Current Status and Outstanding Challenges IVPT Studies

Implementing FDA's IVPT Guidance Recommendations: A Step-By-Step Illustration

Day 1, Session 1: IVPT Recommendations: FDA Guidance Development, Implementation Considerations, and Outstanding Challenges

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Outline

- Recap of product-specific guidances (PSG) for topical products applied to the skin
  - When do we currently recommend IVPT
- Landscape analysis of submitted ANDAs since Generic Drug User Fee Amendments (GDUFA) II – since FY 18
- Observed challenges and opportunities

Establishing Bioequivalence (BE) of Topical Products

Comparative clinical endpoint BE (CCEP BE) study

- In vivo BE study comparing the efficacy of a prospective generic product and the reference standard (RS), and both products are assessed to be superior compared to a placebo
- Can be used for: Majority of topical products

Vasoconstrictor (VC) study

- In vivo clinical BE study comparing the pharmacodynamic effect (i.e., skin blanching) of the prospective generic product and the RS
- Can be used for: Corticosteroid products

Waiver of in vivo BE studies

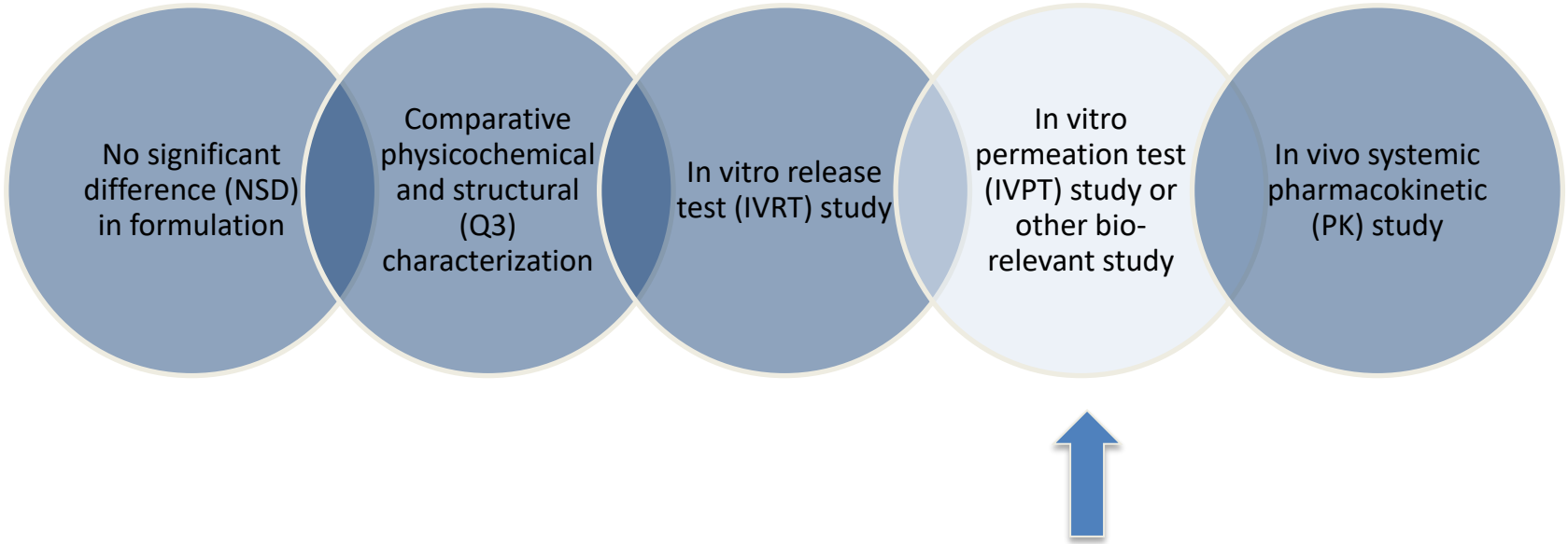
- Comparison of the formulation and/or dosage form of the prospective generic product and the RS
- Can be used for: Simple topical products (e.g., solutions)

