



WHERE THE ART + SCIENCE OF TOPICAL DEVELOPMENT MEET

- From 21 CFR part 320.1
- Definition of Bioavailability and Bioequivalence
- **Bioavailability** means the rate and extent to which an active ingredient is absorbed from a drug product and becomes available at the site of action. For products that are not intended to be absorbed in the blood stream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient becomes available at the site of action.

- **Bioequivalence** means the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.

- For any generic to substitute a brand product, it must have several levels of similarities between the two.
- Pharmaceutical equivalence
 - Where the active ingredients, strength, route and dosage form are the same as the marketed product
- Bioequivalence
 - Where the rate and extent of the active at the site of action are the same
- Therapeutic equivalence
 - Generic dosage form must demonstrate both pharmaceutical and bioequivalence when compared to the marketed product while relying on the marketed product for safety and efficacy.

- Conventional approaches to determine BE between products include:
 - Clinical endpoint BE studies that study clinical response for Test vs. Reference with placebo as control
 - Pharmacodynamic Studies
 - Tissue PK studies
 - Systemic PK BE studies
 - In Vitro BE studies

Regulatory Rationale and Justification to providing Biowaiver

- For some of the complex topicals, the cost of developing a generic form is very high, not allowing some small players to enter the competition
- BE clinical trials are often either not sensitive enough and/or highly variable to differentiate between different formulations and are not conclusive to allow generics to demonstrate equivalence.
- BE trials are sometimes bigger than the original clinical trials requiring lot of testing that can be avoided

IVRT used for Biowaiver

- Allows generic manufactures to use IVRT as a bioequivalence tool to compare their formulations with RLD.
- Allows derisking of clinical trials. By selecting a formulation with the comparable release rate, the outcome of BE clinical study is more accurately predictable.
- Provides strategic advantage and scientific basis for a better generic dosage form.
- While Q1/Q2 criteria can be met by formulation development and/or deformulation, i.e. same excipients in the same ratio as the RLD
- Attaining Q3 criteria requires understanding of microstructure of the dosage form. Properly developed IVRT method can aid in demonstrating the similarities in microstructure of the dosage form.

Q1/Q2/Q3 Concept

- Q1 - Specific components of a dosage form
- Q2 - Specific Ratios of the components in a dosage form
- Q3 - Specific arrangement of components in a dosage form that impact the physico-chemical properties of a dosage form. Also the micro structure of the dosage form can completely determine the success of the dosage form for it's therapeutic equivalence to the RLD.

Examples of properties that can affect micro structure and therefore equivalence:

- pH of a dosage form
- Polymorphic form of the active ingredient
- Particle size and its distribution of the active ingredient and structure forming excipient
- Rheological properties of the formulation
- Release characteristics of the formulation
- The interaction of formulation and skin upon application and the effect of mode of application of the dosage form

- Guidance for Acyclovir Cream
 - New Guidance
 - In Vitro and In Vivo options are required
 - Test formulation must meet Q1/Q2 criteria
 - Test formulation must have similar physico-chemical characteristics as the RLD
 - Test formulation must demonstrate equivalent rate of release by a validated IVRT method compared to RLD
 - Test formulation must be bioequivalent to RLD using an acceptable in vitro permeation test(IVPT).

- **Active ingredient:** Acyclovir
- **Form/Route:** Ointment; Topical
- **Recommended study: 2 Options: *In Vitro* or *In Vivo* Study**
- **I. In Vitro option:**
- To qualify for the in vitro option for this drug product pursuant to 21 CFR 320.24 (b)(6), under which
- “any other approach deemed adequate by FDA to measure bioavailability or establish bioequivalence” may be acceptable for determining the bioavailability or bioequivalence (BE) of a
- drug product, all of the following criteria must be met:
- i. The test and Reference Listed Drug (RLD) formulations are qualitatively and quantitatively
- the same (Q1/Q2).
- ii. Acceptable comparative physicochemical characterization of the test and RLD formulations.
- iii. Acceptable comparative in vitro drug release rate tests of acyclovir from the test and RLD

Guidance is very specific for

- Physico –chemical tests that should be conducted to compare test and RLD
- IVRT method development, validation and comparison of test and RLD
- IVPT method development, validation and protocol for comparing skin permeation rate of test with RLD.

