Considerations for In Vitro Release Test (IVRT) Data and Information Submitted in ANDAs

Tian Ma, Ph.D.
Office of Bioequivalence (OB)
Office of Generic Drugs
CDER | U.S. FDA

IVRT IVPT Workshop – August 20, 2021

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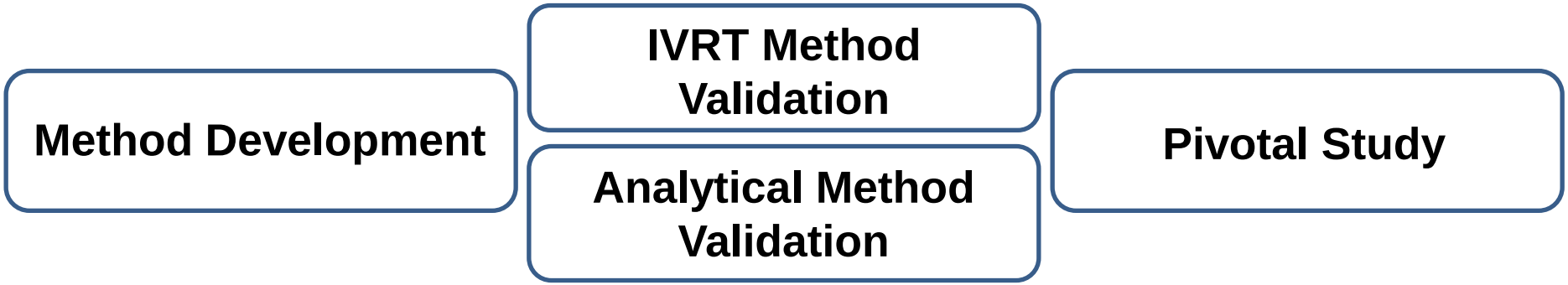
Outline

- Background information for in vitro release testing (IVRT) submissions
- Considerations for a high-quality submission for IVRT
  - General considerations
    - What to submit
    - In which module to submit
  - Submission-related common deficiencies
    - General
    - Method development
    - Method validation
      - IVRT method validation
      - Analytical method validation
    - Pivotal study
- Summary

IVRT Submissions

- Increasing trend of topical product submissions containing IVRT in recent years.
- Deficiencies related to IVRT contribute to bioequivalence (BE) deficiencies being classified as major.
- Many IVRT deficiencies are related to incomplete submissions.

General Considerations Regarding IVRT Submissions



- Separate reports for method development, IVRT method validation, analytical method validation, and pivotal study
- Step-by-step details of test procedures enable reconstruction of how the studies were conducted.
- All necessary data and calculations enable verification of the results.

What and In Which Module to Submit

- Module 2.7.1
  - BE summary tables
- Module 5.3.1
  - Study reports
    - Method development
    - IVRT method validation
    - Analytical method validation
    - Pivotal study
  - Study protocols and standard operating procedures (SOPs) that were effective at the time of study
  - Raw data
    - For all original, reinjected, repeated and reintegrated analytical runs
  - Chromatograms
  - Individual concentration data that was used for calculating the slopes (release rate) for the test and reference formulations in SAS .xpt format

Depending on the data submitted, additional information may be requested during ANDA assessment.

Submission-Related Common Deficiencies – General

- IVRT Method Development
- IVRT Method Validation
- Analytical Method Validation
- Pivotal Study

Missing Study Details

- Apparatus (name and specifications)
- Dose amount
- Dosing application
  - How the dose was applied to ensure full coverage of the edges of the dosing area without air bubbles.
  - Whether or not the sample was occluded
    - Per USP <1724>, for a vertical diffusion cell the dosage chamber is recommended to be occluded.
- Membrane
  - Type and pore size
- Receptor solution
  - Composition, volume and temperature
- Stirring/agitation rate
- Sampling
  - Schedule, duration, and volume

Missing Information Regarding Dosing Syringe

- If a dosing syringe is used to dispense drug product onto membrane surface, the following is often missing:
  - Syringe information, e.g.,
    - Manufacturer/brand name
    - Size
    - Picture, if available
  - Explanation regarding how sheer forces were minimized and consistently controlled (e.g., between different operators, and between test and reference products) during dose administration

Other Common Deficiencies

- Missing study dates
  - IVRT experiment dates
  - Sample analysis dates
- Missing study site name and address
  - In vitro BE site
  - Analytical site
- Missing identity of batches used in each study, e.g.,
  - Batch numbers
  - Whether test or reference product was used.
    - If test product was used, whether it was a scale-up batch, exhibit batch, or altered test product.

