Current Recommendations and ANDA Landscape for Topical Products

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Advancing Generic Drug Development Workshop: Modernizing Bioequivalence Approaches for Topical & Transdermal Products

10 September 2026

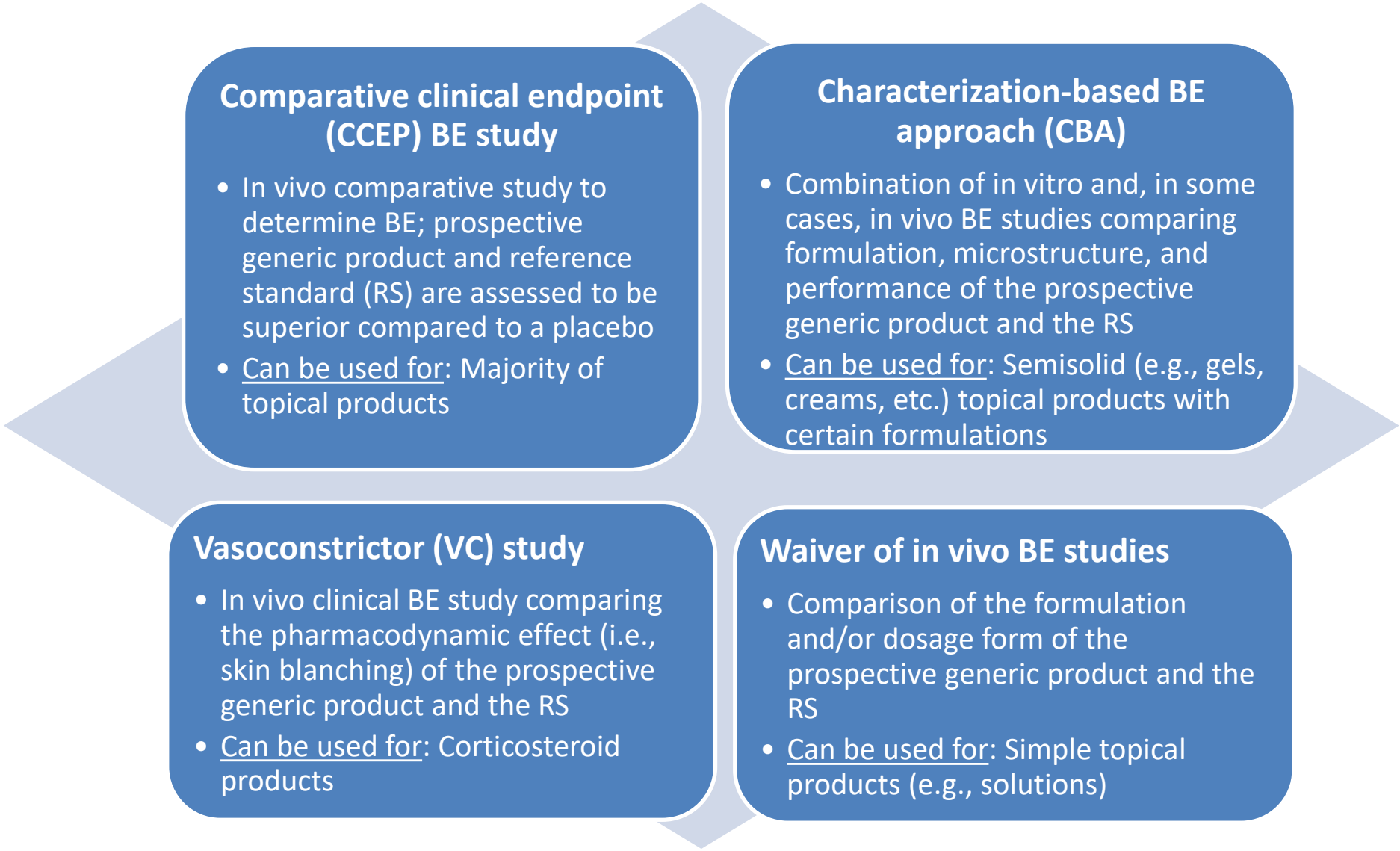
Disclaimer

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

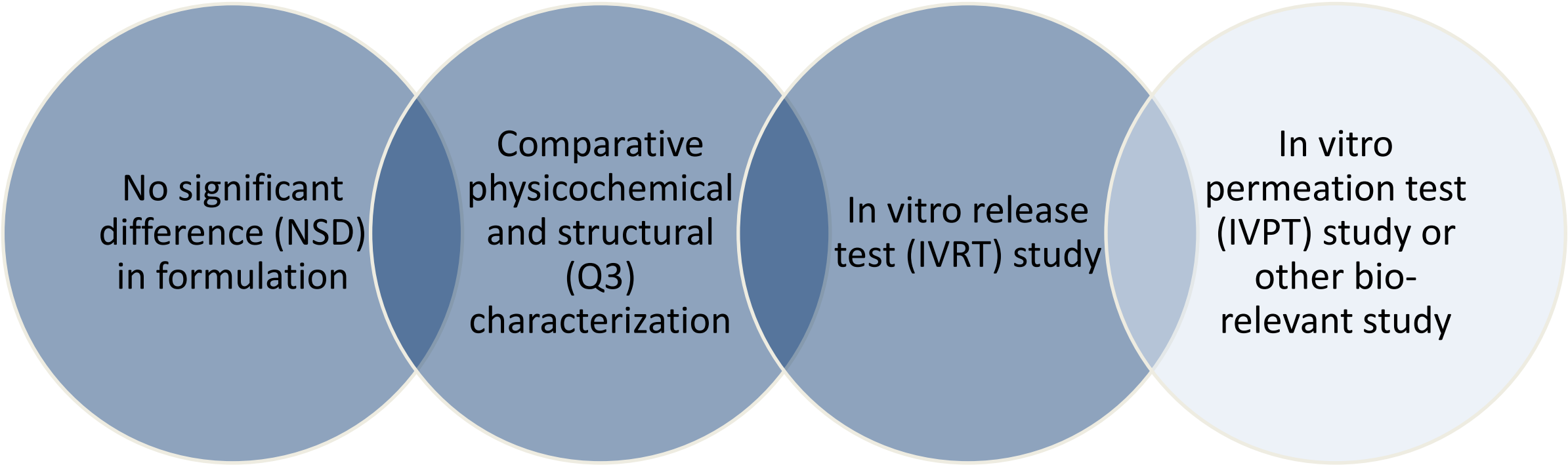
Outline

- Bioequivalence (BE) recommendations
- Product-specific guidance (PSGs) updates
- Abbreviated New Drug Application (ANDA) Landscape
- Alternative strategies for BE

