Streamlining Recommendations for Topical Products Applied to the Skin and Mucosa

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Disclaimer

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

Outline

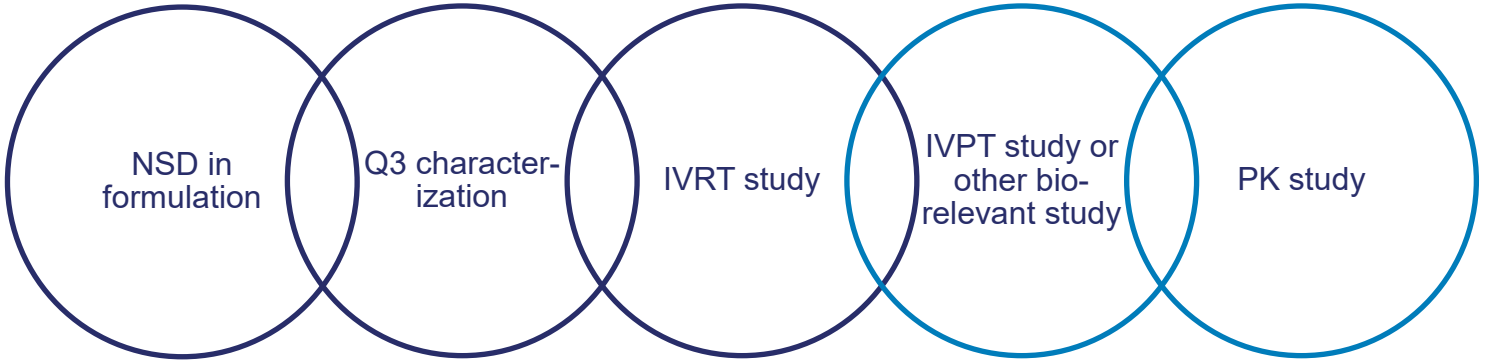
- Topical products applied to the skin and mucosa
  - Efficient BE approaches
  - Waiver of BE studies for an additional strength(s)
  - Practical insights on ANDA submissions

