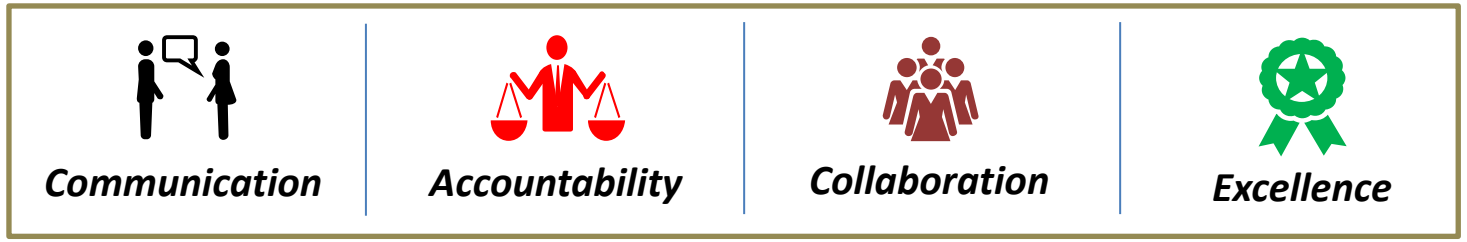
QMS: Study Integrity Considerations



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In Vitro Release Test (IVRT) and In Vitro Permeation Test (IVPT) Methods
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Disclaimer

The opinions and information in this presentation are those of the author, and do not necessarily represent the views and/or policies of the U.S. Food and Drug Administration.

Outline

- Over-arching expectations for IVPT-IVRT studies
- Specifics for IVPT/IVRT Studies
- Considerations for review/assessment team
- Reserve sample requirements

Over-arching expectations Continued

- Good documentation practices, e.g., contemporaneous recording of procedures observations and deviations
- Maintaining suitable records to allow for reconstruction of the study
- Use of validated methods and audit trails for sample analysis
- Study personnel training records and qualifications

Over-arching expectations Continued

- Drug accountability: records for receipt, storage, and use for test and reference products
- SOPs and study protocol; deviations
- SOPs with objective criteria for repeat testing
- Samples collected at time points specified in the protocol

Over-arching expectations Continued

- Stability data from method validation support sample handling conditions during study
- Testing order as recommended in the relevant guidance
- Multi-station diffusion cell system: test and reference samples tested in each run

Over-arching expectations Continued

- Ensure drug product is loaded in donor chamber after the membrane/skin section is equilibrated with receptor solution
- Qualification and calibration of instruments and computerized systems
- If repeat testing is not scientifically justifiable, original results should be reported

IVPT Studies

- Test and reference tested on skin from the same set of donors
- Balanced design
- Apparatus, methodologies, and study conditions appropriately qualified, validated, and verified
- Excised human skin is recommended

IVPT Studies

- Inclusion of non-dosed control from each skin donor
- A pre-dose “zero” sample collected from each diffusion cell is recommended
- Experimental conditions, i.e., skin type and anatomical site, receptor solution, study duration, dose duration, sampling interval,…*etc*. are the same for the pivotal study as study validation

IVRT Studies

- The experimental conditions, i.e., membrane, receptor solution, study duration, dose duration, sampling interval,…*etc*. are the same for the pivotal study as validation study
- Assessment of adsorption/binding of analyte to IVRT membrane during method validation-initial assessment during method development

IVRT Studies

- Chemical compatibility of the membrane with the receptor solution
- Dose depletion calculations conducted as recommended in the relevant guidance

Review/Assessment Considerations

- Appropriate location to submit reports, i.e., Module 5.3.1
- Separate reports for method development, validation, and pivotal studies
- Separate reports for analytical method validation in addition to SOPs and study protocols
- Maintenance and control of the study facility environment and systems

Review/Assessment Considerations Continued

- Experiment dates and information related to Principal Investigator
- Raw data, chromatograms
- Study management and personnel responsibilities

Review/Assessment Considerations Continued

- Quality control (QC) and QC personnel responsibilities
- Quality assurance (QA) and QA personnel responsibilities
- Archival of study records

Reserve Samples: References

- 21CFR* 320.38
- 21CFR 320.63
- Guidance for Industry: Handling and Retention of BA and BE Testing Samples (May 2004, OGD)
- Guidance for Industry: Compliance Policy for the Quantity of Bioavailability and Bioequivalence Samples Retained Under 21 CFR 320.38(c) (August 2020)

*CFR: Code of Federal Regulations

RESERVE SAMPLES-In vitro BE

21 CFR 320.63

The applicant of an abbreviated application or a supplemental application…, or, if bioequivalence testing was performed under contract, the contract research organization shall retain reserve samples of any test article and reference standard used in conducting an in vivo or in vitro bioequivalence study required for approval of the abbreviated application or supplemental application. The applicant or contract research organization shall retain the reserve samples in accordance with, and for the period specified in, 320.38 and shall release the reserve samples to FDA upon request in accordance with 320.38.

Reserve Samples

- Most common deficiency (observation) for in vitro BE studies
  - Reserve samples not retained
  - Improper handling, storage
  - Reserve samples retained under 21 CFR 211 (CGMP* regulations, not bioequivalence)
- Often results in rejection of study
- Important point to consider: use of data determines which regulations apply

*CGMP: Current good manufacturing practices

Reserve Samples
General recommendations

- Reserve samples (test and reference) should be retained from each shipment
- Randomly selected prior to initiation of study
- Adequate quantity*
- Stored in a segregated area with access limited to authorized personnel
- Stored in original containers
- Stored under conditions consistent with product labeling

*Guidance for Industry: Compliance Policy for the Quantity of Bioavailability and Bioequivalence Samples Retained Under 21 CFR 320.38(c): August 2020

Summary

- Important considerations for pivotal IVPT and IVRT studies, mostly in support of BE* determination
- General recommendations from inspectional as well as review perspectives
- Highlighted the significance of reserve sample retention, and relevant regulations and guidances

*BE: Bioequivalence

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*OSIS: Office of Study Integrity and Surveillance

**OGD: Office of Generic Drugs