BE Recommendations in the Topical PSGs

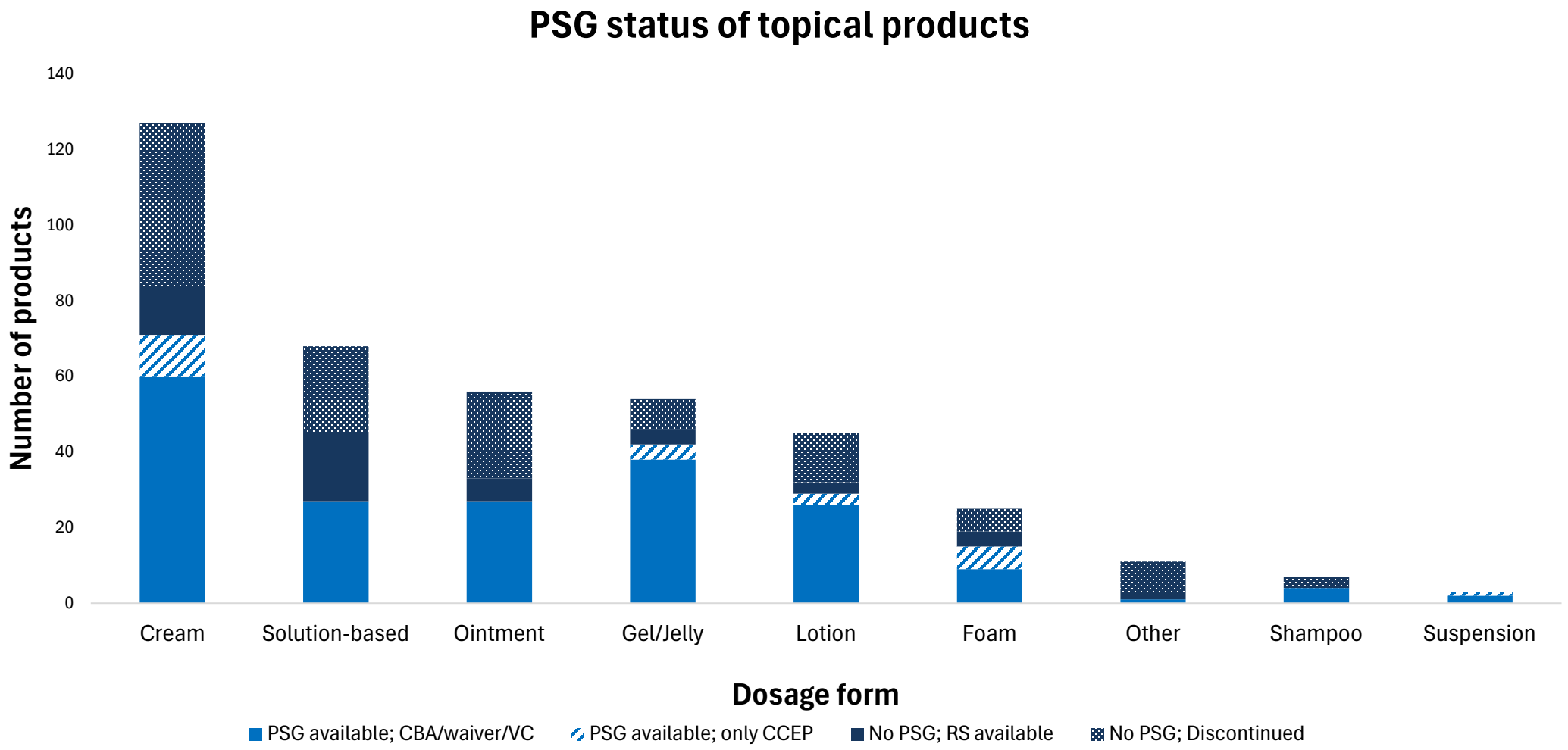


CBA in Topical PSGs



"*Current Trends in Product-Specific Guidance (PSG) Development & Revisions for Topical Products*"

Topical PSGs Grouped by Dosage Form



PSG Prioritization

- New NDAs
- In-house ANDAs without PSGs
- Public requests/interest through pre-ANDA program
- Internal priority to add CBA/ streamline PSGs

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Recent Updates Related to the PSGs Published During Oct 2025-May 2026

New NDAs (New Chemical Entity)

