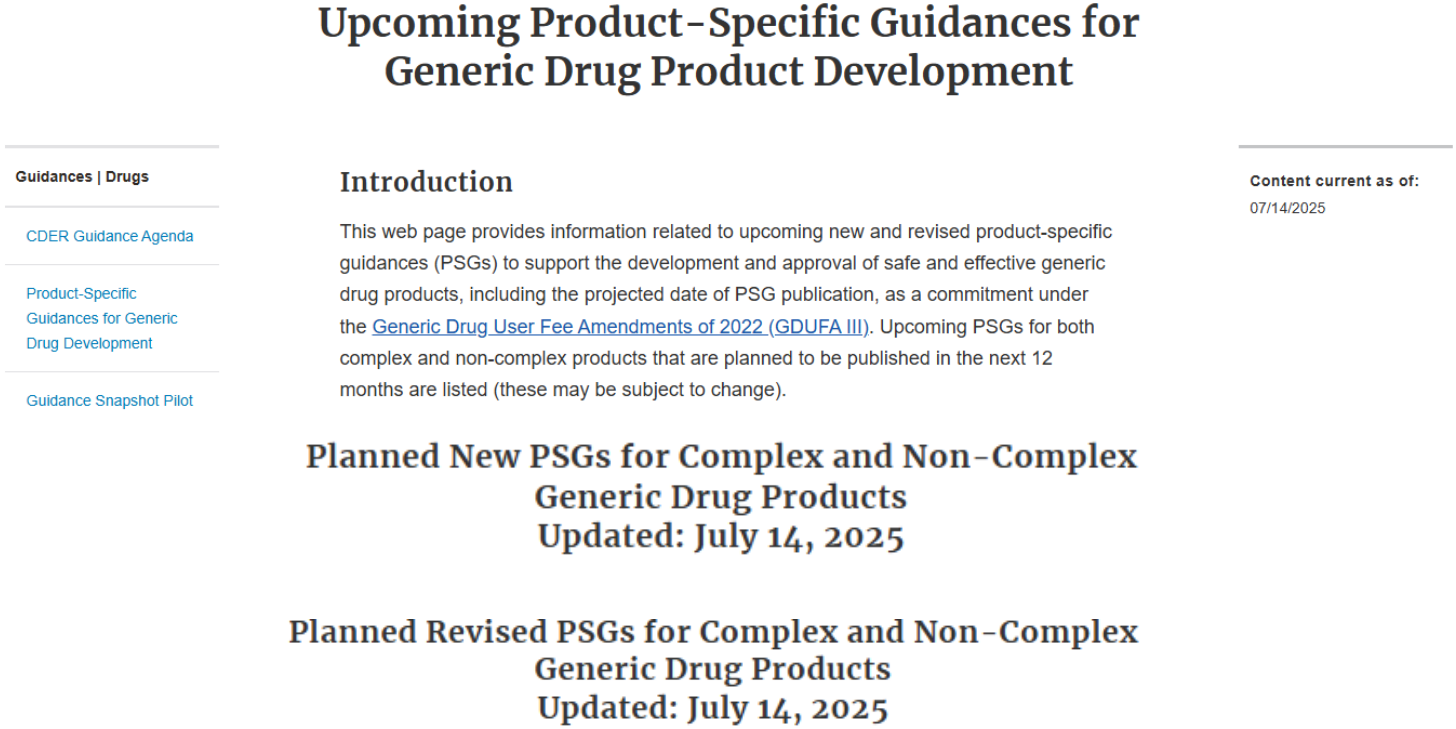
| | |
|---|---|
| **Active Ingredient:** | Terbinafine hydrochloride |
| **Dosage Form; Route:** | Cream; topical |
| **Recommended Studies:** | One study |

1. Type of study: Bioequivalence Study with Clinical Endpoint

## Revised May 2025

| | |
|---|---|
| **Active Ingredient:** | Terbinafine hydrochloride |
| **Dosage Form:** | Cream |
| **Route:** | Topical |
| **Strength:** | 1% |
| **Recommended Studies:** | Two options: (1) one in vitro bioequivalence study and other characterization tests or (2) one comparative clinical endpoint bioequivalence study |

