Common Issues Identified in *In-vitro* Release Test (IVRT) and *In-vitro* Permeation Test (IVPT) Studies Submitted in ANDA to Support Bioequivalence for Topical Products

SBIA 2021: Advancing Generic Drug Development: Translating Science to Approval

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Disclaimer

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

Learning Objectives

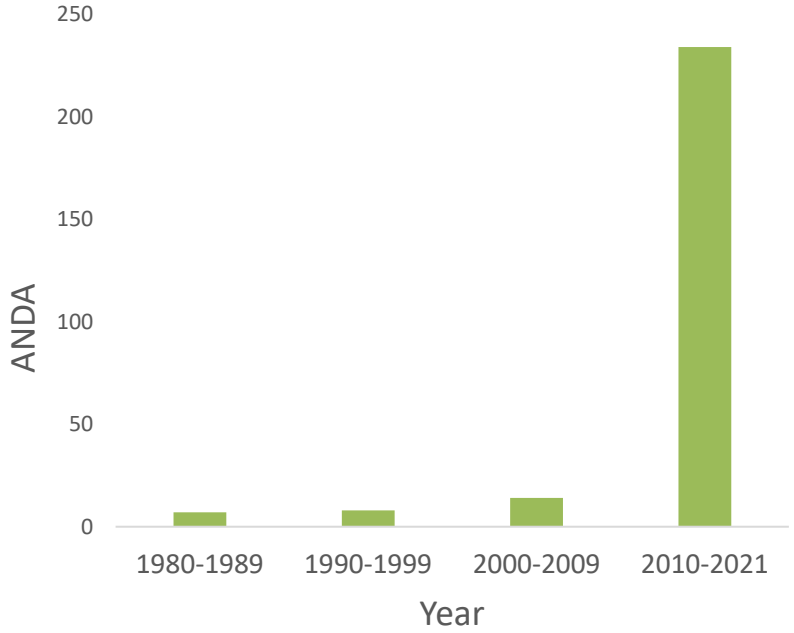
- Recognize the role of IVRT and IVPT to support bioequivalence (BE) and contribution to ANDAs of topical products
- Outline key attributes of IVRT and IVPT
- Identify common observations/challenges across IVRT and IVPT studies submitted in ANDAs
- Describe points to consider/expectations in IVRT and IVPT
- Summary

Role of IVRT/IVPT to Support BE

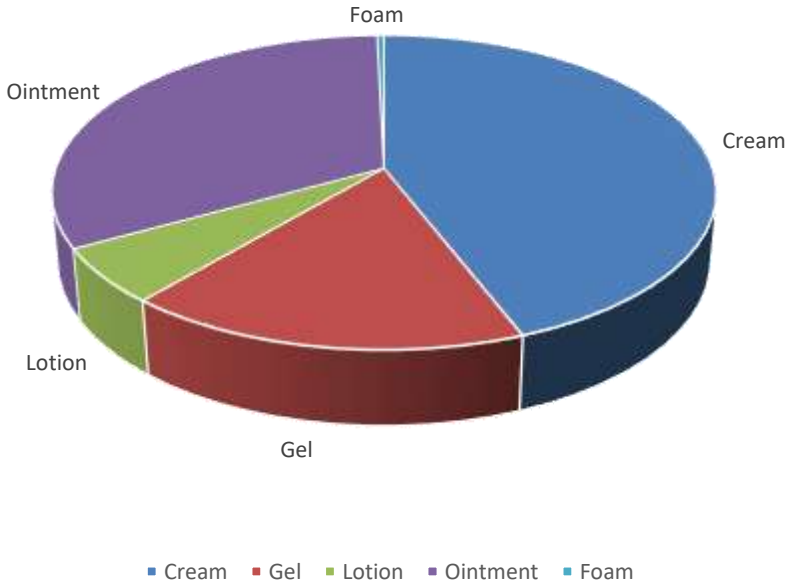
- An in vitro characterization approach to demonstrate BE generally includes assessing the formulation, physicochemical and structural characterization, plus IVRT or IVRT/IVPT
- In general, as the complexity of the dosage form increases, and the potential for failure modes for BE increase, the scope of the in vitro characterization recommendations increases
- Performance tests for evaluating sameness between test and reference products
- Part of collective weight of evidence of in vitro studies to demonstrate BE
  - IVRT: rate of release of active ingredient
  - IVPT: rate and extent of active ingredient availability at or near site of action
- Comparable rate and extent help mitigate risk of potential failure modes for establishing BE that may not be adequately captured by formulation comparison and physicochemical characterization