Application #		Active Ingredient	Dosage Form	Trade Name	Last Posting Date
NDA	217424	BERDAZIMER SODIUM	GEL	ZELSUVMI	Nov-25
NDA	215064	BIRCH TRITERPENES	GEL	FILSUVEZ	Dec-25
NDA	022395	CAPSAICIN	PATCH	QUTENZA	Feb-26
ANDA	072640	CLOTRIMAZOLE	CREAM	CLOTRIMAZOLE	Oct-25
NDA	021234	DICLOFENAC EPOLAMINE	SYSTEM	FLECTOR	Feb-26
NDA	022122	DICLOFENAC SODIUM	GEL	VOLTAREN ARTHRITIS PAIN	May-26
NDA	020126	DOXEPIN HYDROCHLORIDE	CREAM	ZONALON	May-26
NDA	019927	KETOCONAZOLE	SHAMPOO	KETOCONAZOLE	Feb-26
NDA	020310	KETOCONAZOLE	SHAMPOO	NIZORAL ANTI-DANDRUFF	Feb-26
NDA	020612	LIDOCAINE	PATCH	LIDODERM	Feb-26
NDA	207962	LIDOCAINE	PATCH	ZTLIDO	Feb-26
ANDA	201094	LIDOCAINE HYDROCHLORIDE	JELLY	LIDOCAINE HYDROCHLORIDE	May-26
NDA	022029	MENTHOL; METHYL SALICYLATE	PATCH	SALONPAS	Feb-26
NDA	019599; 205975	NAFTIFINE HYDROCHLORIDE	CREAM	NAFTIFINE HYDROCHLORIDE	Oct-25
NDA	019356	NAFTIFINE HYDROCHLORIDE	GEL	NAFTIN	Oct-25
NDA	204286	NAFTIFINE HYDROCHLORIDE	GEL	NAFTIN	Oct-25
NDA	019828	OXICONAZOLE NITRATE	CREAM	OXISTAT	Oct-25
NDA	020209	OXICONAZOLE NITRATE	LOTION	OXISTAT	Oct-25
NDA	217242	ROFLUMILAST	FOAM	ZORYVE	Dec-25
NDA	217347	SOFPIRONIUM BROMIDE	GEL	SOFDRA	Oct-25
NDA	215272	TAPINAROF	CREAM	VITAMA	Dec-25
NDA	019049; 017340; 017522	TRETINOIN	CREAM	RETIN-A	Dec-25

Adding CBA to Antifungal PSGs

Application #		Active Ingredient	Dosage Form	Trade Name	Last Posting Date
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NDA	215064	BIRCH TRITERPENES	GEL	FILSUVEZ	Dec-25
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ANDA	**072640**	**CLOTRIMAZOLE**	**CREAM**	**CLOTRIMAZOLE**	**Oct-25**
NDA	021234	DICLOFENAC EPOLAMINE	SYSTEM	FLECTOR	Feb-26
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Developing/Updating CBA (Noteworthy PSGs)

Application #		Active Ingredient	Dosage Form	Trade Name	Last Posting Date
NDA	217424	BERDAZIMER SODIUM	GEL	ZELSUVMI	Nov-25
NDA	215064	BIRCH TRITERPENES	GEL	FILSUVEZ	Dec-25
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Develop/Update CBA

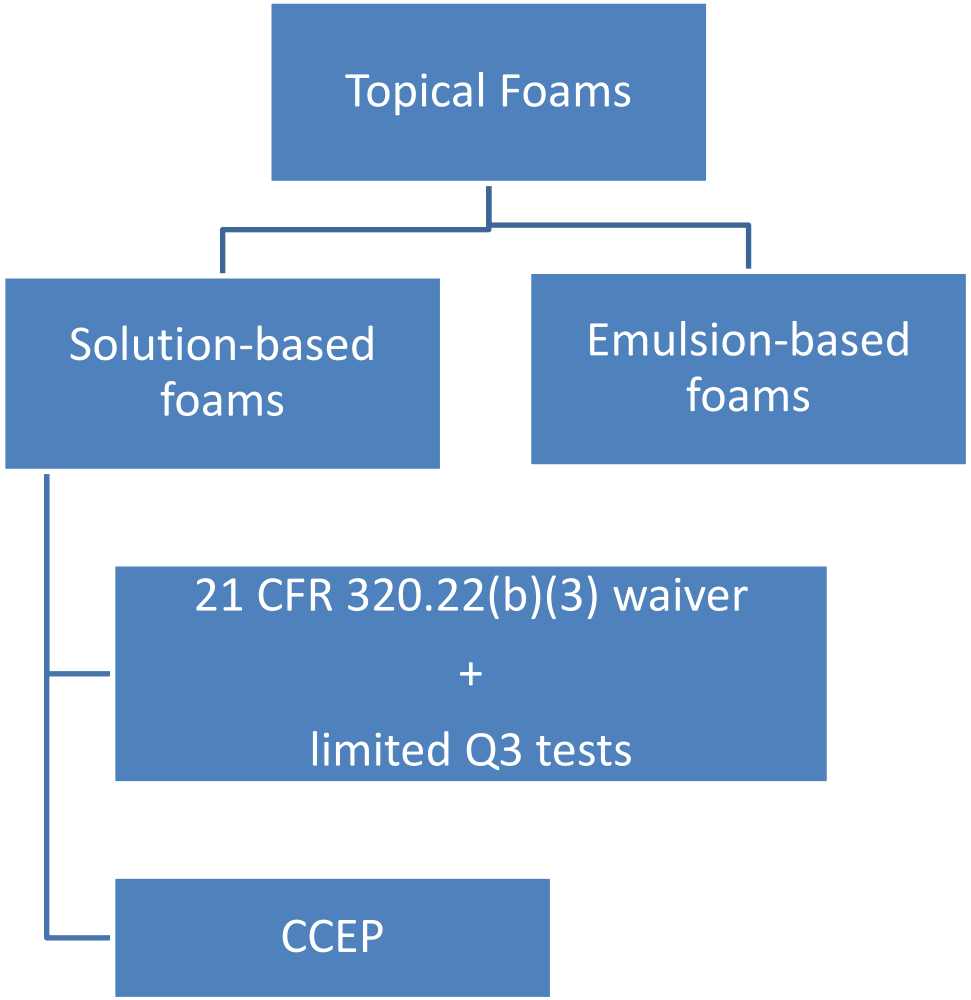
- Developing IVPT methods
  - Tapinarof topical cream, 1%
  - Roflumilast topical cream, 0.15% and 0.3%
- Reducing regulatory burden by removing a performance test from CBA
  - Doxepin hydrochloride topical cream, 5%
  - Diclofenac sodium topical gel, 1%