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

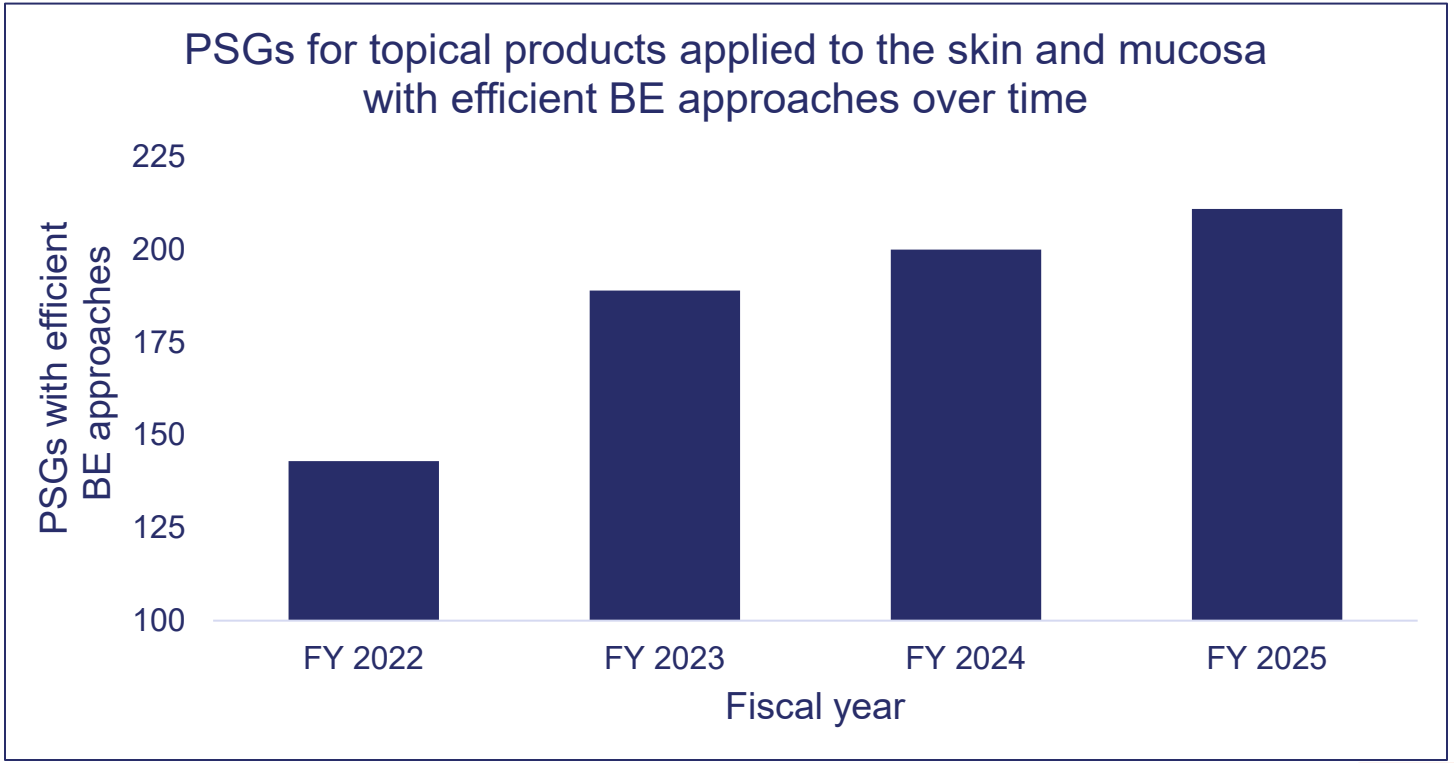


In vivo BE approaches

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

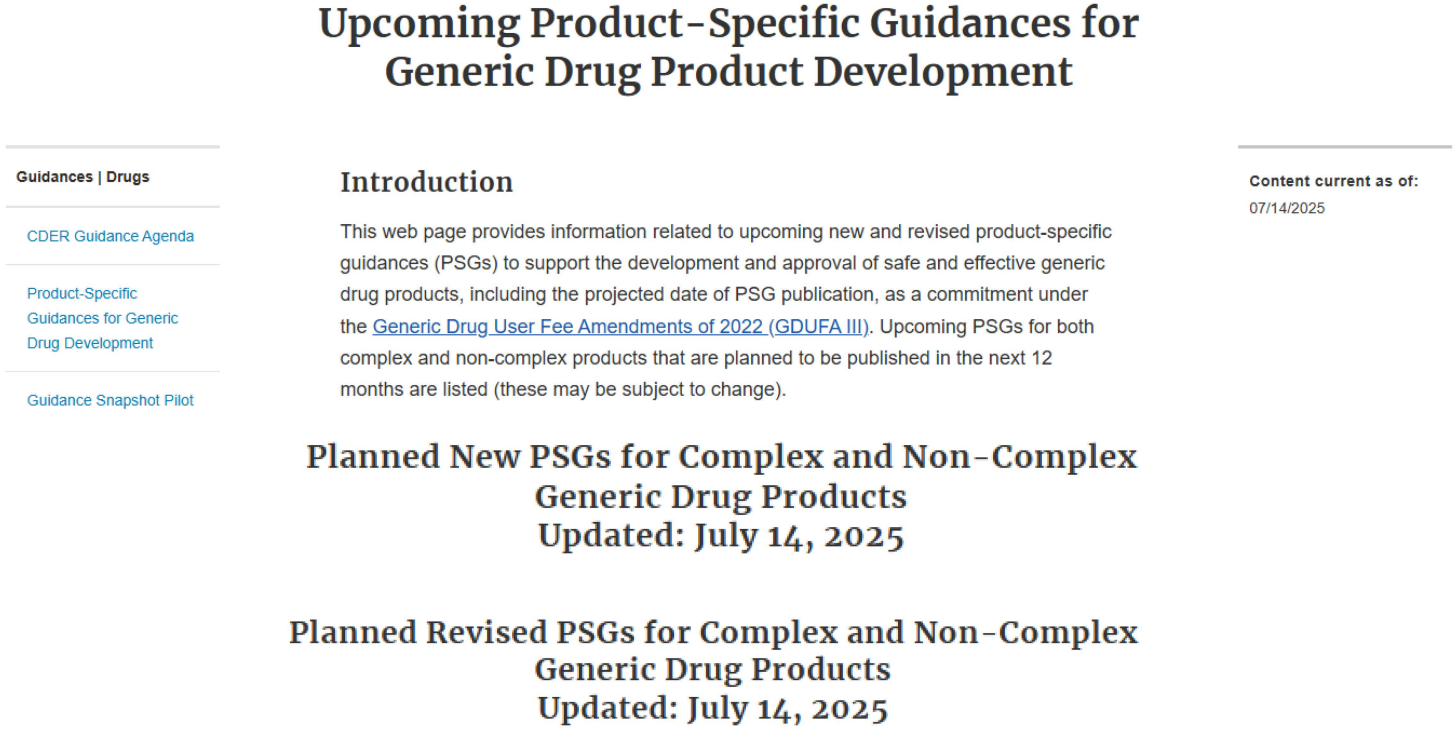
Active Ingredient:	Terbinafine hydrochloride
Dosage Form; Route:	Cream; topical
Recommended Studies:	One study