Other Common Deficiencies (cont'd)

- Discrepancies within the submission, e.g.,
  - Information not consistent between summary tables and study report
- Incomplete submission for studies involving multiple replicates
  - Number of replicates unclear
  - Only summary statistics are provided but not individual data for each replicate tested

Submission-Related Common Deficiencies – IVRT Method Development

- Method parameters, e.g.,
  - IVRT apparatus
  - Product dose amount
  - Sampling times
  - Stirring/agitation rate
- Membrane
- Receptor solution

Missing Rationale for Selecting IVRT Method Parameters, Membrane, and Receptor Solution

- Rationale is not provided for selecting IVRT apparatus, dose amount, sampling times, stirring/agitation rate, membrane, and receptor solution that were used in method development studies.
- Data is not provided to support the selection.

Submission-Related Common Deficiencies – Common to IVRT Method Validation and Pivotal Study

Missing Apparatus Qualification Information

- Diffusion area of the orifice in which the membrane is mounted
- Volume of the receptor solution compartment in each diffusion cell

Provide both empirical measurements made by the laboratory as well as manufacturer's information, if available

- Control of the stirring rate or agitation
- Control of temperature at the IVRT membrane and receptor solution for the duration of the IVRT study
  - Preferably hourly measurements

Missing Ambient Laboratory Temperature and Humidity Data

- Temperature and relative humidity logs that cover the entire duration of the method validation and pivotal studies to demonstrate environmental control

Missing Detailed IVRT Procedure

- Detailed procedures describing how the membrane was mounted on each diffusion cell
- Whether the membrane was pre-soaked, and for how long
- When the receptor solution was added to the diffusion cell
- How air bubbles were removed
- The starting/stopping of the stirrer around sampling times

Missing Detailed IVRT Procedure (cont'd)

- How dosing application and start times were staggered and synchronized with the sampling time for each successive diffusion cell to ensure the precision of the sampling intervals for each diffusion cell.
- Whether the receptor solution was warmed to a specific temperature prior to replacement of the withdrawn aliquot volume for each cell.

Other Common Deficiencies

- Missing rationale for any deviations from USP <1724> Semisolid Drug Products – Performance Tests with supporting data

Submission-Related Common Deficiencies - IVRT Method Validation

- Apparatus qualification
- Membrane qualification
- Receptor solution qualification
- Receptor solution sampling qualification
- Receptor solution sample analytical method validation
- Environmental control
- Linearity and range
- Precision and reproducibility
- Recovery, mass balance and dose depletion
- Sensitivity, specificity and selectivity
- Robustness

Receptor Solution Deficiencies

- Missing details regarding how the solubility testing was conducted, e.g.,
  - The amount of drug added
  - Volume of receptor solution
  - Solubilization and analytical procedures
  - Solubility testing duration
  - Active pharmaceutical ingredient (API) lot number

Receptor Solution Sampling Qualification Deficiencies

- Accuracy and precision data of receptor solution sample collection **at each time point** is not provided
  - Often missing or incomplete in ANDA submissions
  - Purpose of receptor solution sampling qualification:
    - To illustrate that the sample technique can reliably collect a consistent volume of the sample from the well-mixed volume of the receptor compartment **at each sampling event**, and that no artifacts are likely to be created by the sampling technique.