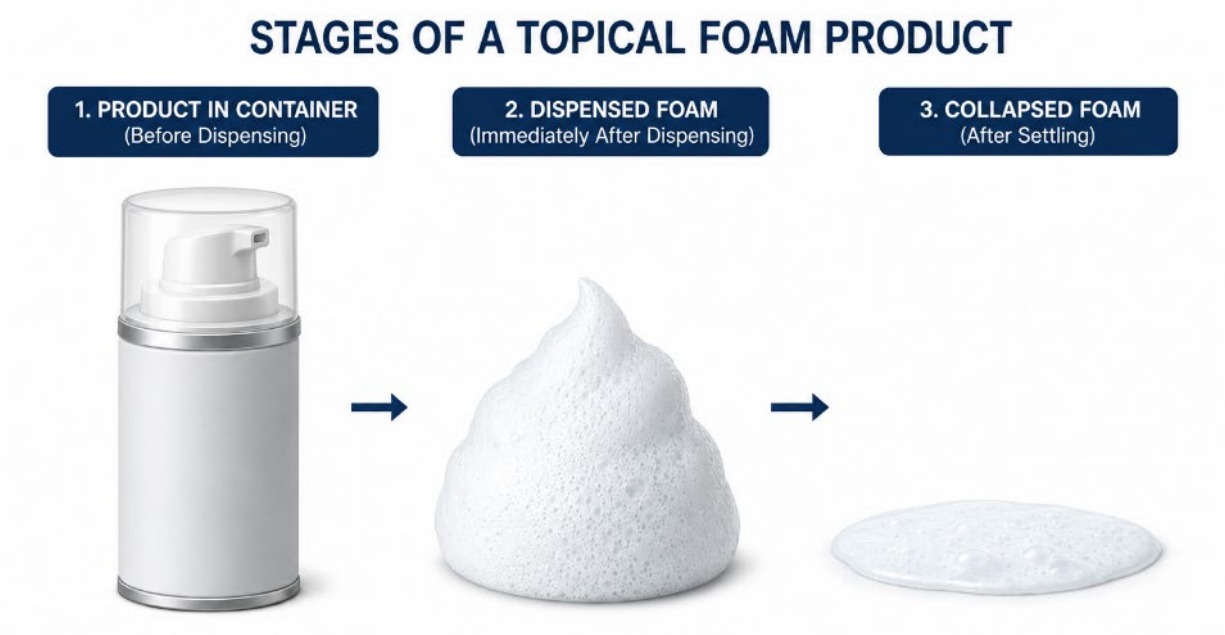
Develop/Update CBA

- Tretinoin topical cream, 0.025%, 0.05%, 0.1%
  - Drug distribution study in lieu of IVPT
  - Waiver of CCEP BE study for additional strengths

Waiver requests: Waivers of in vivo bioequivalence studies may be submitted for the two test products that are not used in the comparative clinical endpoint bioequivalence study. ANDAs for such products containing sufficient data may be approved based on (i) acceptable demonstration of bioequivalence of the 0.025% or 0.1% strength using the bioequivalence approach outlined within Option 2, (ii) the formulations of all three strengths of the test product are exactly the same, except for the amount of tretinoin and the corresponding change in the amount of the diluent, and have the same manufacturing process, (iii) acceptable comparative Q3 characterization tests using a minimum of three batches of each strength of the test product and three batches of each strength of the RS; the relationship of the Q3 attributes across the three strengths of the test product should be compared to the relationship of the Q3 attributes across the three strengths of the RS, and (iv) an acceptable IVRT study with a minimum of one batch of each strength of the test product and one batch of each strength of the RS; the data should be generated using an IVRT method that is validated for all three strengths. The relationship of the tretinoin release rates for the three strengths of the test product should be compared to the relationship of the tretinoin release rates for the three strengths of the RS.

Topical Foams





The schematic was generated by OpenAI. Retrieved from https://chat.openai.com

CBA for an Emulsion-Based Foam

- Roflumilast topical Foam, 0.3%

The comparison of the uncollapsed foam of the test product and RS should include characterizations of the following Q3 attributes:

a. Characterization of visual appearance and texture
b. Characterization of phase states and structural organization of matter
    i. Microscopic examination with representative high-resolution microscopic images at multiple magnifications
c. Characterization of spreadability, if feasible
d. Characterization of foam decay
    i. Analysis of time to break (until complete foam collapse)
    ii. Analysis of foam volume over time
    iii. Analysis of bubble size distribution (at a minimum of two time points)
e. Characterization of drying rate
f. Characterization of foam relative density

The comparison of the collapsed foam of the test product and RS should include characterizations of the following Q3 attributes:

a. Characterization of visual appearance and texture
b. Characterization of phase states and structural organization of matter
    i. Microscopic examination with representative high-resolution microscopic images at multiple magnifications
    ii. Analysis of particle size distribution, crystal habit, and polymorphic form of roflumilast in the drug product, as applicable
c. Characterization of rheological behavior which may be characterized using a rheometer that is appropriate for monitoring the non-Newtonian flow behavior of semi-solid dosage forms. The following evaluations are recommended:
    i. A characterization of shear stress vs. shear rate and viscosity vs. shear rate. At minimum, this should consist of numerical viscosity data at three shear rates (low, medium, and high).
    ii. A complete flow curve across the range of attainable shear rates, until low or high shear plateaus are identified.
    iii. Yield stress values should be reported if the material tested exhibits plastic flow behavior.
    iv. The linear viscoelastic response (storage and loss modulus vs. frequency) should be measured and reported. Any non-linear viscosity behavior over a range of shear rates should also be investigated, measured, and reported.
d. Characterization of specific gravity
e. Characterization of pH

