

Submission of In Vitro Release Test (IVRT) Data and Information for Topical Drug Products under ANDAs

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Learning Objectives

- Identify key components that constitute a high quality IVRT submission
- Describe the level of detail expected for each key component
- Clarify location within the electronic common technical document (eCTD) submission

Outline

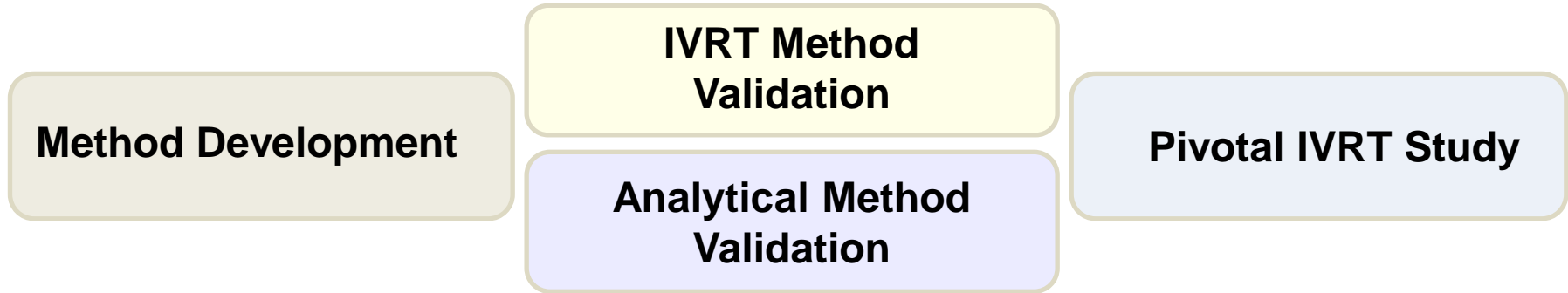
- Introduction on in vitro release test (IVRT)
- General considerations for a high-quality submission
 - What to submit
 - In which module to submit
 - Submission-related common deficiencies
- Summary

Reference: Draft Guidance for Industry, *In Vitro Release Test Studies for Topical Drug Products Submitted in ANDAs* (October 2022)

In Vitro Release Test (IVRT)

- In a characterization-based approach, IVRT is utilized to assess the rate of drug release from a proposed generic (test) topical product, comparing to its reference standard for the purpose of supporting a demonstration of bioequivalence (BE).
- Study Phases:
 - IVRT method development
 - IVRT method validation
 - Pivotal IVRT study

Considerations Regarding IVRT Submissions



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

What and Where to Submit

- Module 2.7.1
 - BE summary tables
- Module 5.3.1
 - Module 5.3.1.2
 - IVRT method development
 - IVRT method validation
 - Pivotal IVRT study
 - Module 5.3.1.4
 - Analytical method validation
 - Sample analysis for pivotal IVRT 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
 - Individual concentration data (SAS.xpt) that was used in the calculation of release rate
 - 20% Chromatograms

IVRT Method Development



- **Module 2.7.1 Summary Table**

- Report No., study title, test site
- Report location in submission
- Apparatus specifications
- Dose amount
- Membrane (type, pore size)
- Receptor solution composition
- Stirring rate
- Sampling (volume and time points)
- Linearity and precision (release rate)

- **Module 5.3.1.2 Study Report and Raw Data**

A detailed IVRT method development report and all the supporting documents

- Rationale for study design (selection of apparatus, membrane, dose amount, receptor medium, sampling time, etc.)
- Detailed procedure for dose application (tool used, air bubble removal, un/occluded, staggered or synchronized, etc.)
- Product information (if test product is used, submit component and composition table, batch size, manufacture date, etc.)

IVRT Method Validation



• Module 2.7.1 Summary Table

- Report No., study title, test site
- Report location in submission
- SOP No. and location
- Diffusion cell specifications (type, orifice area, volume, No. of cells)
- Dose amount
- Membrane (type, pore size, surface temperature)
- Receptor solution composition
- Stirring rate
- Sampling technique (manual or automated)
- Sampling volume and time points
- Temperature, humidity range

• Module 5.3.1.2 Study Report, Protocol, SOPs and Raw Data

A detailed IVRT method validation report contains all the parameters as recommended in IVRT Guidance

- Apparatus qualification data (orifice area, volume of receptor chamber, control of stirring rate, membrane surface temperature)
- Receptor solution sampling qualification
- Detailed procedure for dose application (membrane equilibration, tool used, air bubble removal, staggered or synchronized, receptor solution pre-warmed or not, etc.)
- Test product and altered formulation (component and composition table, batch size, manufacture process information, etc.)
- Individual concentration data, summary statistics and release profiles
- Environmental control (room temperature and relative humidity logs)

Analytical Method Validation



- **Module 2.7.1 Summary Table**

- Report No., study title, test site
- Report location in submission
- Analyte and internal standard (if applicable)
- Brief description of method
- LLOQ (lower limit of quantitation) and calibration standards
- Quality control (QC) samples
- Precision and accuracy
- Stability (stock, bench-top, processed sample, long-term storage, etc.)
- Dilution integrity (if applicable)
- Recovery (if applicable)
- Selectivity and specificity

- **Module 5.3.1.4 Study Report, Protocol, SOPs and Raw Data**

A detailed analytical method validation report and all the supporting documents (e.g., protocol, SOPs, raw data)

- Validation study dates
- Study report and protocol
- Raw numerical data
- Representative chromatograms
- Stability under assay condition

Pivotal IVRT Study

- **Module 2.7.1 Summary Table**

- Report No., study title, test site
- Report location in submission
- Diffusion cell specifications (type, orifice area)
- Dose amount
- Membrane (type, pore size, surface temperature)
- Receptor solution composition
- Stirring rate
- Sampling (volume and time points, manual or automated)
- Statistical summary of IVRT results

- **Module 5.3.1 Study Report, Protocol, SOPs and Raw Data**

A detailed pivotal study report and all the supporting documents (e.g., protocol, SOPs, raw data)

- Test and reference product information
- Sample analysis
 - Summary table for calibration standards and QC samples
 - Rejected, re-injected, repeat analysis
 - Chromatograms and raw data printout
- Individual concentration data and summary statistics
- Environmental control (room temperature and relative humidity logs)

Summary

- It is common that missing or incomplete information is identified by the Agency for method development, method validation and pivotal study in the original submission
- Many of the common deficiencies described today can be avoided.
- Submit all necessary information/data that enable
 - the reconstruction of study process
 - the verification of results

Challenge Question

- What are the key components of an IVRT study submission?
 - A. IVRT method development
 - B. IVRT method validation
 - C. analytical method validation
 - D. pivotal IVRT study
 - E. All of the above

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