Characterization-based BE approach

- Combination of in vitro and, in some cases, in vivo BE studies comparing formulation, microstructure, and performance of the prospective generic product and the RS
- Can be used for: Semisolid (e.g., gels, creams, etc.) topical products with certain formulations

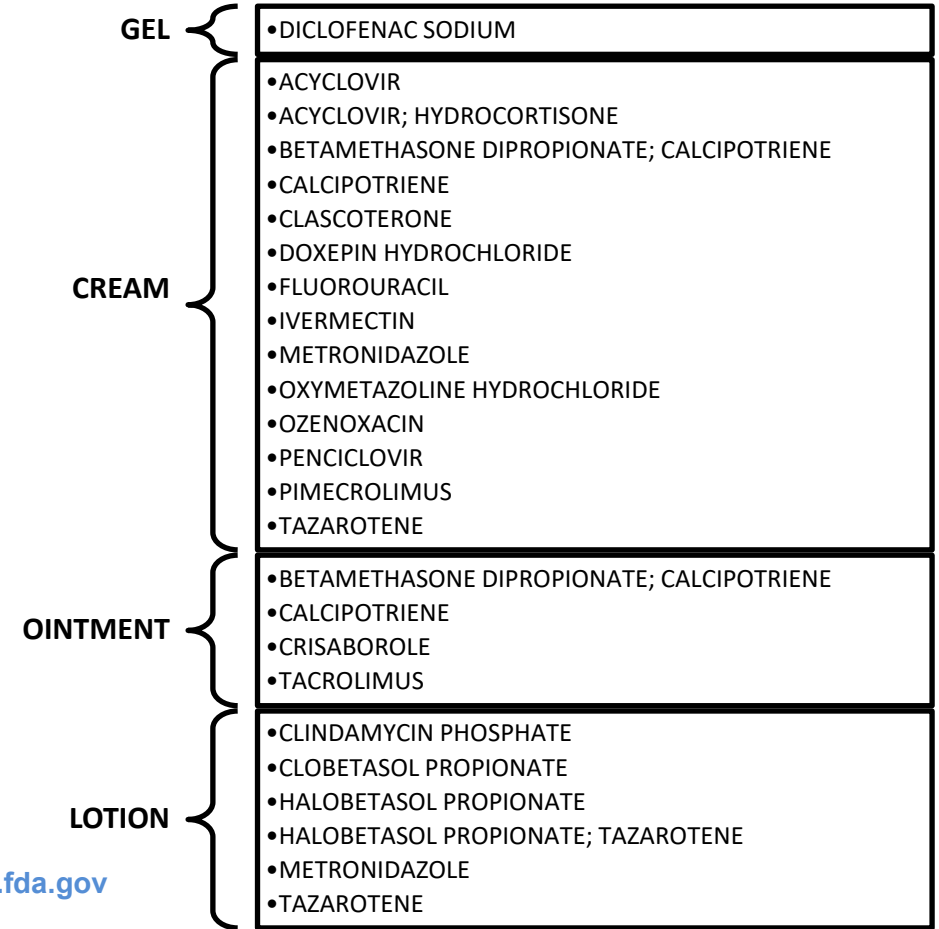