# Upcoming PSGs with efficient approaches



## Upcoming Product-Specific Guidances for Generic Drug Product Development

Guidances | Drugs

CDER Guidance Agenda

Product-Specific Guidances for Generic Drug Development

Guidance Snapshot Pilot

### Introduction

This web page provides information related to upcoming new and revised product-specific guidances (PSGs) to support the development and approval of safe and effective generic drug products, including the projected date of PSG publication, as a commitment under the Generic Drug User Fee Amendments of 2022 (GDUFA III). Upcoming PSGs for both complex and non-complex products that are planned to be published in the next 12 months are listed (these may be subject to change).

Content current as of:
07/14/2025

### Planned New PSGs for Complex and Non-Complex Generic Drug Products
### Updated: July 14, 2025

### Planned Revised PSGs for Complex and Non-Complex Generic Drug Products
### Updated: July 14, 2025

Upcoming Product-Specific Guidances for Generic Drug Product Development website

# Waiver of BE studies for an additional strength(s)

# Historical approach

- All BE studies recommended for each strength
- Example: PSG for tacrolimus topical ointment (Oct 2022):

| **Tacrolimus topical ointment, 0.1%** | **Tacrolimus topical ointment, 0.03%** |
|---|---|
| • Option 1: Characterization-based BE approach<br>  • NSD in formulation<br>  • Comparative Q3 characterization<br>  • IVRT<br>  • IVPT<br>• Option 2: CCEP BE study | • Option 1: Characterization-based BE approach<br>  • NSD in formulation<br>  • Comparative Q3 characterization<br>  • IVRT<br>  • IVPT<br>• Option 2: CCEP BE study |

# New approach

- A waiver of a BE study for an additional strength may be acceptable, provided that the conditions of the waiver are met
- Examples:
  - Characterization-based BE approach→ Waive an IVPT study
  - In vivo BE approach→ Waive a CCEP BE study

# New approach

- A waiver of a BE study for an additional strength may be acceptable, provided that the conditions of the waiver are met
- PSG for tacrolimus topical ointment (Nov 2024):

