In-vitro Permeation Test (IVPT) Method Development, Validation, and Transfer

Panel Discussion

In-vitro Release Test (IVRT) and In-vitro Permeation Test (IVPT) Methods Best Practices and Scientific Considerations for ANDA Submissions Virtual Public Workshop

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Considerations for the Apparatus

➢ What are different types of apparatus which can potentially be used to conduct IVPT studies?

➢ How to select appropriate apparatus to conduct IVPT studies?

➢ What is the difference between “selection of apparatus” and “qualification of the apparatus”? 
Skin Selection, Preparation, and Storage

- Selection of the anatomical site for the IVPT studies
- Skin preparation in accordance with the drug product (e.g., type of skin, site of action, practical and logistical considerations, etc.)
- Criteria for skin thickness
- Number of freeze and thaw cycle(s) for the skin sections prior to conducting the IVPT studies
- Importance of using consistent skin anatomical sites and skin thickness across the studies
Skin Barrier Integrity Testing

**Trans-Epidermal Water Loss (TEWL)**

Test results reported as TEWL (g/m²/hr)

**Tritiated Water (³H₂O)**

Test results reported as permeated amount of tritiated water per skin area (eq. µL/cm²)

**Trans-Epidermal Electrical Resistance (TEER)**

Test results reported as resistance (kΩ) or conductance (1/kΩ or mS). Units may also involve normalization of skin area.
Skin Barrier Integrity Testing

➢ What is the purpose of skin barrier integrity testing?

➢ What are the considerations to assure that the skin barrier is not compromised using respective approach of integrity testing?

➢ What is the impact of critical elements (e.g., adapter size for TEWL, test parameters and diffusion cell specifications, etc.) on testing procedure?

➢ How to determine the acceptance criteria and cutoff value to discriminate between competent (intact) and compromised skin barriers?
Receptor Solution Selection

➢ Selection of the composition and pH of the receptor solution

➢ Solubility considerations
  ▪ Is it appropriate to use solubility enhancers in the receptor solution for hydrophobic drug products?
  ▪ Example(s) of chemical agents that can be used or avoided for IVPT studies

➢ Stability considerations

➢ Importance for the use of selective anti-microbial agent and its strength/concentration

➢ Selection of analytical method in accordance with the receptor solution
Receptor Solution Sampling Qualification

How to demonstrate qualification of receptor solution sampling?

- Specific considerations for different types of diffusion cells
  - Flow-through diffusion cell Vs Vertical diffusion cell
  - Aliquot sampling Vs. Full replacement of samples
  - Automated Vs. Manual Sampling
Optimization of IVPT Parameters

➢ Selection of Dose

- How to select “target dose”?
- Does the selected “target dose” for IVPT studies need to be clinically relevant?
- How critical is the dosing procedure (e.g., dispensing and spreading) and its impact on permeation profiles?

➢ Selection of Sampling Intervals

- How to select sampling intervals to capture high (temporal) resolution of the permeation profile, mainly to adequately capture the $J_{\text{max}}$?
Optimization of Permeation Profiles

➢ Observations related to $J_{\text{max}}$

- The first sampling time point provides $J_{\text{max}}$
- The last sampling time point provides $J_{\text{max}}$
- The corresponding sampling time ($T_{\text{max}}$), that represent $J_{\text{max}}$, may differ across donors
IVPT Sensitivity

➢ When should the IVPT sensitivity studies be conducted?

➢ What can be considered as an appropriate minimum number of donors and replicates for each treatment?

➢ Which drug product should be utilized to conduct IVPT sensitivity studies?
IVPT Sensitivity

Approaches to demonstrate IVPT sensitivity

- Modulation of Dose amount
  - Factors to be considered on selecting the lower and higher dose amounts compared to the target/nominal dose amount

- Modulation of Dose duration
  - Factors to be considered for the study design (e.g., drug wipe-off procedure, selection of wipe-off time, sampling frequency, clinical relevance of the dose duration, etc.)

- Modulation of Product strength
  - Suitability of this approach compared to other approaches
IVPT Sensitivity

➢ Data Analysis

- What are the expectations to demonstrate adequate IVPT sensitivity using the selected approach?

- Is the interpretation of data qualitative or quantitative in nature?
  - For the qualitative approach, what would be considered adequate difference in permeation profiles with the selected approach, i.e., either different dose amounts or different dose durations?
  - For quantitative approach, which method of statistical analysis have the potential to assess the IVPT sensitivity data?
IVPT Selectivity/Pilot Studies

Study design

- Parallel assessment of the reference product, the test product, and an altered formulation with same strength of the drug product (designed to be different from the reference product)

- What can be considered as an appropriate minimum number of donors and replicates for each treatment?

- Once the target dose amount or dose duration is determined during IVPT sensitivity studies, is it necessary to have the same target dose amount/duration for the conduct of IVPT selectivity/pilot studies?

- What are the considerations for altered formulation design?
IVPT Selectivity/Pilot Studies

Data Analysis

- What are the expectations to demonstrate adequate IVPT selectivity, in terms of comparing permeation profiles between (i) test and reference products, (ii) reference product and altered formulations?

- When the statistical analysis is performed for potentially underpowered study, what are the expectations to demonstrate adequate IVPT selectivity?

- Is it appropriate to use qualitative analysis to interpret the IVPT selectivity data?
Reference Product’s Variability

Variability factors to be considered

- Batch to batch variability
- Type of dosage form (e.g., cream vs gel vs ointment vs suspension, etc.)
- The age of the drug product during its shelf life

What do you think about the impact of all these sources of variability on the IVPT study design to demonstrate bioequivalence?
Designing the Pivotal Study

➢ Power analysis for selecting the number of donors and replicates for each treatment

▪ What are the considerations for theoretical T/R ratios and point estimate ranges?

▪ Is it appropriate to use the variability of (i) reference product only or (ii) reference and test products from the results of pilot studies?

▪ How consistent is the extrapolation of the data, in terms of variability, from the pilot studies, considering the number of donors/replicates?
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