Characterization-based BE approach

In PSGs for topical products…



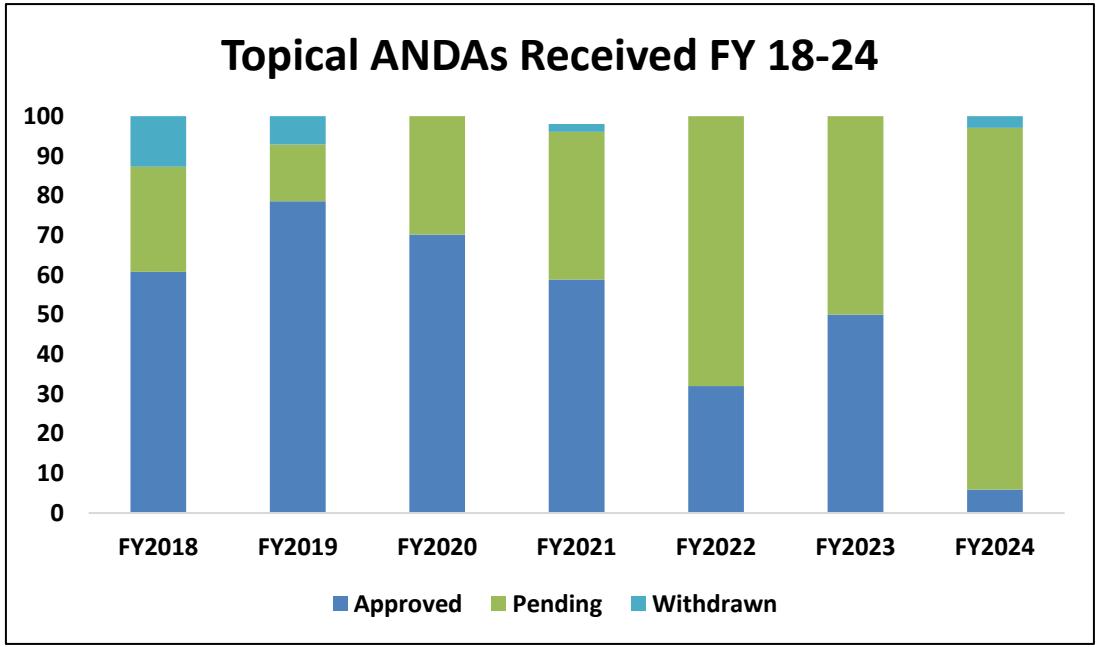
"Current Trends in Product-Specific Guidance (PSG) Development & Revisions for Topical Products"

IVPT in PSGs



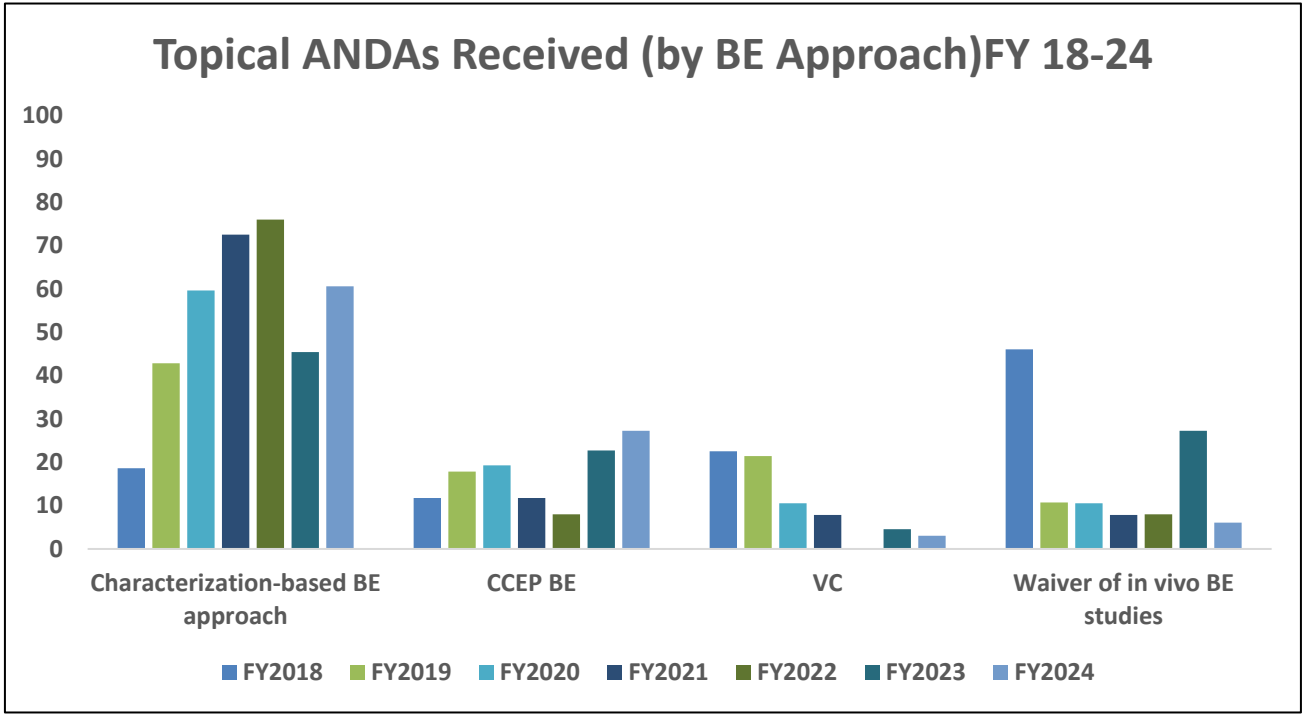
https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm

Submitted Topical ANDAs



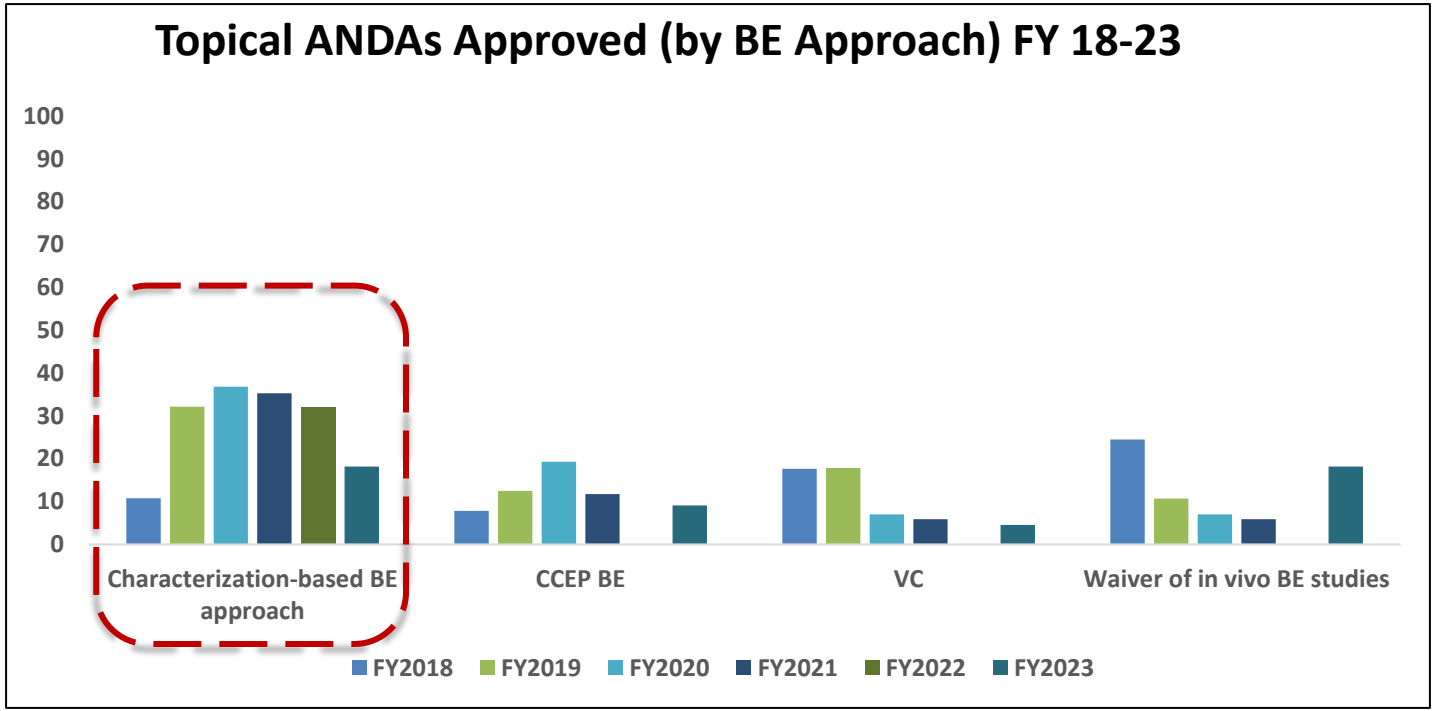
Application status as of February 2025

Submitted Topical ANDAs



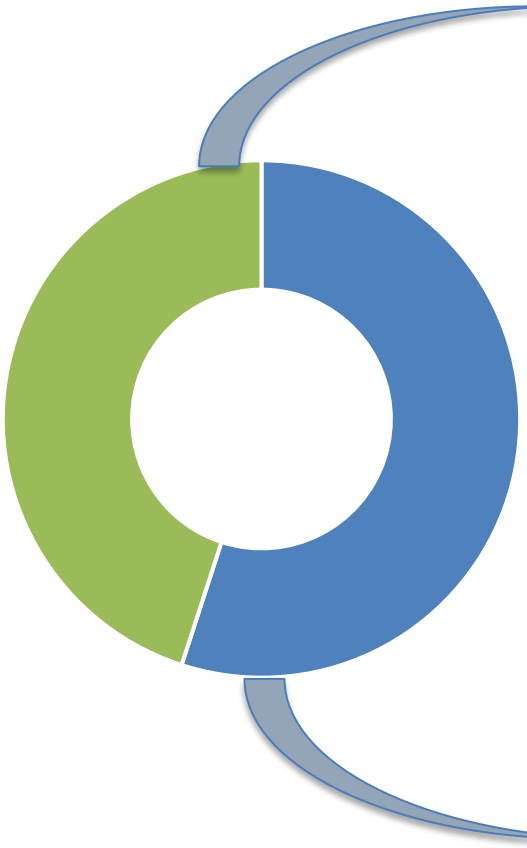
Data are normalized by total number of Topical ANDAs in a given FY
Application status as of February 2025

Approved Topical ANDAs



Data are normalized by total number of Topical ANDAs in a given FY
Application status as of February 2025
IVRT: In Vitro Release Testing
IVPT: In Vitro Permeation Testing