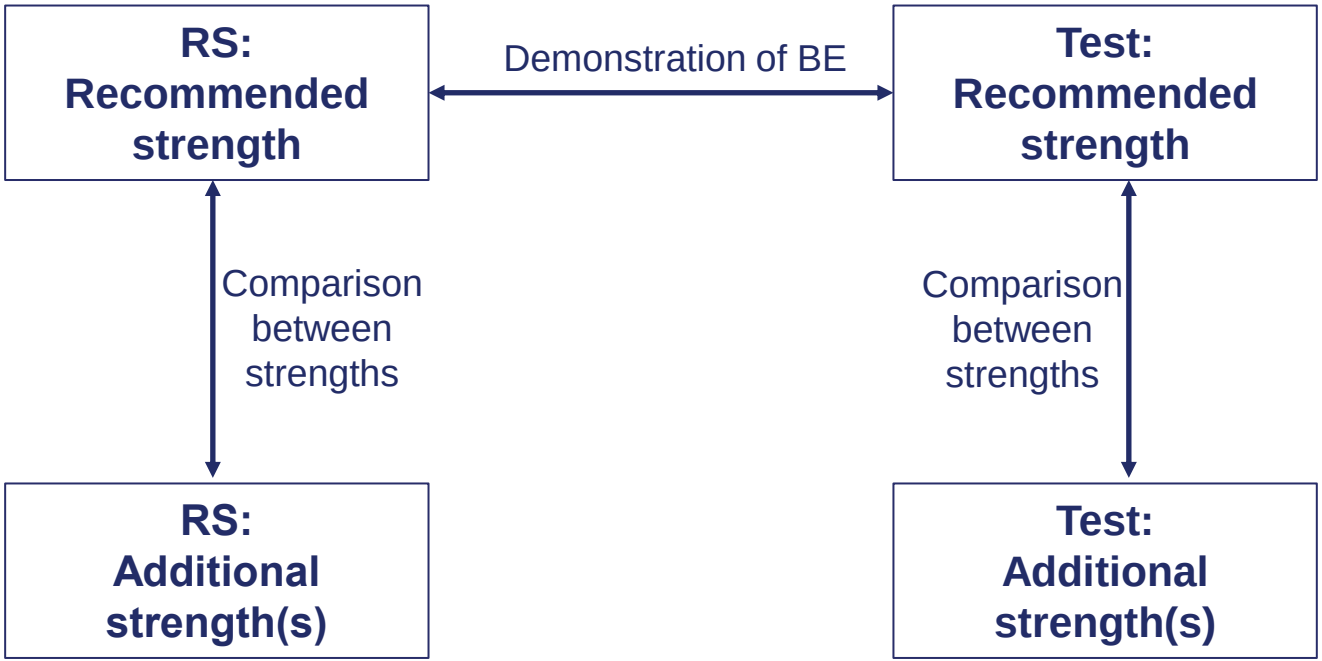
**Tacrolimus topical ointment, 0.1%**

- Option 1: Characterization-based BE approach
  - Formulation sameness
  - Comparative Q3 characterization
  - IVRT
  - IVPT
- ~~Option 2: CCEP BE study~~ (waived)

**Tacrolimus topical ointment, 0.03%**

- Option 1: Characterization-based BE approach
  - Formulation sameness
  - Comparative Q3 characterization
  - IVRT
  - ~~IVPT~~ (waived)
- Option 2: CCEP BE study