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
  • NSD in formulation
  • Comparative Q3 characterization
  • IVRT
  • IVPT
• Option 2: CCEP BE study
	• Option 1: Characterization-based BE approach
	  • NSD in formulation
	  • Comparative Q3 characterization
	  • IVRT
	  • IVPT
	• 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

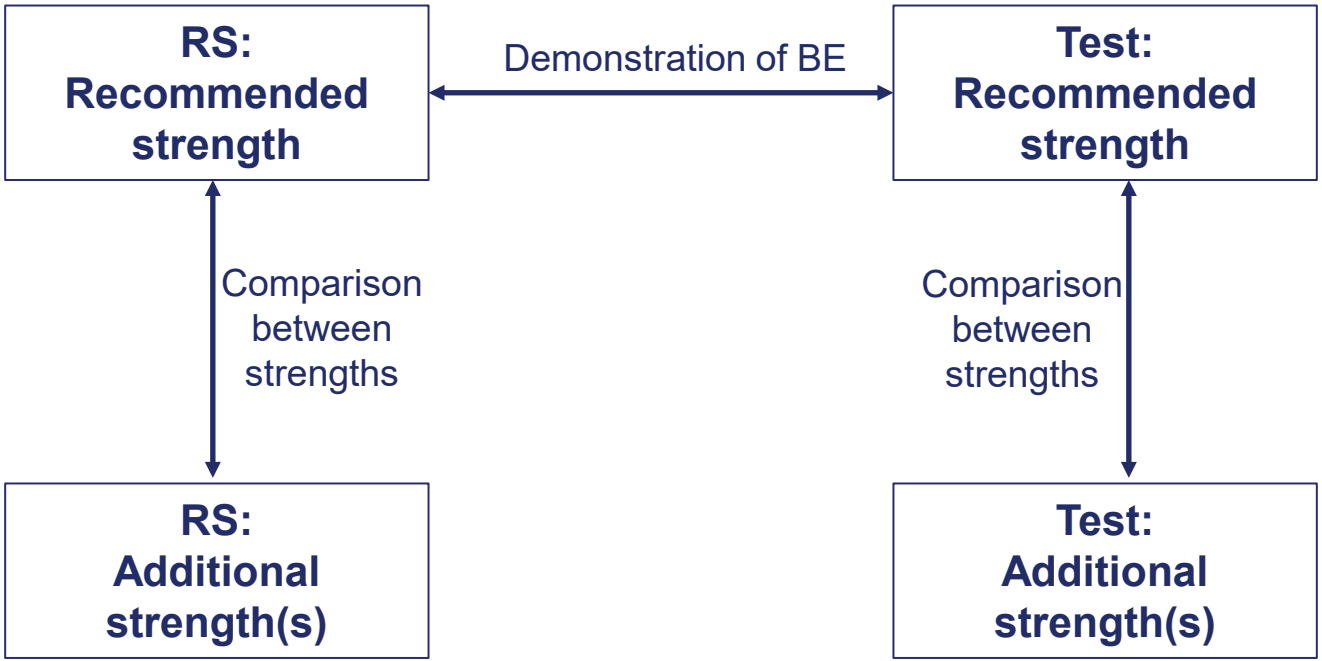
- A waiver of a BE study for an additional strength may be acceptable, provided that the conditions of the waiver are met
- PSG for tacrolimus topical ointment (Nov 2024):

