General Guidances Related to Characterization-Based Bioequivalence Approaches for Topical Products

(Part II)

SBIA 2023 – Advancing Generic Drug Development: Translating Science to Approval

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Disclaimer

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Learning Objectives

- Discuss general recommendations pertaining to critical aspects related to conduct and analysis of in-vitro release test (IVRT) and in-vitro permeation test (IVPT) studies for submission in ANDAs for topical drug products

- Identify important updates provided in the scientific recommendations within the general guidance for IVRT and IVPT studies

In-vitro Release Test

Before October 2022…

Contains Nonbinding Recommendations

Draft Guidance on Acyclovir

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Acyclovir

Dosage Form; Route: Cream; topical

Recommended Studies: Two options: in vitro or in vivo study

I. In vitro option:

To qualify for the in vitro option for this drug product the following criteria should be met:

A. The test and Reference Listed Drug (RLD) products are qualitatively (Q1) and quantitatively (Q2) the same as defined in the Guidance for Industry *ANDA Submissions – Refuse-to-Receive Standards*, Revision 1 (May 2015).[1]

B. The test and RLD products are physically and structurally similar based upon an acceptable comparative physicochemical characterization of a minimum of three lots of the test and three lots (as available) of the RLD product.

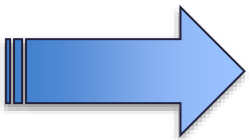
C. The test and RLD products have an equivalent rate of acyclovir release based upon an acceptable in vitro release test (IVRT) comparing a minimum of one lot each of the test and RLD products using an appropriately validated IVRT method.

D. The test and RLD products are bioequivalent based upon an acceptable in vitro permeation test (IVPT) comparing the rate and extent of acyclovir permeation through excised human skin from a minimum of one lot each of the test and RLD products using an appropriately validated IVPT method.

Additional comments: Specific recommendations are provided below.

[1] Guidance for Industry ANDA Submissions – Refuse-to-Receive Standards, Revision 1 (May 2015).

Recommended Dec 2014; Revised Dec 2016



Since October 2022…

In Vitro Release Test Studies for Topical Drug Products Submitted in ANDAs

Guidance for Industry

DRAFT GUIDANCE

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Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Susan Levine at 240-402-7936.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

October 2022
Generic Drugs

Noteworthy Updates in the Scientific Recommendations within the IVRT Guidance

IVRT Method Development

- **Foundation:**
  - IVRT method parameters, Receptor solution, and Membrane
- Consistent with USP General Chapter <1724>, the typical study duration should be between 4 and 6 hours
  - Duration of < 4 hours may be insufficient to assess whether the release rates represent the steady state drug release kinetics
  - Duration of < 4 hours (which is not recommended) may be justified by compelling experimental data in limited circumstances
- The linearity of the drug release rate (slope) across all time points should ideally have an **r^2 value of ≥ 0.97**

IVRT Method Validation

- Recommendations to support membrane surface temperature are further elaborated for equipment* qualification.
- Membrane inertness should be evaluated in relation to membrane binding of the drug in the receptor solution at a concentration relevant to the **range of drug concentrations** in the receptor solution during the test.
- Further expansion on the expectation for receptor solution sampling qualification.
- For precision and reproducibility, a minimum of three independent runs is recommended.

* termed as “Apparatus” in the draft PSG of Acyclovir Cream

IVRT Method Validation

- The linearity of the drug release across all time points should be calculated and reported for **each diffusion cell** and compared within and across all IVRT runs.
- For the release rate to be considered suitably linear, it should have an **r^2 value ≥ 0.97 across IVRT study duration**.
- Recommends to report Dose Depletion
  - The IVRT method may be considered adequate despite a dose depletion of greater than 30% when experimental evidence illustrates that the release rate (slope) remains suitably linear for each diffusion cell when plotted versus the square root of time.

IVRT Method Validation

- Discrimination Sensitivity, Specificity, and Selectivity
  - Comparing the release rates from the test formulation with that from two comparable formulations, with a higher strength (150%) and a lower strength (50%)
  - If precipitation of the active ingredient is observed when formulating the 150% strength, it may be necessary to use different strategies, which may be discussed with the Agency before the submission of an ANDA.
  - To be considered suitably specific, an IVRT method should be proportionally linear for the correlation of the formulation concentration to the average IVRT release rate with a **minimum r^2 value ≥ 0.95**

IVRT Method Validation

- Discrimination Sensitivity, Specificity, and Selectivity (Cont'd….)
  - Selectivity: The release rate from the formulation at 50% and 150 % of the nominal strength should fail to show equivalence to the release rate from the nominal strength formulation using the statistical approach described in USP General Chapter <1724>.
  - Supplemental selectivity:
    - The supplemental demonstration of the selectivity of the IVRT method validates that it can detect differences in the release rate which are associated with aspects of the formulation other than the strength.
    - The altered formulation may include changes in inactive ingredients and/or its concentration(s), the manufacturing processes, or combinations of these.

Additional Updates…

- Separate section about sample analytical method validation with further details
- Handling and Retention of Samples
- Control of study procedures with quality management system
- Submitting the study information in an ANDA
  - The IVRT protocols, SOPs and reports to be submitted in module 5.3.1.2
  - The protocols, SOPs and reports for sample analytical method validation to be submitted in Module 5.3.1.4

Challenge Question #1

- If the dose depletion is higher than 30 % for the IVRT study (despite the linearity of IVRT method greater than 0.99 for all cells), the IVRT method is not considered acceptable.