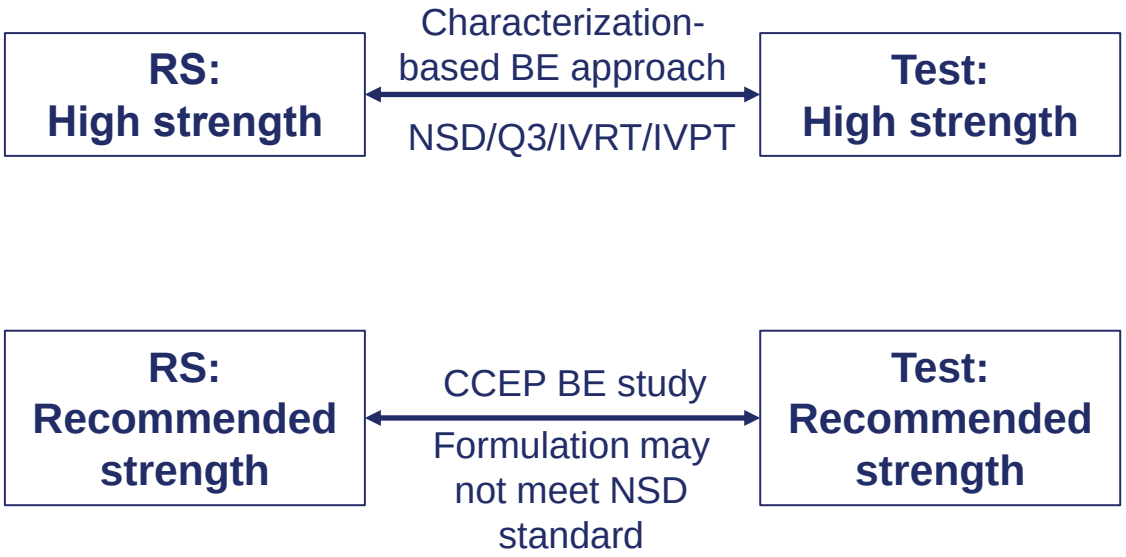
# Components of waiver approach




RS: Reference standard

# Components of waiver approach

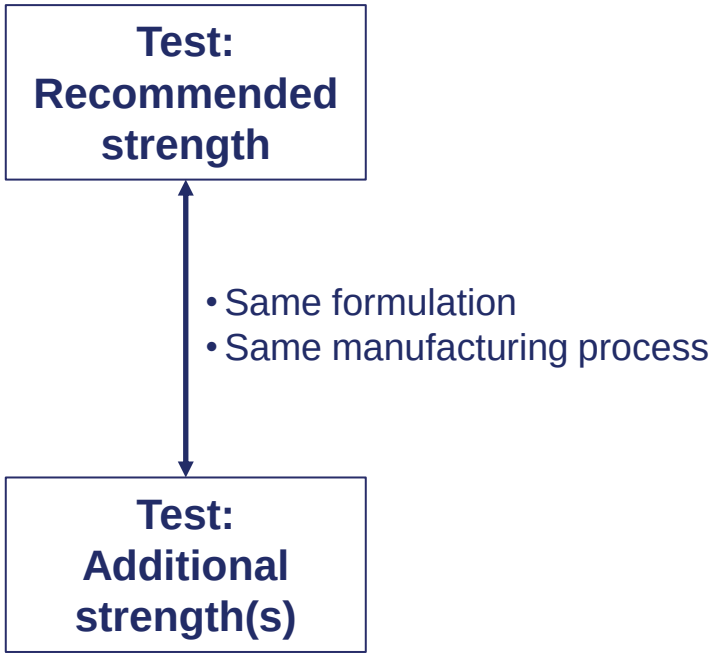
Acceptable **demonstration of BE of the recommended strength**



# Components of waiver approach

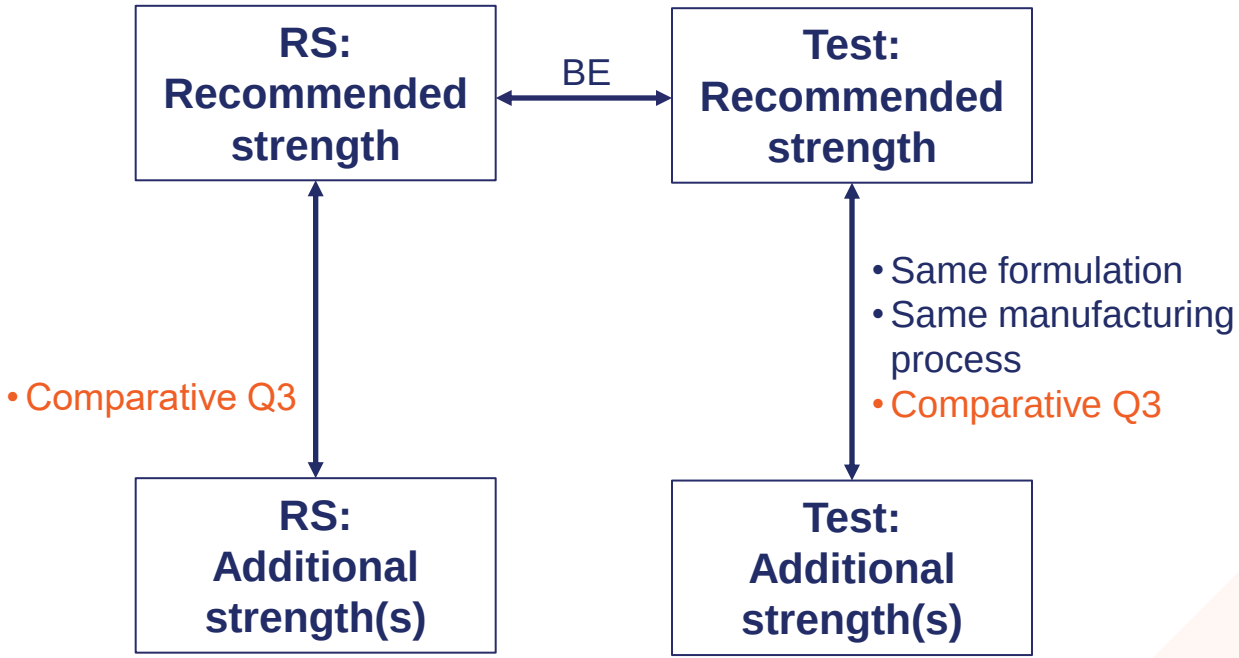
The **formulations of the lower and higher strengths** of the test product are **exactly the same**, except for the amount of drug and the corresponding change in the amount of the diluent