ANDAs with IVRT and/or IVPT for Topical Products

ANDA submission trend



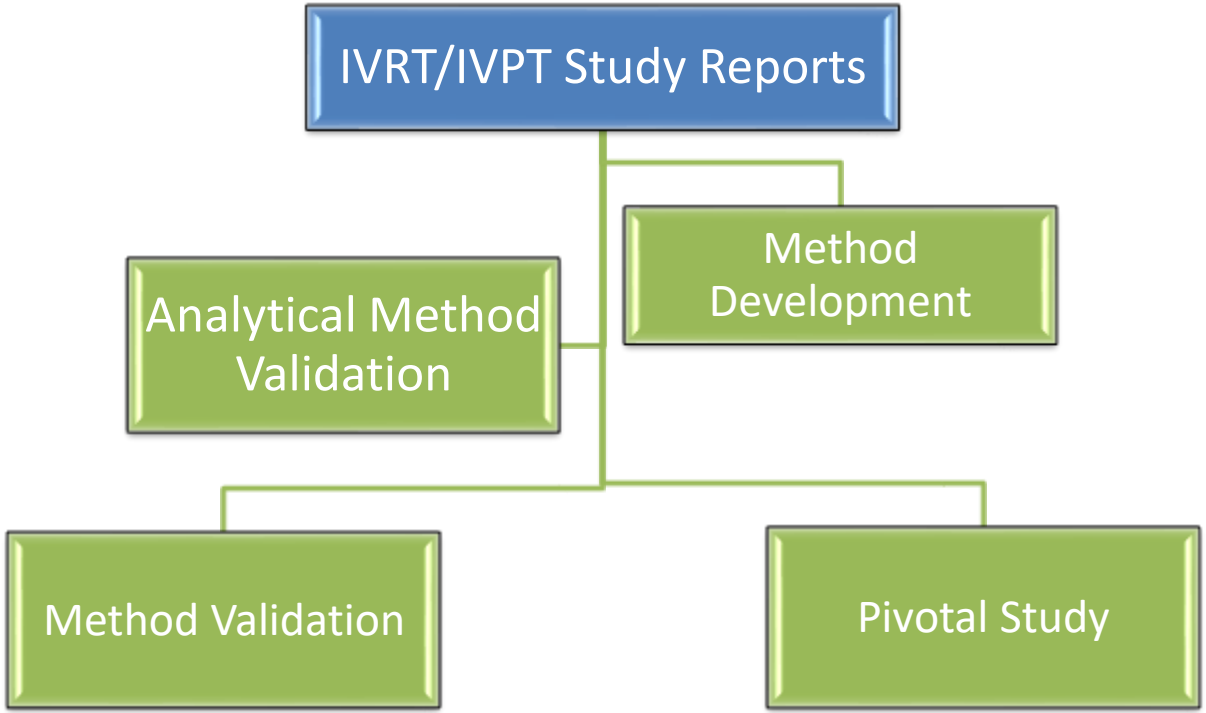
Category of dosage forms



Key IVRT and IVPT Attributes

Attributes	IVRT	IVPT
Receptor solution	Aqueous or organic media	Physiological media with antimicrobial agent
Membrane	Synthetic	Human skin
Dosing	Pseudo-infinite dose	Finite dose
Occlusion (Yes or No)	Yes	No
Endpoint parameters	Release rate (slope)	Flux and Cumulative amount permeated
Statistical analysis	Wilcoxon Rank Sum/Mann-Whitney rank test	90% confidence interval using Average BE or Reference Scaled Average BE approach
Variability	Intra/inter run variability is relatively consistent (e.g., ≤ 15%)	Adequate control of study procedures to minimize intra/inter donor variability