Tacrolimus topical ointment, 0.1%	**Tacrolimus topical ointment, 0.03%**

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

• ~~Option 2: CCEP BE study~~ (waived)	• Option 2: CCEP BE study

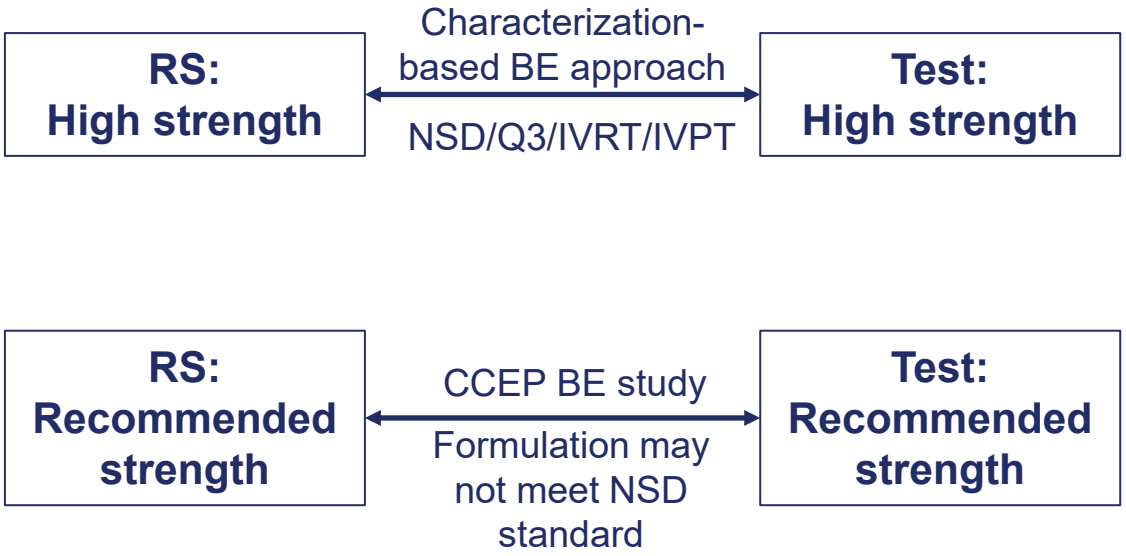
Components of waiver approach



RS: Reference standard

Components of waiver approach

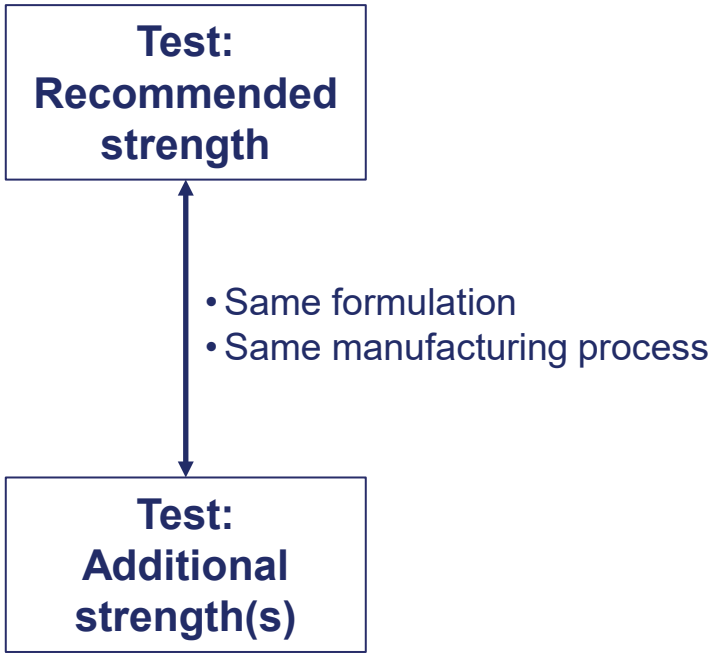
Acceptable **demonstration of BE of the recommended strength**