The lower and higher strength of the test product have the **same manufacturing process**



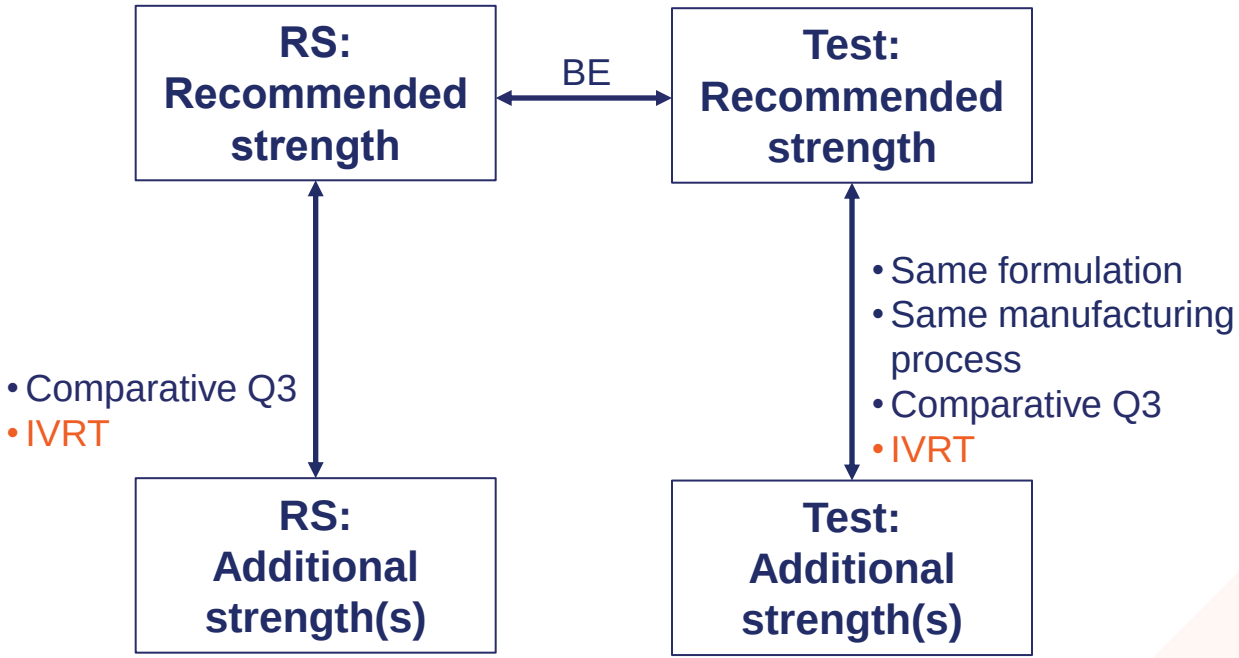
# Components of waiver approach

Acceptable **comparative Q3 characterization tests** using a minimum of **three batches** of each strength of the test product and the RS



