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

August 18, 2021

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

Panelists

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Vijendra Nalamothu, PhD	Chairman and Chief Executive Officer, Tergus Pharma

Considerations for the Apparatus

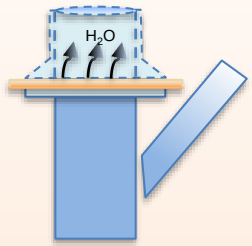
- What are different types of apparatus which can potentially be used to conduct IVPT studies?
- How to select appropriate apparatus to conduct IVPT studies?
- What is the difference between “selection of apparatus” and “qualification of the apparatus”?

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

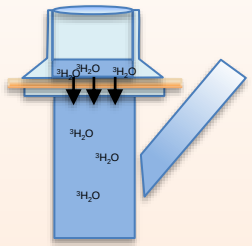
Skin Barrier Integrity Testing

Trans-Epidermal Water Loss (TEWL)



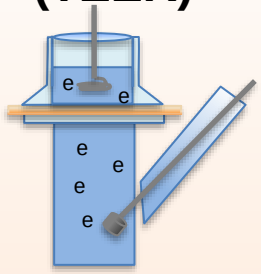
Test results reported as TEWL ($g/m^2/hr$)

Tritiated Water (^3H_2O)



Test results reported as permeated amount of tritiated water per skin area (eq. $\mu L/cm^2$)

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_{max}?

Optimization of Permeation Profiles

- Observations related to J_{max}
  - The first sampling time point provides J_{max}
  - The last sampling time point provides J_{max}
  - The corresponding sampling time (T_{max}), that represent J_{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?

Acknowledgements

- Anil K. Nair, PhD
- Kuldeep Dhariwal, PhD
- Diana Vivian, PhD
- Xiaojian Jiang, PhD
- Hongling Zhang, PhD
- Nilufer Tampal, PhD
- Bing Li, PhD
- Partha Roy, PhD
- Ying Jiang, PhD
- Tannaz Ramezanli, PhD
- Priyanka Ghosh, PhD
- Sam Raney, PhD
- Eric Mahoney, MS, CNPR, CPM
- Bioequivalence Assessors
- Organizing Committee Members
- Panelists

Thank you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