A. True

B. False

In-vitro Permeation Test

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Noteworthy Updates in the Scientific Recommendations within the IVPT Guidance

IVPT Method Development Parameters

Parameters	Examples
Equipment*	Vertical Diffusion Cell (VDC)
Dose Amount	15 mg/cm^2
Skin Source	Cadaver
Skin Type	Posterior torso
Skin Preparation	Dermatomed
Skin Barrier Integrity Test	Trans-Epidermal Water Loss (TEWL) and acceptance criteria
Dose Duration	6 hours
Study Duration	48 hours

* termed as “Apparatus” in the draft PSG of Acyclovir Cream

Considerations for Optimization

- **Dose Amount**
  - Process of selecting an optimal dose amount
- **Sampling schedule and Study duration**
  - Ideally include a complete flux profile to identify the maximum (peak) flux and a decline in the flux thereafter across multiple subsequent time points
  - Recommendation to utilize wiping off the applied dose after a suitable duration from the skin and continue to monitor the receptor solution for an extended period when there is no decline in the flux profile for the dose that remains on the skin for the duration of the study and may continue to deliver the drug for a sustained period

Skin Barrier Integrity Testing

- Common types of testing: Trans-Epidermal Water Loss, Tritiated Water, Electrical Based [e.g., Trans-Epidermal Electrical Resistance (TEER)]
- Provide detailed recommendations about the process for each type of testing
- Considerations on acceptance criteria for each type of testing
- The testing data may not correlate with permeation of most topically applied active ingredients

IVPT Method Validation

Receptor Solution Qualification

- The receptor solution should be qualified in relation to:
  - Stability of the drug in the receptor solution
  - The use of an anti-microbial agent in the receptor solution (e.g., ~0.1% sodium azide or ~ 0.01% gentamicin sulfate)
  - Solubility of the drug in the receptor solution
    - 0.1% or 0.2% polyoxyethylene[20]oleyl ether (also known as Oleth-20, Volpo-20, or Brij-20) is commonly used as a solubility enhancer for hydrophobic drugs
  - Compatibility with the skin (i.e., no alteration in the skin permeability)
    - Inclusion of organic solvents and alcohols in the receptor solution are not recommended

Discrimination Sensitivity and Selectivity

Sensitivity

- Typically performed toward the end of the IVPT method development phase
- Key purpose is to establish IVPT method parameters like the target dose amount and dose duration

Selectivity

- Performed once the IVPT method parameters are established
- Typically performed as a part of IVPT pilot study which supports multiple IVPT method validation parameters

IVPT Sensitivity

- **Modulation of dose amount**
  - Recommendations on selection of lower and higher dose amounts (i.e., 3-fold) compared to target dose amount
  - Scientific considerations for the dosage form and formulation along with its limitations
- **Modulation of dose duration**
  - Recommendations on selection of lower and higher dose duration compared to target dose duration using the controlled dose amount across all treatments
- **Modulation of product strength**
  - Utility of this approach under only certain situations because of the overall limitations of this approach

IVPT Pilot Study

- Recommended to conduct with three parallel treatments: Test, Reference and a topical product or formulation that is known or designed to be different from the reference topical product
- Recommended to perform with skin sections from multiple donors (e.g., 4 – 6) with minimum 4 replicates per donor per treatment
- Supports a validation of IVPT method parameters like permeation profile, range, precision, reproducibility, dose depletion, and selectivity
- The data can help to estimate the number of donors that may be needed to adequately power the pivotal IVPT study

Pivotal IVPT Study

IVPT Endpoints

- Maximum flux (J_{max})
  - The flux (rate of drug permeation) profile should be plotted as the flux (e.g., ng/cm^2/hr) on the Y-axis versus time on the X-axis.
- Total cumulative amount (AMT)* permeated into the receptor solution across the study duration
  - The extent of drug permeation should be plotted, as the total cumulative amount of drug permeated (e.g., ng/cm^2) on the Y-axis versus time on the X-axis.

* termed as “AUC” in the draft PSG of Acyclovir Cream

Statistical Analysis

- If $S_{WR} \geq 0.294$, use the scaled average bioequivalence (SABE) approach to determine bioequivalence (BE) for the individual IVPT endpoint(s)
- If $S_{WR} < 0.294$, use the regular average BE (ABE) approach through the two one-sided tests (TOST) procedure to determine BE for the individual IVPT endpoint(s)
- At the completion of the study,
  - If the number of skin replicates are the same for all donors in the test and reference topical product treatment groups in the IVPT study, a statistical analysis using a **balanced design** is recommended.
  - If skin sections or diffusion cells are excluded from the final statistical analysis because of experimental loss/issues, and the resulting data set is unbalanced, a statistical analysis using an **unbalanced design** is recommended.

Additional Updates…

- Separate section about sample analytical method validation with further details
- Handling and Retention of Samples
- Control of study procedures with quality management system
- Submitting the study information in an ANDA
  - The IVRT protocols, SOPs, and reports to be submitted in module 5.3.1.2
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Challenge Question #2

- To support IVPT sensitivity using modulation of dose duration approach, the dose amount should be the same across different dose durations (i.e., low, target, and higher dose duration).

A. True

B. False

Resources to Refer…

- Draft Guidance for Industry: In Vitro Release Test Studies for Topical Drug Products Submitted in ANDAs

- Draft Guidance for Industry: In Vitro Permeation Test Studies for Topical Drug Products Submitted in ANDAs

- The recordings and meeting materials from virtual public workshop hosted by the FDA and the Center for Research on Complex Generics (CRCG) on August 18-20, 2021, In Vitro Release Test (IVRT) and In Vitro Permeation Test (IVPT) Methods: Best Practices and Scientific Considerations for ANDA Submissions. Available at http://www.complexgenerics.org/IVRTIVPT/.

- USP Chapter <1724>: Semisolid Drug Products- Performance Tests

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FDA

Questions?

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