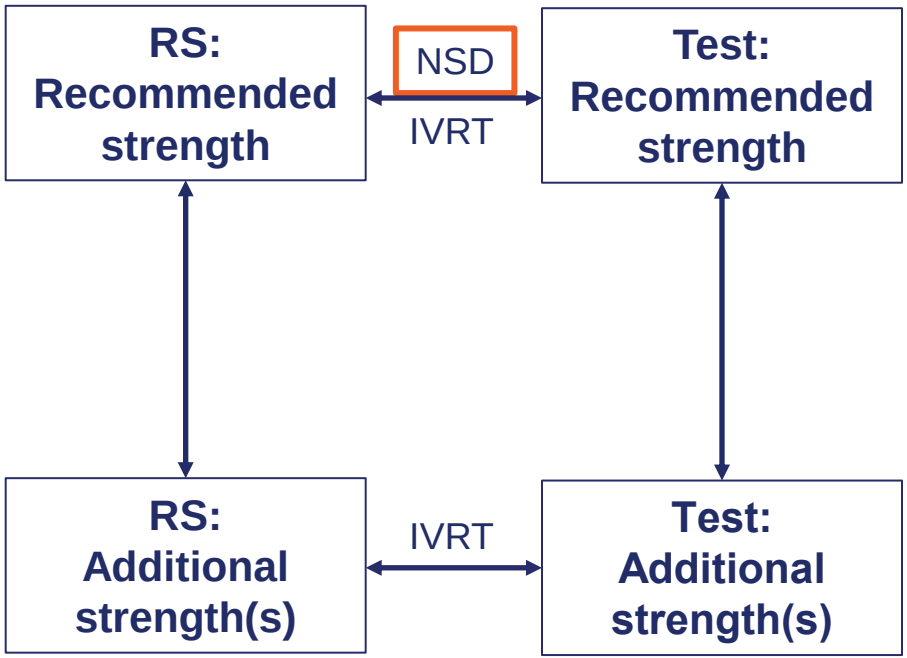
# Components of waiver approach

An acceptable **IVRT study** with a minimum of **one batch** of each strength of the test product and the RS



# Components of waiver approach

An acceptable **IVRT study** with a minimum of **one batch** of each strength of the test product and the RS



# Components of waiver approach

Acceptable **demonstration of BE of the recommended strength**

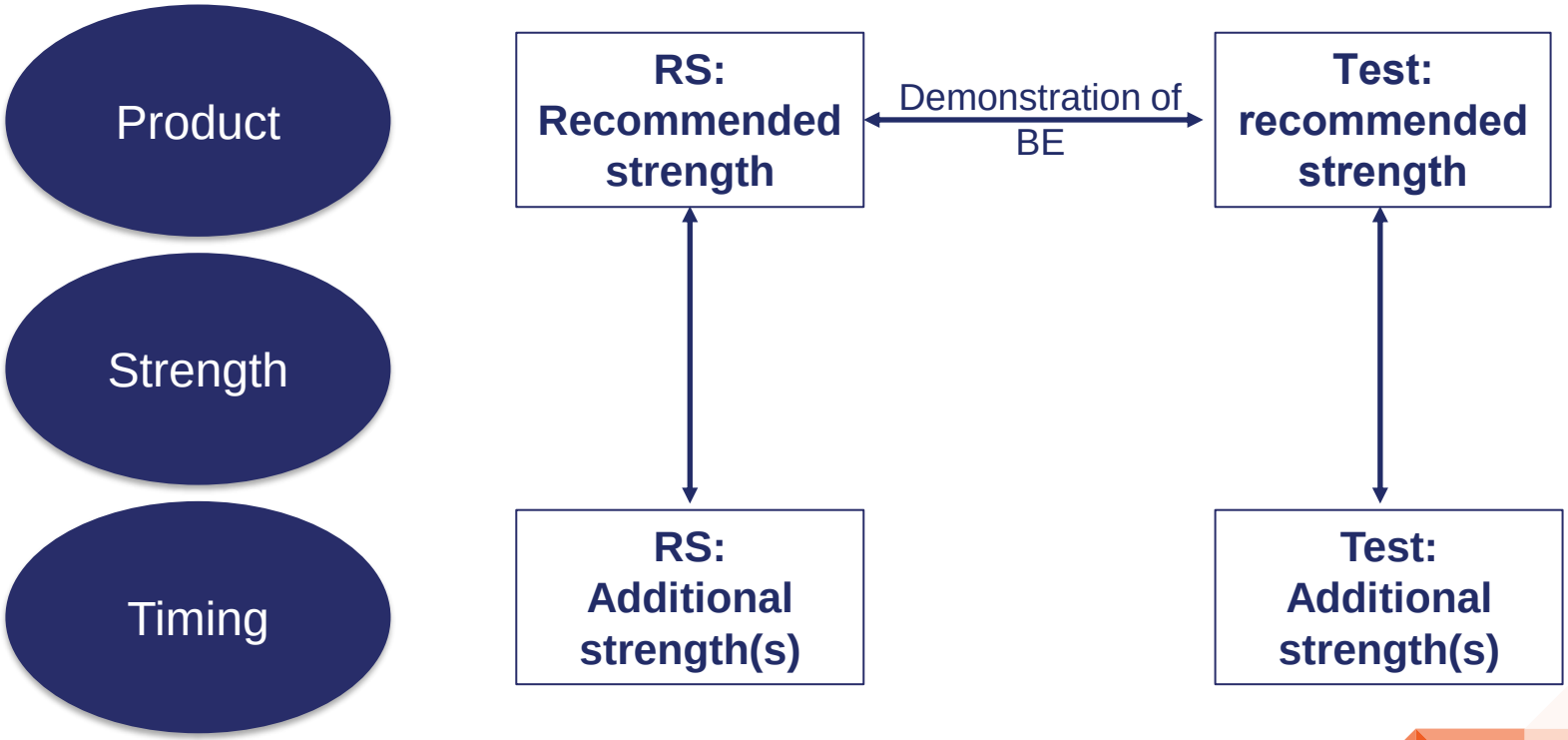
The **formulations of the lower and higher strengths** of the test product are **exactly the same**, except for the amount of drug and the corresponding change in the amount of the diluent