Components of waiver approach

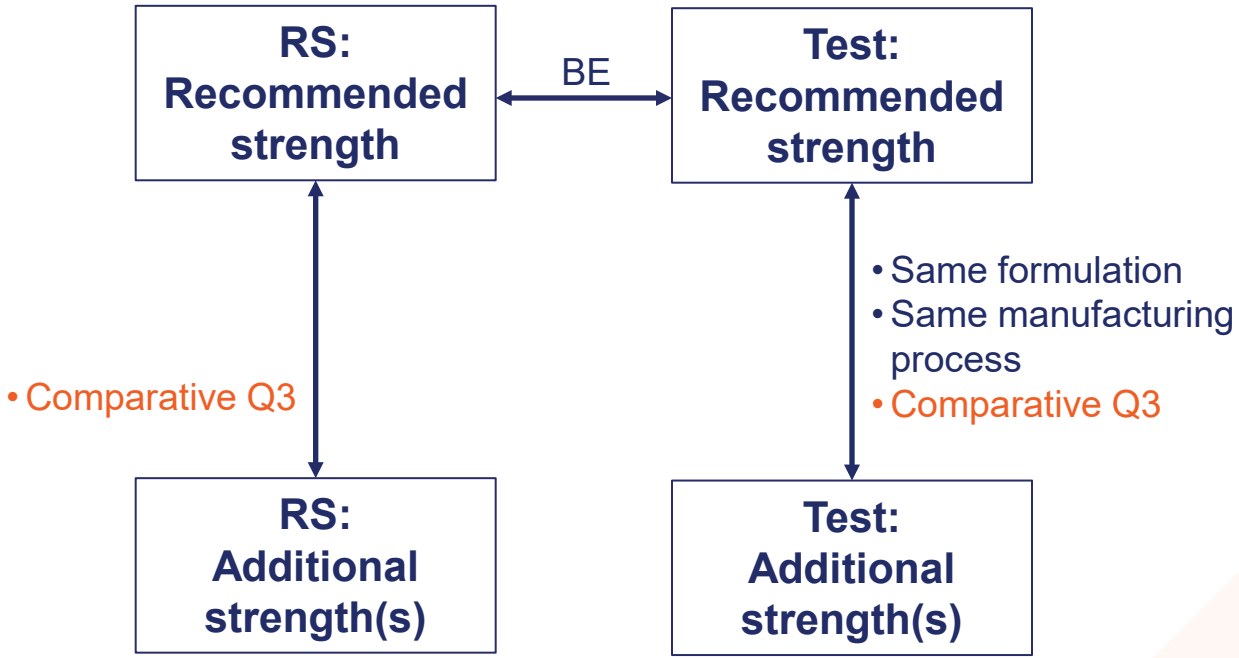
The **formulations of the lower and higher strengths** of the test product are **exactly the same**, except for the amount of drug and the corresponding change in the amount of the diluent