CBA for an Emulsion-Based Foam

- Roflumilast topical Foam, 0.3%

Type of study: Bioequivalence study with IVRT endpoint
Design: Single-dose, two-treatment, parallel, multiple-replicate per treatment group study design using an occluded pseudo-infinite dose, in vitro
Strength: 0.3%
Test system: A synthetic membrane in a diffusion cell system
Analyte to measure: Roflumilast in receptor solution
Equivalence based on: Roflumilast (IVRT endpoint: drug release rate)
Additional comments: Refer to the most recent version of the FDA guidance for industry on *In Vitro Release Test Studies for Topical Drug Products Submitted in ANDAs*[a] for additional information regarding the development, validation, conduct and analysis of acceptable IVRT methods/studies. The batches of test product and RS evaluated in the IVRT bioequivalence study should be included among those for which the Q3 attributes are characterized. The collapsed foam should be used for dosing in the IVRT bioequivalence study. The methodology and environmental conditions for preparation of the collapsed foam should be consistent between the test product and RS across the Q3 characterization tests, the IVRT bioequivalence study, and the IVPT bioequivalence study.

Type of study: Bioequivalence study with IVPT endpoints
Design: Single-dose, two-treatment, parallel, multiple-replicate per treatment group study design using an unoccluded finite dose, in vitro
Strength: 0.3%
Test system: Barrier-competent human skin from male and/or female donors of at least 18 years of age in a diffusion cell system
Analyte to measure: Roflumilast in receptor solution
Equivalence based on: Roflumilast [IVPT endpoints: total cumulative amount (AMT) and maximum flux (J_{max})]
Additional comments: Refer to the most recent version of the FDA guidance for industry on *In Vitro Permeation Test Studies for Topical Drug Products Submitted in ANDAs*[a] for additional information regarding the development, validation, conduct and analysis of acceptable IVPT methods/studies. The batches of test product and RS evaluated in the IVPT bioequivalence study should be the same as those evaluated in the IVRT bioequivalence study. The collapsed foam should be used for dosing in the IVPT bioequivalence study. The methodology and environmental conditions for preparation of the collapsed foam should be consistent between the test product and RS across the Q3 characterization tests, the IVRT bioequivalence study, and the IVPT bioequivalence study.

CBA for a Topical Shampoo

The schematic was generated by OpenAI. Retrieved from https://chat.openai.com

CBA for a Topical Shampoo

- Ketoconazole Topical Shampoo, 1% & 2%
  - NSD
  - Comparative Q3: “The comparative Q3 characterization should be conducted with (1) the test and RS shampoo dispensed from the container closure system, (2) the foamed shampoo that is formed after lathering the test and RS shampoo (which includes diluting the shampoo with water at multiple dilution ratios, taking into consideration the in-use conditions per the product labeling), and (3) the residual formulation after the decay of the foamed shampoo.”
  - IVRT of the dispensed shampoo