The lower and higher strength of the test product have the **same manufacturing process**

Acceptable **comparative Q3 characterization tests** using a minimum of three batches of each strength of the test product and the RS

An acceptable **IVRT study** with a minimum of one batch of each strength of the test product and the RS

# IVRT method development, validation, and pivotal study



# Practical insights on ANDA submissions for topical products applied to the skin and mucosa

# Formulation assessment

Draft guidance for industry *Content and Format of Composition Statement and Corresponding Statement of Ingredients in Labeling in NDAs and ANDAs* (April 2024)

**APPENDIX — EXAMPLES OF COMPOSITION STATEMENT IN NDAs AND ANDAs AND CORRESPONDING STATEMENT OF INGREDIENTS IN LABELING**

Inactive ingredient functions clearly identified using nonambiguous terminology

Composition of Drugozide Injection 125 mg/5 mL (25 mg/mL) vial

| Component | Reference Quality Standard | Function | Quantity (% w/v) | Quantity (%w/w) | Quantity (mg) mg/mL | Quantity (mg) mg/vial |
|---|---|---|---|---|---|---|
| Sodium Drugozide[i] | USP | API | 2.73% | 3.00% | 27.3 | 136.5 |
| Sodium Chloride | USP | Tonicity | 0.25% | 0.28% | 2.5 | 12.5 |
| Trisodium Citrate Dihydrate[ii] | USP | Buffer | 0.10%[iii] | 0.11% | 1 | 5 |
| Citric Acid Monohydrate[iv] | USP | Buffer | 0.10% | 0.11% | 1 | 5 |
| Edetate Disodium Dihydrate[v][vi] | USP | Preservative | 0.06% | 0.06% | 0.554 | 2.77 |

Units clearly identified

Hydration state clearly identified with footnotes for expressed quantities

Content and Format of Composition Statement and Corresponding Statement of Ingredients in Labeling in NDAs and ANDAs (April 2024)

"General Considerations for the "No Significant Difference" Evaluation for a Proposed Generic Formulation"

# Common responses for formulation assessments

…the characterization-based BE approach recommended within Option I of the aforementioned PSG **may be appropriate to support a demonstration of BE** for your proposed test formulation compositions "Formulation 1" and "Formulation 2"…

As it relates to proposed test formulation "Formulation 3"…the characterization-based BE approach…**may be appropriate to support a demonstration of BE** for your proposed test formulation.

However, **we strongly encourage you to review the Agency's Inactive Ingredient Database (IID)** and ensure that your proposed test formulation does not contain any inactive ingredient at a concentration that exceeds the concentration listed in the IID for the relevant route of administration **taking into consideration the context of use of the proposed drug product without justification**.