Documentation, Organization, and Submission of Reports



- Individual study reports for method development, validation, pilot and pivotal studies should be submitted separately
- Reports should be organized in eCTD Module 5.3.1; summary tables in Module 2

Common Observations Themes

Insufficient details on apparatus qualification; experimental set-up; method controls

Missing information/insufficient data for validation of method parameters

Inability/inadequate data showing discriminatory ability of method

Insufficient information on data analysis/data presentation

Lack of submission of raw data (.xpt files, chromatograms, related SOPs/Protocols)

Understanding IVRT common observations/challenges and considerations/expectations

Validation Category	Observations/Challenges	Considerations/Expectations
Apparatus qualification	Missing information to justify the selected diffusion apparatus and laboratory qualification	Provide manufacturer's measurement of diffusional area of orifice and volume of receptor solution compartment for each cells, if available; in addition, provide empirical measurements from the in-vitro BE study site
Membrane validation	Insufficient data showing membrane inertness, compatibility with receptor medium	Provide data following incubation without membrane to monitor for drug loss not related to membrane binding and with membrane, to assess any decrease in the amount of drug in solution
	Lack of details regarding membrane treatment and equilibrium before dosing	Follow recommendations from USP General Chapter <1724>. Provide scientific rationale for any deviations

Validation Category	Observations/Challenges	Considerations/Expectations
Receptor solution	Inadequate information/data for the selection of final receptor solution	Provide information on solubility, stability, variability and linearity of release rate among replicates, and maintenance of steady state release kinetics among replicates
Dosing procedures	Dosing of formulation for selected diffusion cell apparatus is inconsistent with recommendations in USP Chapter <1724> Inadequate information provided for dosing and synchronization with sampling time	Follow recommendations in USP Chapter <1724>. Provide rationale with supporting evidence, if different. Since deviation of dosing using the selected apparatus may introduce additional variability

Validation Category	Observations/Challenges	Considerations/Expectations
Sampling duration/Sampling times	Inadequate supportive evidence for selected study duration, lack of explanation for any deviation from USP General Chapter <1724>	Follow recommendations in the USP General Chapter <1724>. Provide explanations or supporting data for any deviation
Robustness	Data submitted does not support robustness of the method; acceptance criteria not pre-defined	Provide detailed explanation of data table; pre-defined acceptance criteria

Validation Category	Observations/Challenges and Expectations
Discriminatory ability of method (sensitivity, selectivity and specificity)	Provide details of formulations (composition and procedures of preparation of altered formulations) Use altered formulations with 50%-150% variation in strengths for sensitivity and fundamental selectivity to demonstrate a reasonably discriminatory method Change of multiple critical attributes in altered formulation for supplemental selectivity, consider changing one attribute at a time Provide qualitatively results of selectivity (such as individual concentrations, cumulative amount released, slopes, correlation coefficient, plots. Selectivity demonstrated quantitatively per the USP General Chapter <1724>) to establish inequivalence; Specificity plot should be provided, and results discussed

Understanding IVPT common observations/challenges and considerations/expectations

Validation Category	Observations/Challenges	Considerations/Expectations
Apparatus qualification	Missing information to justify the selected diffusion apparatus and laboratory qualification	Provide manufacturer's measurement of diffusional area of orifice and volume of receptor solution compartment for each cells, if available; in addition, provide empirical measurements from the in-vitro BE study site
Dosing amount/procedures	Inadequate data submitted for selection of target dose amount and procedures	Control of accuracy and precision of dose amount applied; details of dose spreading procedure; how dosing times are staggered and synchronized with sampling time
Dose duration /sampling time	Inadequate data submitted for selection of dose duration /qualification of sampling time	Selected dose duration should identify maximum (peak) flux and decline in flux; precision/accuracy of sampling at each timepoint should be determined