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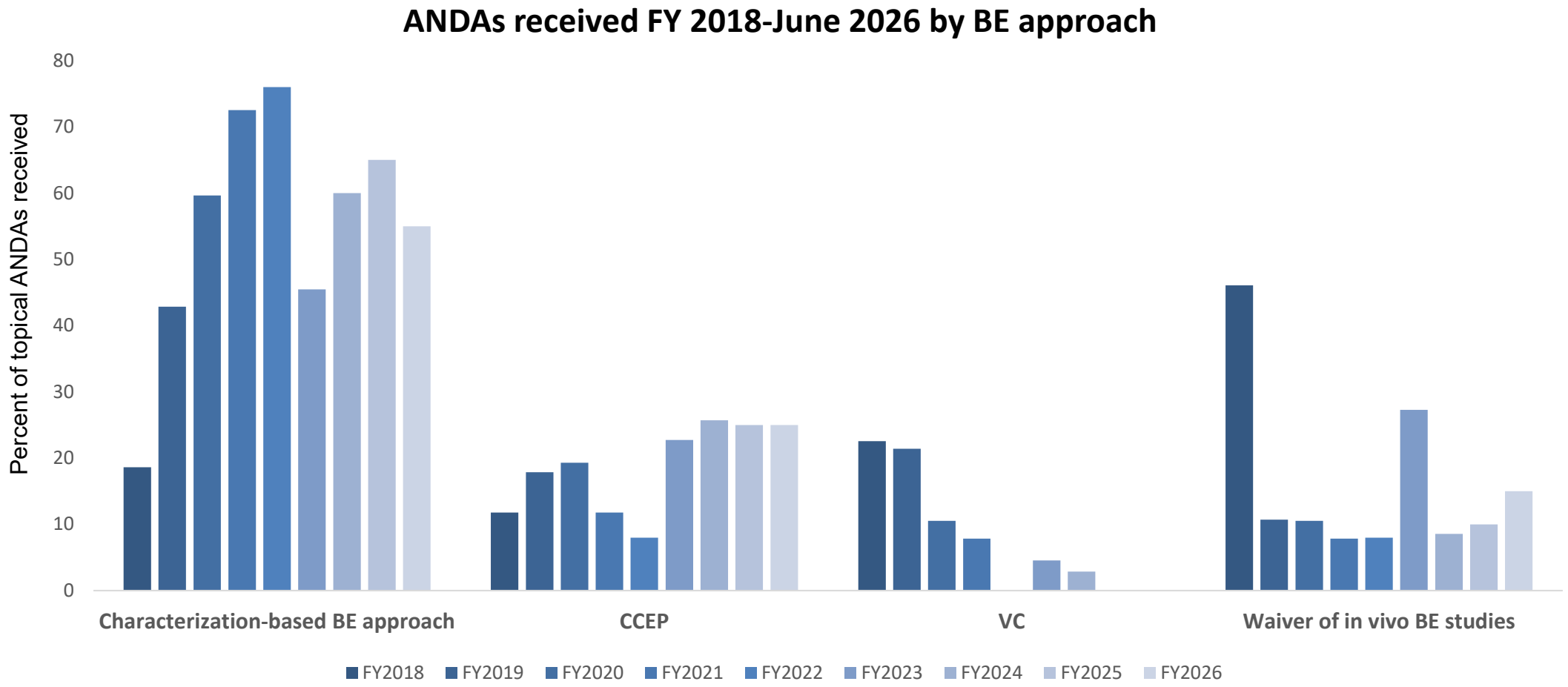
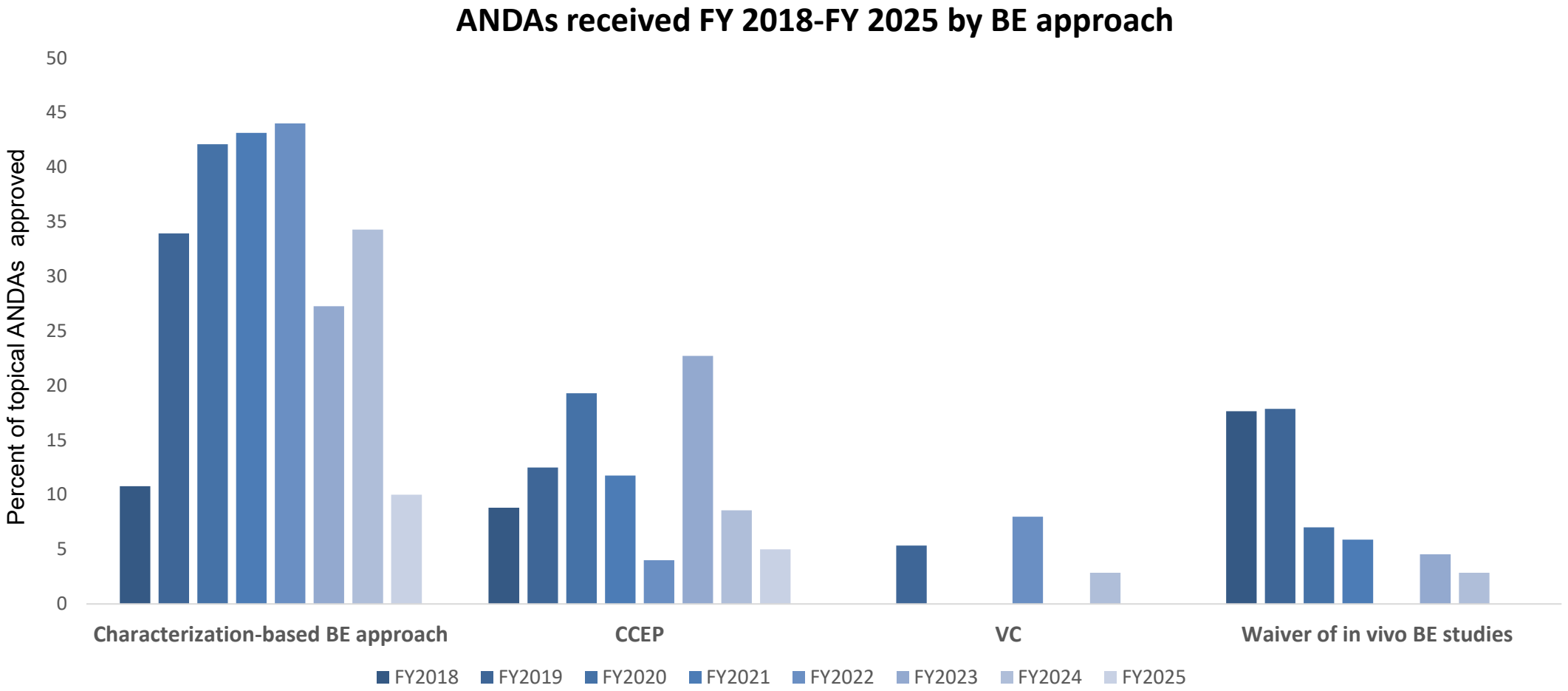
ANDA Landscape

BE Approaches used in Topical ANDAs



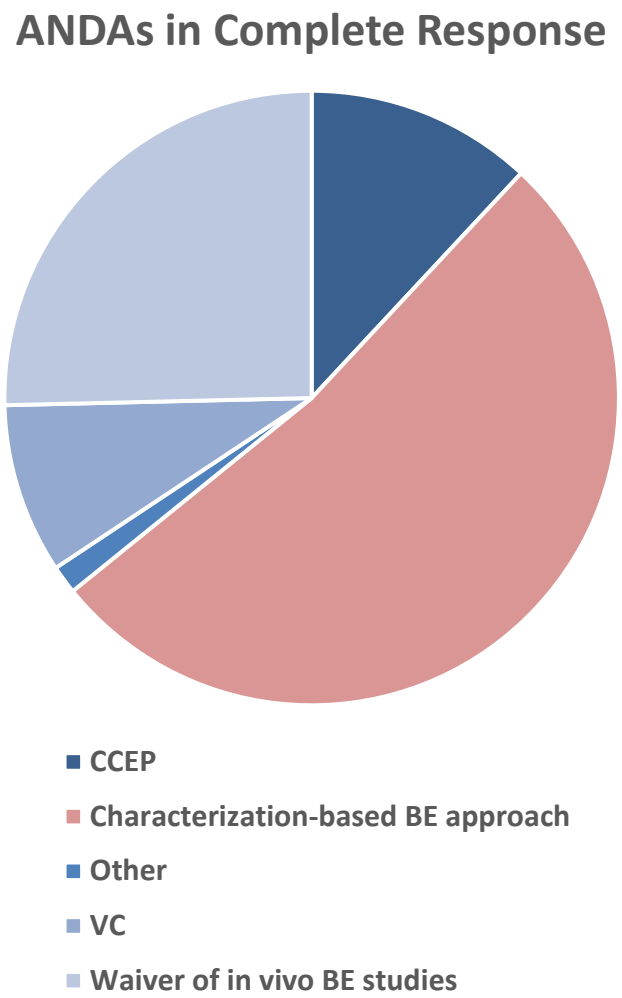
Bars represent ANDAs received using a given BE approach normalized by the total number of topical ANDAs received in a given FY.

