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

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Disclaimer: This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

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

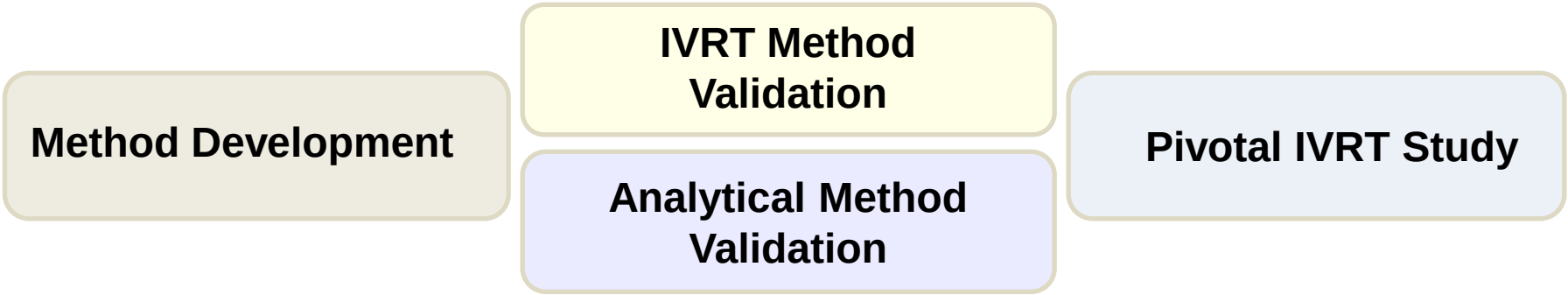
- Introduction on in vitro release test (IVRT)
- General considerations for a high-quality submission
  - What to submit
  - In which module to submit
  - Submission-related common deficiencies
- Summary

Reference: Draft Guidance for Industry, *In Vitro Release Test Studies for Topical Drug Products Submitted in ANDAs (October 2022)*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