Linearity and Robustness Deficiencies

- Linearity study
  - Missing validation data calculating the linearity of drug release rate (slope) across the range of selected sampling times and linearity comparison within and across all runs
- Robustness study
  - Missing robustness study data, e.g.,
    - Temperature variations
    - Dose volume variations
    - Receptor solution variations
    - Mixing rate variations

Sensitivity, Specificity and Selectivity Deficiencies

- Missing detailed product information for batches (especially modified test product) used in the sensitivity, specificity and selectivity studies, including but not limited to:
  - Batch formula
  - Manufacturing date
  - Manufacturing process
  - Batch size
  - Potency, if available
  - Content uniformity, if available
- No information regarding whether different formulations in the sensitivity study were evaluated in parallel on the same day

Supplemental Selectivity Deficiencies

- Study procedures and study data, and detailed product information
  - Often missing or incomplete in ANDA submissions
  - The demonstration of IVRT supplemental selectivity is **distinct from** IVRT selectivity.
    - IVRT selectivity validates the ability of the IVRT method to discriminate differences in release rates under conditions when the release rate may be expected to differ in a predictable manner (i.e., when there are **different concentrations** of drug in the formulation).
    - IVRT supplemental selectivity validates that the IVRT method can detect differences in the release rate that are associated with **aspects of the formulation for products at a given strength**.

Precision and Reproducibility Deficiencies

- Consider providing a minimum of three independent precision and reproducibility runs.
  - Runs for precision and reproducibility evaluation may be organized to facilitate a simultaneous evaluation of intra/inter-instrumentation and/or intra/inter-operator precision and reproducibility.
- Missing inter-operator/instrument precision and reproducibility data when multiple operator/instrument were used

Submission-Related Common Deficiencies - Analytical Method Validation

Sample Processing Procedure and Sample Storage Deficiencies

- No information regarding if and how the samples were processed prior to HPLC analysis, e.g.,
  - By dilution of samples
    - Detailed dilution procedure (e.g., dilution factor, dilution medium, timing of dilution)
    - Provide dilution integrity data
- Missing information for the maximum storage period and storage condition (i.e., temperature) for the IVRT samples
  - To confirm the adequacy of stability data

Stability Deficiencies

- Missing detailed study procedure, e.g.,
  - Temperature
    - Whether evaluated under the highest relevant temperature in the receptor solution for the duration of the IVRT
  - Concentrations

Submission-Related Common Deficiencies – Pivotal Study

Missing Summary Information for Calibration Curve Standard and Quality Control Data for IVRT Analysis

- For calibration curve standards and quality controls (QCs)
  - Accuracy (% actual)
  - Precision (% CV), if applicable
- Linearity (range of R^2 values)
- Linearity range
- Sensitivity/lower limit of quantitation (LLOQ) concentration

Missing Information Regarding Rejection, Repeat Analysis, Reinjection and/or Reintegration of Samples/Runs

- Did not specify if any samples and/or runs were rejected, repeat analyzed, reinjected, and/or reintegrated
  - Provide summary table of the original value, repeated/reinjection/reintegration value and the reported value
- Missing detailed reason for sample/run rejection, repeat analysis, reinjection, and/or reintegration, if applicable, supported by pre-established criteria
- Missing SOPs that were effective at the time of study, including but not limited to
  - Analytical batch acceptance criteria
  - Identification and reporting criteria for sample repeat analysis, reinjection and reintegration

Summary

- The number of ANDA submissions containing IVRT has increased in recent years.
- The common deficiencies described today are often classified as major.
- Many of these deficiencies can be avoided.
  - Provide detailed data and rationale to support the selection of IVRT method parameters, membrane, and receptor solution.
  - Provide complete and detailed information of the study procedure and calculations.

Acknowledgement

- Amanda Jones, Ph.D. (OGD/OB)
- Rong Wang, Ph.D., Pharm.D. (OGD/OB)
- Utpal Munshi, Ph.D. (OGD/OB)
- Archana Manerikar, M.S., Pharm.D. (OGD/OB)
- Hiren Patel, Ph.D. (OGD/OB)
- Josephine Aimiuwu, Ph.D. (OGD/OB)
- Usha Katragadda, Ph.D. (OGD/OB)
- Nilufer Tampal, Ph.D. (OGD/OB)
- Bing V. Li, Ph.D. (OGD/OB)
- Priyanka Ghosh, Ph.D. (OGD/ORS)
- Sameersingh Raney, Ph.D. (OGD/ORS)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