Practical Considerations for IVRT Studies with Topical Drug Products Submitted in ANDAs

Best Practices for Topical Generic Product Development and ANDA Submission

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Learning Objectives

• Describe considerations for IVRT study design and validation when used as a component of characterization-based bioequivalence (BE) approaches

• Provide clarifications related to IVRT best practices and common questions
IVRT

- IVRT is a performance test to study the arrangement of matter.
- In characterization-based approach, IVRT is considered an in vitro BE study.

Major IVRT Study Phases:

- IVRT method development
- IVRT method validation
- IVRT pivotal study

Image courtesy of PermeGear
IVRT Method Development

• Exploratory in nature

• Report which IVRT studies were done using a validated analytical method

• Sequence of selecting method parameters:
  – Equipment
  – Receptor solution
  – Membrane
  – Others (e.g., product dose amount, sampling times, stirring/agitation rate, etc)
IVRT Method validation
Equipment Qualification

• Empirical measurements along with manufacturer information (e.g., dimensions of the orifice, volume of the receptor compartment) of the diffusion cells.

• The equipment should control the diffusion cell thermoregulation.

• Membrane surface temperature is verified to be stable before dosing (e.g., at 32°C ± 1°C).
Qualification of the Receptor Solution

- Empirical solubility of the drug in the receptor solution: drug solubility exceeds the highest sample concentration in the IVRT, ideally by an order of magnitude

- Stability of the drug in the receptor solution

- Acceptable linearity and precision of the resulting drug release rate in an IVRT ($r^2$ value of $\geq 0.97$)
Membrane Qualification

• Membrane’s effective pore size (e.g., 0.45 µm)

• Membrane inertness 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 IVRT

• Chemical compatibility with the receptor solution

• Acceptable precision and linearity ($r^2$ value of ≥ 0.97)
Receptor Solution Sampling Qualification

• Accuracy and precision of receptor sample collection
• Sampling technique can reliably collect a consistent volume of the sample from the well-mixed volume of the receptor compartment
• Submit manufacturer’s specification for the accuracy and precision of receptor solution sampling
Receptor Solution Sampling

- Sampling frequency
- Number of sampling timepoints
Acceptable Linearity

- 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 $\geq 0.97$ across IVRT study duration.
Duration of the IVRT Study

• IVRT duration (e.g., 4-6 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
Dosing

• Dose amount (pseudo-infinite dose)

• Dosing procedure for a selected apparatus

• Dose application method and its impact on product’s microstructure

• The applied dose should be occluded during the IVRT study.
Dose Depletion (DD)

- DD is expressed as a percentage of the amount of drug in the applied dose. The average DD should be reported.

- Steady state release kinetics is assumed when DD is < 30%.

- For some topical products, steady state release kinetics may continue to be observed at higher percentage DD.

- A DD of >30% may be acceptable if the release rate remains suitably linear.
Precision and Reproducibility

• The intra-run and inter-run precision and reproducibility may be compared for the release rate calculated for each diffusion cell.

• A minimum intra-run and inter-run %CV ≤ 15% is recommended.

• A minimum of three independent precision and reproducibility runs is recommended.
IVRT Discrimination: Sensitivity

- Comparing the release rate from the nominal reference strength formulation with that from two comparable formulations: a higher strength (150%) and a lower strength (50%)

- Allowance may be made if a higher strength of test product is not feasible to formulate without substantial reformulation.
IVRT Discrimination

• Selectivity
  – Establish **non-equivalent** release rate between Test (T)/Reference standard (RS) product and altered strengths (**50% and 150% nominal strength**).
  – 6 cells of nominal strength of the RS (100%) compared with 6 cells of altered strength (50% or 150%). All 12 cells being compared should have been run in parallel on the same day.

• Supplemental selectivity
  – Using products at the **same nominal strength**, but altered composition and/or manufacturing process
  – The altered formulation may include changes in inactive ingredients, changes in inactive ingredient concentration(s), changes in the manufacturing processes, **or combinations thereof**. However, not all variations in a formulation will necessarily produce a difference in the release rate.
IVRT Discrimination: Specificity

• E.g., the IVRT method is proportionally linear in its response to differences in release rates

• A minimum $r^2$ value $\geq 0.95$
IVRT Robustness

Robustness testing encompasses

• Temperature variations (i.e., -1°C and +1°C relative to 32°C ± 1°C)
• Dose volume variations (e.g., +10% and -10% in the dose volume)
• Receptor solution variations (e.g., change in composition and/or pH)
• Mixing rate variation (i.e., differences in stirring speed, or without stirring)
Sample Analytical Method Validation

• IVRT validation and pivotal studies should use a validated analytical method for the receptor solution samples.

• Separate and specific reports should be submitted for the sample analysis method validation and for the IVRT method validation.

• The validation should be performed using chromatography software with audit trails and should include a multi-point calibration curve (not a single point).
IVRT Pivotal Study

- A single batch each of a designated RS and T product are evaluated
- Blinding, dosing (alternating pattern ABABAB or BABABA)
- The release rates for T and R products are compared utilizing a Wilcoxon Rank Sum/Mann-Whitney rank test
References

• 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>
• Other relevant FDA guidances
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Questions?

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