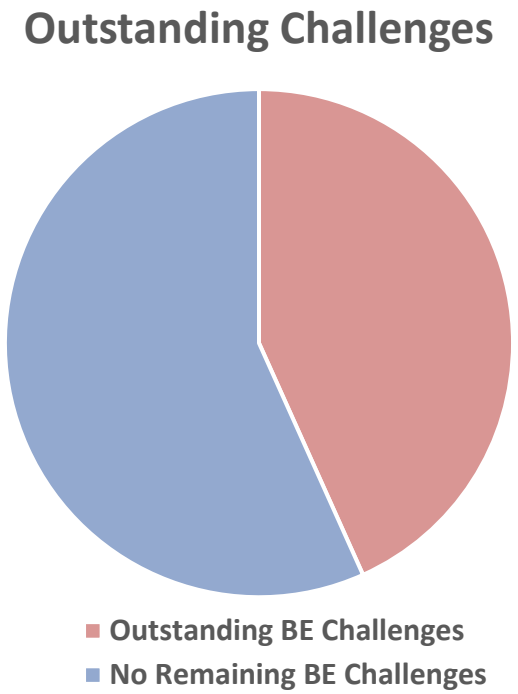
Approved ANDAs for Topical Products

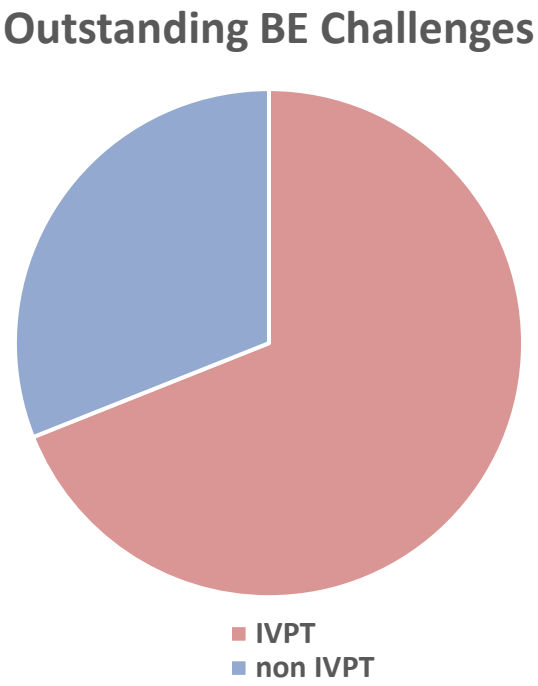


Bars represent ANDAs approved/tentatively approved based on a given BE approach normalized by the total number of topical ANDAs received in a given FY.

Challenges in Topical ANDAs







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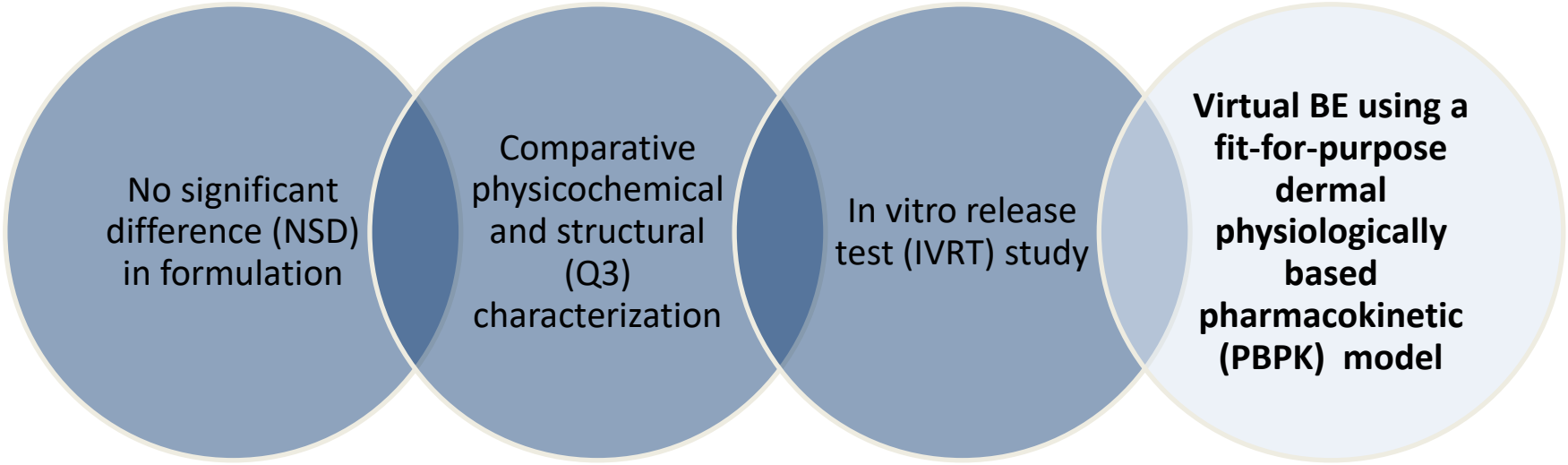
Proposing Alternative BE Strategies

BE Strategy for Q3 Similar Products

- Request formulation assessment
- Strategy to manage remaining risks for BE may be identified on a case-by-case basis
  - *Risks related to differences in bioavailability (BA): Assess change in thermodynamic activity, rate and extent of permeation,…*
  - *Risks related to use of the product and therapeutic equivalence (beyond BA)*

Submit your proposed BE strategy with preliminary data in a product development meeting

Virtual BE in Lieu of Pivotal IVPT



- The PBPK model should be verified and validated.
- The IVPT data used to inform the model should be generated using an IVPT method that has been validated for its intended purpose.