- Comparison of Physico-chemical parameters:
 - Appearance
 - Polymorphic form of acyclovir in dosage form
 - Particle size distribution and crystal habit of acyclovir
 - Rheological properties of the dosage form using apparatus that is appropriate for non-newtonian flow
 - Specific gravity, pH, water activity and other similar tests

- IVRT Comparison:
 - Pivotal comparison to be compatible with chapter <1724>
 - IVRT validation and pivotal study to follow Guidance for Industry “Handling and Retention of BA and BE testing samples and draft guidance for Bioanalytical method validation.
 - Detailed protocol to be provided for blinding. To properly execute, attention must be paid to the packaging of the test and RLD samples
 - During Pivotal study, IVRT cells to be dosed in alternate sequence that is randomly selected

- IVRT Comparison(Continued)
 - IVRT Method validation to include:
 - IVRT apparatus qualification
 - IVRT Membrane qualification
 - IVRT receptor solution and sampling qualification
 - Sampling analytical method including linearity and IVRT method precision, specificity, and reproducibility and range
 - IVRT linearity and range
 - IVRT recovery, mass balance, dose depletion
 - IVRT discrimination, specificity, selectivity and sensitivity
 - IVRT robustness

IVPT Comparison

- Pivotal study is a parallel, single dose, multi replicate per treatment group study that compares cutaneous pharmacokinetics of Test and RLD
- General BE guidelines apply for pivotal study and reference is made to the Guideline for Industry Handling and retention of BA and BE test samples.
- IVPT samples to be dosed in alternating sequence which is randomly selected

- IVPT Comparison(Continued)
 - IVPT method validation to include:
 - IVPT apparatus qualification
 - IVPT skin qualification
 - IVPT receptor solution and sampling qualification
 - IVPT analytical method qualification
 - IVPT pilot study: multi donor
 - IVPT permeation profile and range
 - IVPT precision and reproducibility
 - IVPT recovery, dose depletion and mass balance
 - IVPT discrimination, sensitivity and selectivity
 - IVPT robustness
 - IVPT qualification and control of study procedures

- IVPT inclusion criteria are defined:
 - Skin from normal healthy volunteers, male or female of 18 years or older
 - Consistent source of skin is recommended. Protocol to define the same anatomical region from which the skin from all donors should be used
 - Inclusion criteria to include the storage conditions for storage of skin prior to the test.
 - Protocol to specify the thickness of the skin to be used
 - Inclusion criteria to specify the acceptance criteria for skin based on barrier integrity test.

- Exclusion criteria Defined are:
 - Skin with tattoos, any other abnormality is not to be used
 - Skin with a higher than normal density of hair to be excluded
 - Skin that is either washed, has been shaved with a blade or has been tape stripped should be excluded,
 - Skin from donors with significant levels of Acyclovir or other agents that can affect determination of acyclovir

- Guidance provides detailed, specific instructions for calculation of flux and other cutaneous pharmacokinetic parameters.
- Guidance also provides instructions for the use of SAS statistical analysis to compare flux and other parameters between test and RLD formulations.
- Other control procedures described in IVRT pivotal comparison such as packaging and blinding of test and RLD also apply.
- Guidance also provides specific instructions on Method development aspects for both IVRT and IVPT.

- This level of evolution of guidance documents shows a much greater input and commitment from agency on their attempts to facilitate development of higher quality generic dosage forms.
- **Quality for a Drug Product Means:**
 - The totality of features and characteristics of a product that bear on its ability to satisfy stated or implied needs...(ISO)
 - Good pharmaceutical quality represents an acceptably low risk to achieve desired clinical attributes. ..Dr. Janet Woodcock, FDA, CDER

Taking Your Topical Programs to a Higher Level

THANK YOU

Questions???

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