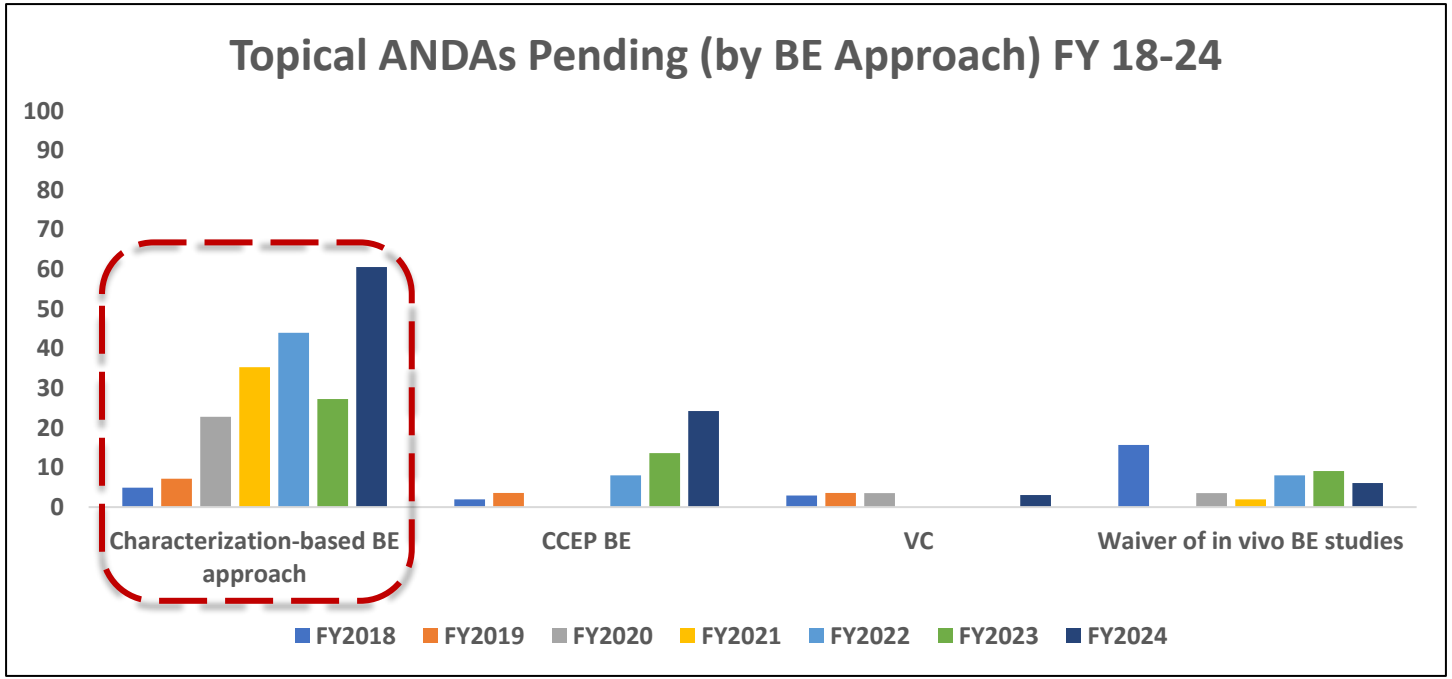
Pending Topical ANDAs

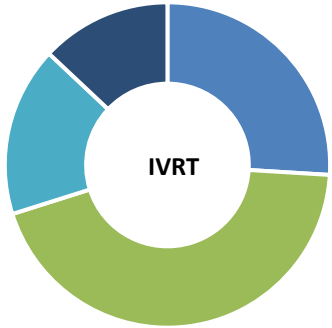


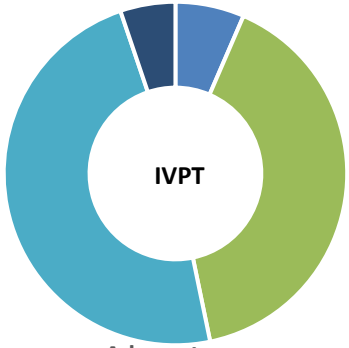
Outstanding challenges related to
- Bioequivalence
- Pharmaceutical quality
- Others (e.g., Labeling)

Outstanding challenges related to
- Pharmaceutical quality
  - Drug substance
  - Drug product
  - Manufacturing (& facility)
- Labeling

Pending Topical ANDAs







Data are normalized by total number of Topical ANDAs in a given FY
Pending ANDAs include ANDAs in pending and complete response status
Application status as of February 2025

IVPT Challenges in Topical ANDAs

Challenges with Method Development
- Inadequate optimization
  - Receptor solution
  - Dose/Dosing technique
  - Sampling duration/frequency