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



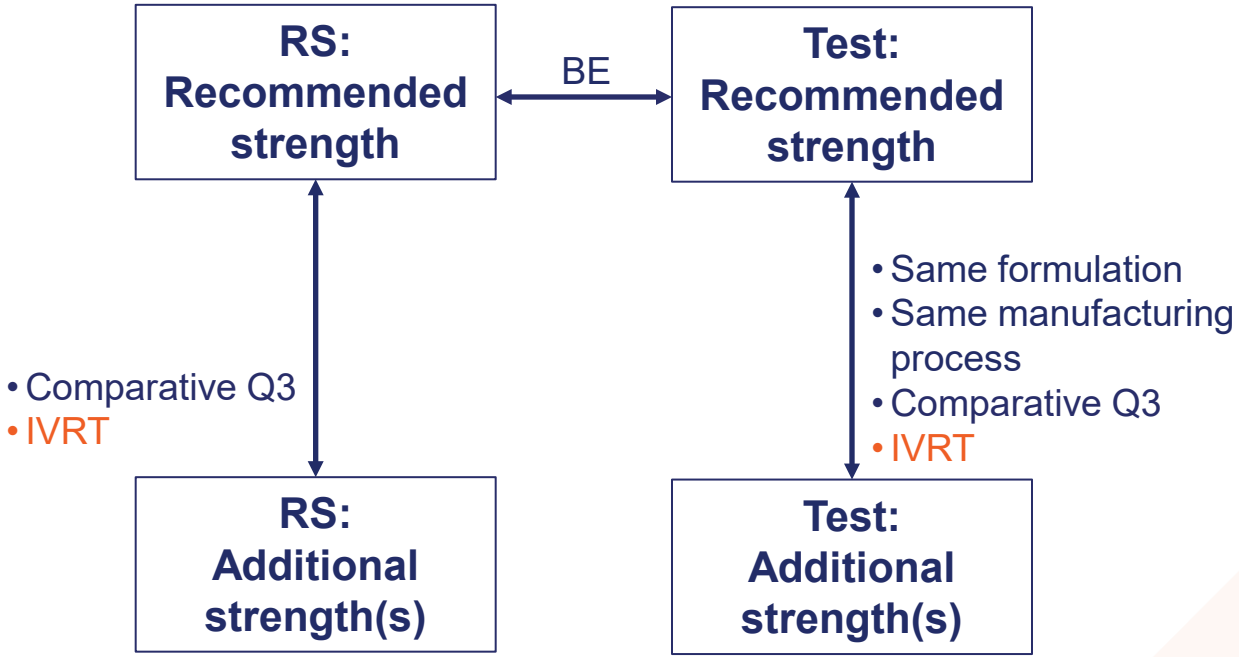
Components of waiver approach

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



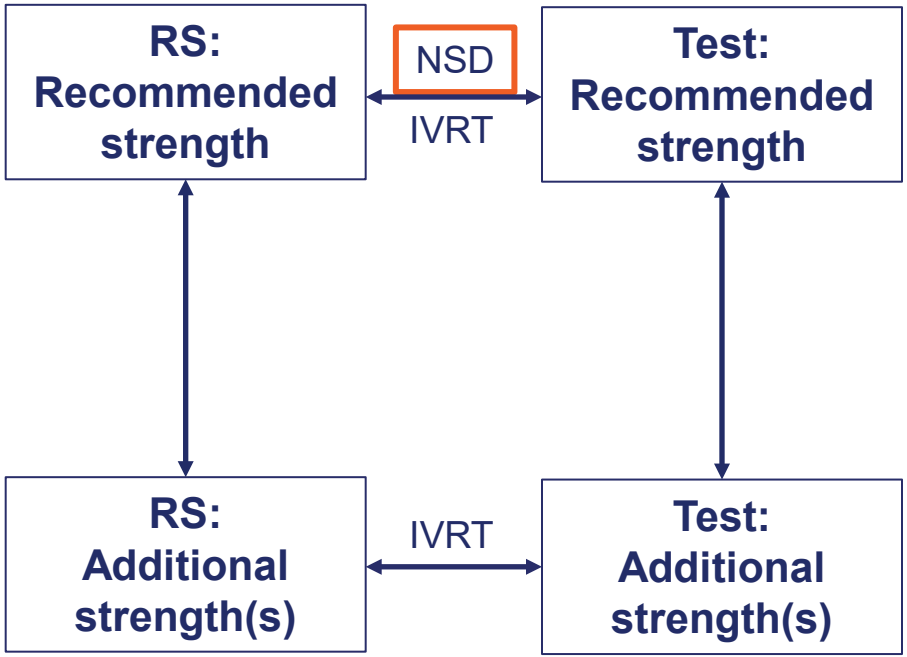
Components of waiver approach

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**

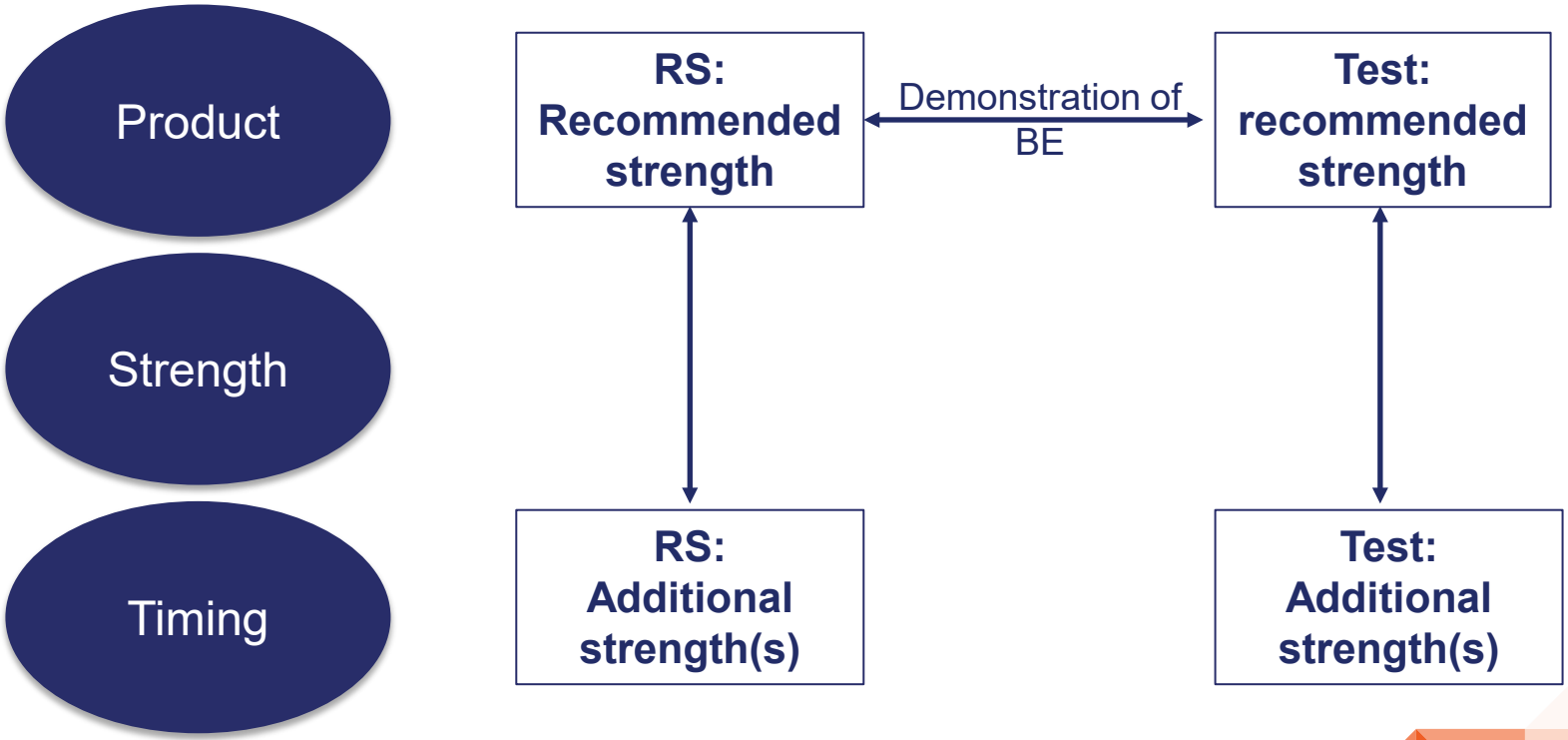
The **formulations of the lower and higher strengths** of the test product are **exactly the same**, except for the amount of drug and the corresponding change in the amount of the diluent

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.

Acknowledgements

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- 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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