Submit your proposed BE strategy that includes use of PBPK modeling with preliminary data in a product development meeting

Alternative Designs for CCEP BE studies

See PSG for FDA recommended CCEP BE study design, which usually include the follow arms:

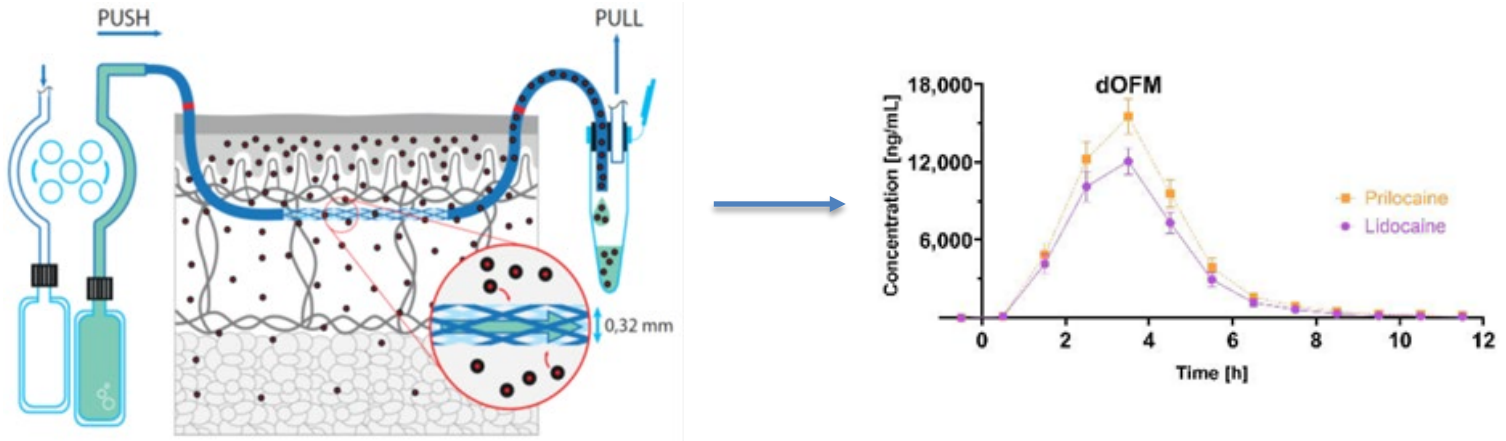
- Test
- Reference
- Placebo

Appropriate study design includes selecting proper sample size for each arm.
Care must be taken with regard to inclusion/exclusion criteria – especially with regards to disease severity. Populations selected should be relevant to care of the U.S. population.

Submit your alternative CCEP BE study design, along with the risk mitigation strategies that support any deviation from the PSG recommended CCEP BE study design, in a product development meeting.

Cutaneous PK-based BE Approach

- Applicable for many topical products, based on the proposed test formulation and site of action



- The approach includes a pilot study followed by pivotal BE study

Submit your proposal for cutaneous PK-based BE study using a dermal sampling technique with preliminary data in a product development meeting

Conclusions

- PSGs for complex topical products have evolved over time to incorporate efficient BE approaches based on cutting-edge research.
- An analysis of the topical ANDAs suggest that characterization-based BE approaches have been predominantly used to support ANDA submission in the recent years, among other approaches
- For ANDAs that utilized a characterization-based BE approach, the outstanding BE challenges are often associated with IVPT
- Engagement with the Agency to gain feedback on proposed formulations, BE strategy and challenges associated with the BE studies (e.g., IVPT) prior to ANDA submission can be beneficial

Acknowledgments

U.S. Food & Drug Administration

- Priyanka Ghosh, PhD
- Megan Kelchen, PhD
- Mengmeng Niu, PhD
- Ying Jiang, PhD
- Sam Raney, PhD
- Markham Luke, MD, PhD
- Eleftheria Tsakalozou, PhD
- Pahala Simamora, PhD
- Ahmed Zidan, PhD
- Bing Cai, PhD
- Elena Rantou, PhD
- Likan Liang, PhD
- Ying Fan, PhD
- Robert Lionberger, PhD

Resources

Presentations:

- "An Overview of the Current Product-Specific Guidances for Topical Products" (presented on 09/13/2023)
- "Current Status and Outstanding Challenges IVPT Studies (presented on 05/29/2025)
- Cutaneous PK-based Techniques: Translating Scientific Advances to Regulatory Methods (presented on 11/03/2022)
- "Redesigned Pre-Submission Meetings in GDUFA III: Benefits for ANDA Submission and Approval" (presented on 05/09/2024)

Guidances:

- Final guidance for industry: *Physicochemical and Structural (Q3) Characterization of Topical Drug Products Submitted in ANDAs* (March 2026)
- Draft guidance for industry: *In Vitro Permeation Test (IVPT) Studies for Topical Drug Products Submitted in ANDAs* (October 2022)
- 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

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Thank You

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