→ Day 1, Session 2 → PDEV

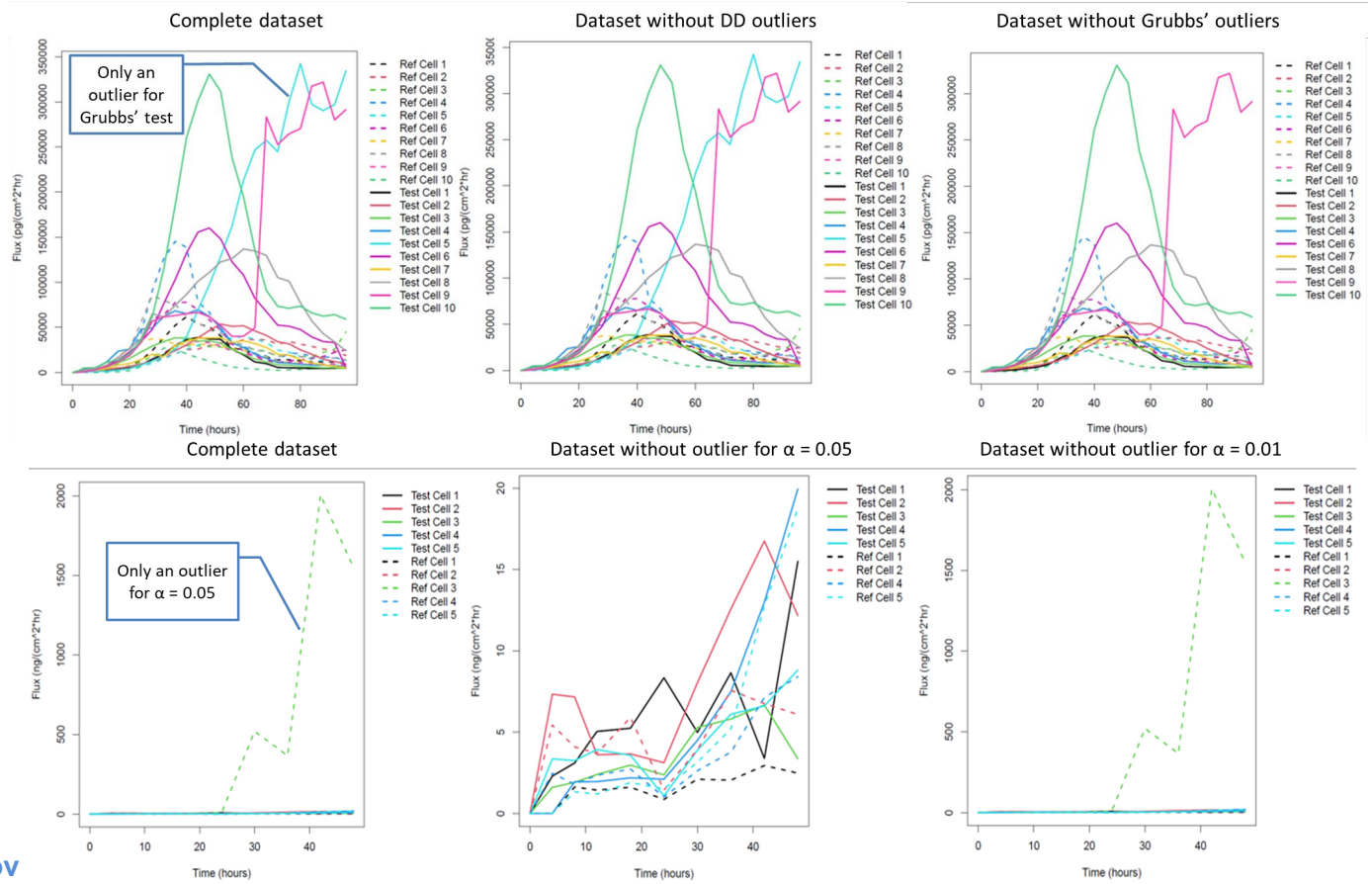
Challenges with Method Validation
- Selection of dose/product for studies
- Assessing sensitivity and selectivity

→ Day 2, Session 1 → PDEV PSUB

Other Issues
- Aberrant Data

PDEV: Product Development Meeting
PSUB: Pre-Submission Meeting
https://www.fda.gov/drugs/news-events-human-drugs/redesigned-pre-submission-meetings-gdufa-iii-benefits-anda-submission-and-approval-05092024

IVPT Challenges in Topical ANDAs



DD- Dean and Dixon Outlier Test

IVPT Challenges in Topical ANDAs

Analyzed 41 Pivotal IVPT studies

	Dean-Dixon, α = 0.05	Grubbs, α = 0.05	Dean-Dixon, α = 0.01
Percentage of studies with at least one outlier	95.12%	95.12%	78.05%
Average outlier percentage (overall)	2.26%	2.30%	0.74%
Average outlier percentage (adequate studies)	2.27%	2.39%	0.85%
Average outlier percentage (inadequate studies)	2.25%	2.25%	0.68%
Studies that only pass after removing outliers	2 of 41 (4.9%)	2 of 41 (4.9%)	0 of 41 (0%)
Studies that only fail after removing outliers	7 of 41 (17.1%)	6 of 41 (14.6%)	4 of 41 (9.8%)
Maximum outlier percentage	4.38%	4.06%	2.19%

Conclusions

- An analysis of the topical ANDAs suggest that characterization-based BE approaches have been predominantly used to support ANDA submission during GDUFA II, among other approaches
- ~200 (57%) topical ANDAs received since FY 18, have been approved
- For ANDAs that utilized a characterization-based BE approach, there are significant challenges associated with IVPT studies, in particular
- Challenges appear to arise due to inadequate method development and/or method validation (discriminatory ability)
- Engagement with the Agency utilizing the PDEV and/or PSUB meetings can assist with resolving some of the observed challenges

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Thank You

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