In-vitro Bioequivalence Studies of Topical Drug Products: Challenges and Promises of *In-vitro* Release Test (IVRT) and *In-vitro* Permeation Test (IVPT)

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Session 1: Method Development / Validations for Non-traditional Analytical Methods
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This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Outline

- Introduction/Background
- Common Observations
- Observations related to IVRT
- Observations related to IVPT
- Concluding Remarks

Bioequivalence of Topical Products

- Traditional methods to establish bioequivalence (BE)
  - *In-vivo* Pharmacokinetic Studies
  - *In-vivo* Pharmacodynamic Studies
  - *In-vivo* Comparative Clinical Endpoint Studies
- Alternative methods to establish BE
  - *In-vitro* Characterization Based Approaches:
    - No difference in inactive ingredient components and the quantitative composition. E.g., Qualitative (Q1) and Quantitative (Q2) Sameness
    - Physical and Structural (Q3) Sameness
    - *In-vitro* Release Test (IVRT)
    - *In-vitro* Permeation Test (IVPT)

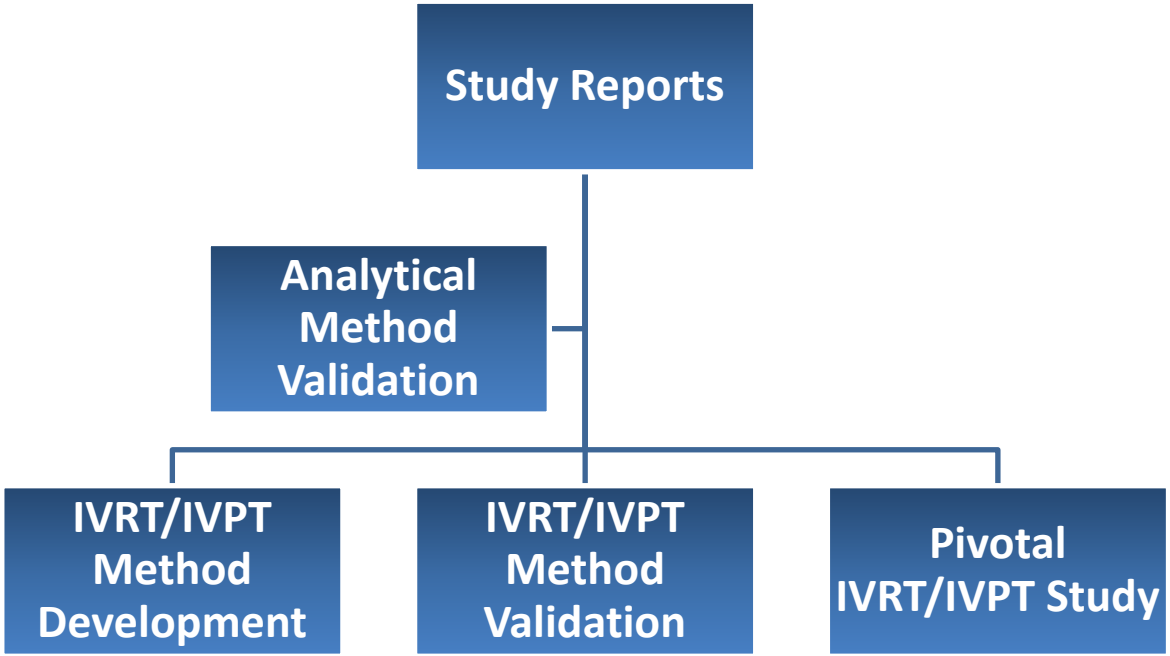
Alternative Methods: Promises

- ✓ Well defined, robust and reproducible methods
- ✓ Assessments of different formulations with evaluation of impact of process and quality control changes
- ✓ Assess the impact of post-approval changes to excipients
- ✓ Relatively cost effective and time saving
- ✓ More open to automation, ability to control the conditions of experiment
- ✓ Demonstrate batch-to-batch uniformity

Comparison of *In-Vitro* BE Tests

Attributes	*In-vitro* Release Test	*In-vitro* Permeation Test
Membrane	Synthetic membrane	Human skin
Dosing	Infinite and Occluded Dose	Finite and Un-occluded Dose
Receptor Solution	Mostly hydro-alcoholic mixtures	Physiological media containing anti-microbial agent(s)
	Relatively high amount of drug during testing (e.g., µg to mg range)	Relatively low amount of drug during testing (e.g., pg to ng range)
Endpoint(s)	Release rate (slope)	Flux and Cumulative amount
Variability	Relatively consistent	Intra/inter- donor variability
Scope	The data provide release of drug from the formulation, however, unable to provide correlation/prediction of *in-vivo* performance	The data may be used for *in-vitro in-vivo* correlation which may potentially mimic the *in-vivo* performance

IVRT/IVPT Study Reports



Observation: The reports are combined across different sections instead of providing individual sections separately

Contents of Study Report

- IVRT/IVPT Development, Validation and Pivotal Study
  - Experimental set-up
    - Membrane treatment prior to dosing
    - Membrane equilibrium
    - Randomization and blinding procedure
    - Dosing procedure and synchronization with sampling time
    - Occluded vs un-occluded cells
    - Automated vs manual sampling
    - Environmental control data
    - Experiment dates

Contents of Study Report

- IVRT/IVPT Development, Validation and Pivotal Study (Continued..)
  - Handling of samples
    - Condition (i.e., temperature) and duration of samples storage
  - Sample Analysis
    - Dilution procedure and date of analysis
  - Data Analysis
    - Calculations for release rate/flux and cumulative amount
  - Raw Data, Chromatograms, Related SOPs/Protocol

In-vitro Release Test

IVRT Method Development

Purpose:

- To assure all the possible attempts made to select and optimize the specific IVRT method parameters for the particular drug product
- To identify the study design, method parameters and protocol from the systematically developed IVRT method for further validation/pivotal studies

Observations:

- Insufficient information/data/explanation on the selection of
  - Receptor medium, and solubility of drug
  - Diffusion membrane and its inertness, binding
  - Amount of drug product in the donor chamber, sampling times, study duration, stirring/agitation rate

IVRT Method Validation

Purpose:

- To validate, qualify, verify, and/or justify the developed IVRT method in terms of the apparatus, methodologies, and study conditions for the specific drug product to compare test and reference products

Observations:

- Missing data/information to support IVRT apparatus qualification
  - The empirical measurements for diffusional area of orifice and the volume of the receptor solution compartment for each diffusion cell carried out at the *in-vitro* BE site
  - The data available from the manufacturer (if provided)

IVRT Method Validation

Observations:

- Selection of short study duration (e.g., less than 4 hours) without any supportive data/explanation
- Inadequate information/data for
  - Intra-run and inter-run precision and reproducibility (using intra/inter-instrumentation and/or intra/inter-operator)
  - IVRT robustness

IVRT Method Validation

Observations:

- Lack of adequate information/data to support IVRT Discrimination Sensitivity, Specificity, and Selectivity
  - Selection of altered strengths
  - Study design in terms of number of cells
  - Statistical analysis (per USP General Chapter <1724>) which demonstrate inequivalence with altered strengths
  - Supplemental selectivity
  - The composition and procedures for preparation of the altered formulations

In-vitro Permeation Test

IVPT Method Development

Purpose:

- To assure all the possible attempts made to select and optimize the specific IVPT method parameters for the particular drug product
- To identify the study design, method parameters and protocol from the systematically developed IVPT method for further validation/pivotal studies

Observations:

- Insufficient information/data/explanation on the selection of
  - Apparatus, dose amount, study duration, sampling times
  - Receptor solution and solubility of drug
  - Skin source, type, skin preparation and its barrier integrity test along with acceptance criteria

IVPT Method Validation

Purpose:

- To validate, qualify, verify and/or justify the developed IVPT method in terms of the apparatus, methodologies, and study conditions for the specific drug product to compare test and reference product

Observations:

- Missing data/information to support IVPT apparatus qualification
  - The empirical measurements for diffusional area of orifice and the volume of the receptor solution compartment for each diffusion cell carried out at the *in-vitro* BE site
  - The data available from the manufacturer (if provided)

IVPT Method Validation

Observations:

- Insufficient information/data
  - Dosing procedure
    - Points to consider: Accuracy of dose amount applied, Dose spreading procedure
  - Receptor solution qualification
    - Points to consider:
      - The use of chemical agents, which may have potential to alter the permeability of the skin, is discouraged
      - The selection of the amount of anti-microbial agent in the receptor solution to prevent potential bacterial decomposition of the dermis/epidermis in the diffusion cell

IVPT Method Validation

Observations:

- Missing information/data on membrane (i.e., skin) qualification
  - Points to consider:
    - Skin handling during procurement and shipping
    - Skin processing (e.g., dermatomed or heat separated epidermis)
    - Skin storage conditions
    - Number of freeze-thaw cycles of skin prior to use
    - The difference in the anatomical site of skin between pilot/validation and pivotal studies is discouraged

IVPT Method Validation

Observations:

- Missing information/data on membrane (i.e., skin) qualification (continued)
  - Points to consider:
    - Skin barrier integrity testing along with supportive data for proposed acceptance criteria
    - Skin equilibrium with receptor medium
    - Skin temperature measurement
    - Sampling and replacement technique of receptor solution

IVPT Method Validation

Observations:

- Inadequate information/data to support IVPT Sensitivity
  - Number of donors
  - Selection of specific approach (e.g., different dose amount vs. different dose duration vs. altered strengths) to demonstrate variation in drug permeation profile
  - Points to consider: The permeation profile using optimized IVPT method parameters should be compared using specific approach as noted above to demonstrate higher and lower amount of drug permeated from the same donors

IVPT Method Validation

Observations:

- Lack of adequate information/data for pilot study
  - Selectivity
    - Parallel assessment of test, reference and altered formulation
    - Number of donors
  - Format of data submission for each diffusion cell to support (i) IVPT permeation profile and range, (ii) IVPT precision and reproducibility
  - The composition and procedures for preparation of the altered formulations

IVPT Data Analysis

Observations:

- Inappropriate approach to calculate flux
- Exclusion of data generated from an adequately controlled study, in general, is discouraged
- Lack of adequate control of the study parameters can potentially render the interpretation of the BE data questionable

Analytical Report for IVRT/IVPT

Observations:

- Lack of adequate information/data
  - Stability of drug in receptor solution with highest relevant temperature
  - Preparation of calibration curve and quality control samples for IVPT, considering the matrix effect
  - Selection of quality control samples

Concluding Remarks

- ✓ A controlled pivotal study using a well developed, optimized and validated IVRT/IVPT method would be a promising alternative method to demonstrate bioequivalence for Topical products
- ✓ Proactive considerations of the observations discussed in the presentation are encouraged to improve the quality of future submissions
- ✓ This can lead to reduce number of review cycles with faster approval process

Challenge Question #1

- Per USP <1724>, the sampling is generally performed over a _____ time period to conduct IVRT study.

  A. 1-2 hours

  B. 2-4 hours

  C. 4-6 hours

  D. 6-10 hours

Challenge Question #2

- The comparative permeation profiles from 1-2 donors are considered sufficient to demonstrate adequate IVPT sensitivity and selectivity for method validation.

A. True

B. False

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Questions ?


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