Validation Category	Observations/Challenges	Considerations/Expectations
Membrane (Skin) validation	Missing/inadequate information submitted	Provide details of skin handling/processing; skin thickness distribution; equilibration of skin; use same anatomical site of skin for all studies; skin temperature measurement
	Concerns related to overhydration of skin (e.g., soaking of skin in receptor medium/ water for longer duration prior to dosing)	Consider thawing skin in a sealed plastic bag immersed in warm water (e.g., ~32 °C) for 5 minutes prior to dermatoming
	Insufficient description of procedures for measuring skin barrier integrity; data to support acceptance criteria	Procedures for calibration of instrument should be provided; pre-defined acceptance criteria with supportive data to be able to discriminate between skin sections with compromised and competent barrier integrity; selection of appropriate measurement mode for specific adapter

Validation Category	Observations/Challenges	Considerations/Expectations
Receptor solution/sampling qualification	Use of chemical agents that have potential to alter the permeability of skin; missing information of how sampling was done and replacement	Provide details/data of the observations mentioned; type/explanation of replacement of receptor solution volume; sampling technique
Discriminatory ability of method (sensitivity)	Inadequate data submitted to determine the sensitivity of method	Use sufficient number of donors /replicates; details of composition/ procedures for altered strengths should be provided; in addition to average data and plots with and without error bars, individual donor data, individual plots with and without error bar should be provided

Validation Category	Observations/Challenges	Considerations/Expectations
Pilot study	Flux and cumulative permeation results/profiles are not reported for each diffusion cell at each timepoint; details describing summary statistics for intra-donor and inter-donor average are missing	Study design should be detailed and clear, data values should be clearly associated with specific donors, replicates, treatment groups, timepoints
Pilot study; selectivity	Selectivity studies not conducted during pilot study; flux and cumulative permeation results/profiles not properly formatted or reported for each diffusion cell at each timepoint Lack of description of summary statistics for intra-donor and inter-donor average; composition and procedures of altered formulation missing	

Pivotal studies	Observation/Challenges and Expectations
Test and RLD batches	Same batches of drug products should be used for all studies to demonstrate BE, whenever possible
Lack of documentation/information related to control of method parameters	Details of study design, dosing, randomization/blinding, study dates should be provided, non-dosed control diffusion cell should be run in parallel with the other replicate dosed diffusion cells; adequate control of study parameter should be documented
Calculation of flux	Use of nominal receptor solution compartment volumes to calculate results. Flux should be calculated based upon the precise empirically measured volume of that specific diffusion cell which may vary between individual cells
Data exclusion	Exclusion of data generated during pivotal study is generally not advisable without documented protocol violations or experimental errors

Pivotal studies	Observation/Challenges and Expectations
High variability across all study	If unusually high variability is observed, check control of study parameters, understand factors controlling permeation; study drug; explain/rationale for inconsistent variability across validation, pilot and pivotal study results
Data analysis/results	Qualitative and quantitative comparison of flux and cumulative permeation data, including individual profiles, average profiles with and without error bars; provision of all relevant results from statistical analysis
Analytical validation/report	Selection of calibration curve to cover concentration range; selection of relevant quality control samples; matrix effect; stability of drug in receptor solution with highest relevant temperature

Summary

- Proper understanding of factors controlling release or permeation can guide improvement of IVRT/IVPT submissions
- Endeavor to optimize and validate methods to be discriminatory and reproducible
- Use well controlled IVRT/IVPT method to conduct pivotal study
- Special attention to FDA guidance documents and considerations of the observations discussed in the presentation to improve quality of future submissions
- FDA and applicants working together will help extend resources, reduce number of review cycles and achieve faster approval

Challenge Question #1

Change of multiple critical attributes for an altered formulation is appropriate when conducting supplemental selectivity study for IVRT:

A. True

B. False

Challenge Question #2

Which of the following statements is NOT true?

A. IVPT statistical analysis is determined by comparing test and reference product using Wilcoxon Rank Sum/Mann-Whitney rank test

B. IVPT is usually conducted using physiological media with microbial agent

C. IVPT endpoint parameters are the rate (flux) and extent (cumulative amount permeated) of active ingredient availability at or near site of action

D. IVPT statistical analysis is determined using 90% confidence interval of log-transformed Jmax and cumulative amount permeated using average BE or reference scaled average BE

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Questions?

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