# In vivo BE studies

- Confirm the levels of inactive ingredients in your proposed test formulation acceptable for submission in a prospective ANDA
  - Consider the context of use (e.g., route of administration, duration of use, patient population, etc.)
  - Confirm prior to conducting the in vivo BE studies
- We encourage you to maintain photographic evidence documenting the clinical severity of all enrolled patients and the impact of treatment at baseline and end of treatment when possible (e.g., when conducting CCEP BE studies for acne).

# TDS products


| RLD/RS used in the reviewed ANDA studies | | ANDA Information | | |
|---|---|---|---|---|
| RLD | API | Applications | Irritation failures | Sensitization failures |
| N021306 | Buprenorphine | 5 | 2 | -- |
| N018891 | Clonidine | 1 | -- | -- |
| N020538 | Estradiol | 2 | 1 | -- |
| N203752 | Estradiol | 2 | 1 | -- |
| N021180 | Ethinyl Estradiol; Norelgestromin | 1 | -- | -- |
| A200910 | Ethinyl Estradiol; Norelgestromin | 2 | -- | -- |
| N019813 | Fentanyl | 1 | -- | -- |
| N020612 | Lidocaine | 5 | -- | -- |
| N021514 | Methylphenidate | 1 | -- | 1 |
| N021351 | Oxybutinin | 1 | -- | -- |
| N022083 | Rivastigmine | 5 | -- | -- |
| N017874 | Scopolamine | 4 | -- | -- |
| | | | | |
| Total | | 30 | 4 | 1 |

*"In some circumstances, an in vivo sensitization evaluation of a TDS product may be unnecessary if adequate justification is provided..."*

TDS: Transdermal/Topical delivery system; Data between 10/01/2012-09/30/2022

Russo J et al. Poster Presentation at the American Academy of Dermatology 2024 Annual Meeting. San Diego, CA, Mar. 08, 2024.

Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs (April 2024)

# IVRT and IVPT BE study protocol review

**Purpose**

- Discuss challenges with IVRT and IVPT BE studies
  - Method development
  - Method validation

**Information to be submitted**

- Method development report
- Method validation report
- Data to illustrate observed challenges

# Summary

- PSGs for topical products applied to the skin and mucosa evolve over time to incorporate efficient BE approaches based on cutting-edge research.
- The “waiver of BE studies” approach for topical products applied to the skin and mucosa with two or more strengths can significantly reduce the regulatory burden to support the approval of multiple strengths of complex locally-acting semisolid drug products.
- Engagement with the Agency to gain feedback on proposed formulations and BE studies prior to the ANDA submission can be beneficial.

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- Bing Cai, PhD
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- Siwei Zhang, PhD
- John Stephen Yap, PhD
- Jessica Kim, PhD
- Stella Grosser, PhD

# Resources

## Presentations:

- "An Overview of the Current Product-Specific Guidances for Topical Products" (presented on 09/13/2023)
- "General Considerations for the "No Significant Difference" Evaluation for a Proposed Generic Formulation" (presented on 12/06/2022)
- "Redesigned Pre-Submission Meetings in GDUFA III: Benefits for ANDA Submission and Approval" (presented on 05/09/2024)

## Guidances:

- Draft guidance for industry: *Physicochemical and Structural (Q3) Characterization of Topical Drug Products Submitted in ANDAs* (October 2022)
- Draft guidance for industry: *In Vitro Release Test (IVRT) Studies for Topical Drug Products Submitted in ANDAs* (October 2022)
- Draft guidance for industry: *In Vitro Permeation Test (IVPT) Studies for Topical Drug Products Submitted in ANDAs* (October 2022)
- Draft guidance for industry: *Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs* (April 2024)
- Final guidance for industry: *Controlled Correspondence Related to Generic Drug Development* (December 2020)
- Final guidance for industry: *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* (October 2022)

## Websites:

- Product-Specific Guidances for Generic Drug Development website
- Upcoming Product-Specific Guidances for Generic Drug Product Development website
- FDA's Inactive Ingredient Database website

# Questions?

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Division of Therapeutic Performance I, Office of Research and Standards,
Office of Generic Drugs
CDER | U.S. FDA