



Considerations for In Vitro Permeation Test (IVPT) Data and Information Submitted in ANDAs

In Vitro Release Test (IVRT) and IVPT Methods | Best Practices and Scientific Considerations for ANDA Submissions
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Outline



- Goals
- How to organize the information that you submit
 - Modules 2.7, 5.3.1.2 and 5.3.1.4
- What to submit
 - General considerations
 - Specific considerations
 - IVPT Method Development (MD)
 - IVPT Method Validation (MV) [including pilot]
 - IVPT pivotal study
 - Analytical (ANA) MV and sample analyses
- Summary

Goals



- To discuss considerations pertaining to IVPT information and data submitted in ANDAs
 - Organization within the electronic Common Technical Document (eCTD) submission
 - Information and data
- To help generic applicants enhance the quality of the IVPT submissions
- To facilitate reduction in the number of deficiency comments and ANDA review cycles



How to organize the information that you submit



Organization by Modules

- Module 2.7
 - Summary tables
- Module 5.3.1.2
 - Pertaining to all IVPT studies
 - Potential sub-folders:
 - [IVPT Method Development](#)
 - [IVPT Method Validation \(including pilot\)](#)
 - [IVPT Pivotal Study](#)
- Module 5.3.1.4
 - Pertaining to ANA MV and sample analysis for IVPT studies
 - Potential sub-folders:
 - [Analytical Method Validation for IVPT Samples](#)
 - [IVPT Sample Analyses](#) (sub-folders for each IVPT study, as applicable)

What to Submit

General Considerations

All IVPT Studies

- Detailed, well-organized and separate study reports:
 - IVPT studies: MD, MV (including pilot) and pivotal
 - Clearly segregate and separately identify experiments and results that were part of the MD as compared to the MV stage
 - ANA studies: ANA MV
 - Sample analysis: pertaining to MV (including pilot) and pivotal studies
- Standard documents [e.g., protocols and Standard Operating Procedures (SOPs)/Standard Test Procedures (STPs)]
 - i. Relevant to the IVPT method as well as study conduct (at each stage)
 - ii. Relevant to the ANA method and IVPT sample analyses

All IVPT Studies (cont'd)

- Standard documents (cont'd)

- For each standard document:

- Document #

- Document title

- Brief description

- Effective date

- Validity period

- (as applicable)

- Evidence of adequate control of study procedures and method parameters, e.g.:

- **Skin:** Preparation of skin sections, mounting on diffusion cells, skin storage conditions, and measurements of skin thickness and barrier integrity

- **Sampling:** Sampling time, sampling technique, duration of sampling and replacement of receptor solution, sample volume or flow rate, and sample handling and storage

All IVPT Studies (cont'd)



- Evidence of adequate control of study procedures and method parameters, e.g. (cont'd):
 - **Dosing:** Area of dose application, applied dose amount, dosing technique, and dose duration
 - **Measurement of pre-dose concentrations:** To help identify potential contamination associated with each skin section and/or each diffusion cell
 - **Use of control cells:** For periodic monitoring/reporting of temperature control at skin surface and receptor solution (e.g., using a calibrated infrared thermometer) over the study duration and to ensure that drug concentrations monitored in the receptor solution are associated with the dose applied and not drug contamination in the skin

All IVPT Studies (cont'd)



- Details of all product lots used in IVPT studies[§], e.g.:

- Batch/lot #

- Batch formula

- Batch size

- Product strength

- Potency (if available)

- Content uniformity (if available)

- Manufacturing date

- Description: altered manufacturing processes (if applicable)

- For altered formulations: details and rationale of the alteration

- Pertaining to skin sections used in IVPT studies[§], e.g.:

- i. Details of skin sections

- Donor identification # (ID)

- Supplier

- Anatomical site (skin collection)

- Donor (age, race and sex)

- Skin thickness (individual values, mean and % CV)

- Skin integrity test results (individual values, mean and % CV)

[§] Separate set of details for each IVPT study is preferred

All IVPT Studies (cont'd)



- Details pertaining to skin sections used in IVPT studies, e.g. (cont'd):
 - ii. Details of handling for each skin section (as applicable):

- Conditions of the receipt and subsequent storage prior to retrieval of skin
- Donor sample receipt from vendor
- Retrieval of skin from deep freezer (specify temperature)
- Restorage of skin sections in deep freezer
- # of freeze thaw cycles

All IVPT Studies (cont'd)



- Consider providing a detailed discussion of experimental observations that may have the potential to influence the interpretation of the study results, as well as of any protocol or SOP deviations.
- Submission of chronological stepwise procedural details, along with data and calculations help to reconstruct how the studies were conducted and verify the reported results.

What to Submit

Specific Considerations

IVPT Method Development (MD)

IVPT MD

- In addition to a detailed, and well-organized MD report, consider providing the following summary information[§], e.g.:

- Study duration
- Sampling time points (minimum of 8 non-zero time points)
- Sampling volume
- Receptor solution (molarity, and pH)

- Study #
- Study title
- Study dates
- Analytical dates
- Report #
- Report location

- Skin source
- Skin anatomical site
- Skin thickness
- Skin integrity test type
- Skin integrity test instrument
- Temperature at skin surface

[§] Separate table for each IVPT MD study is preferred

IVPT MD (cont'd)

- Summary information, e.g. (cont'd):

- Range, mean values, and % CV for (i) J_{max} and (ii) AMT
- (i) Mean profiles and (ii) tables containing mean values, Standard Deviation (SD), and % CV for:
 - Flux
 - Cumulative amount of drug permeated into the receptor solution at each sampling time point

- Diffusion apparatus evaluated
- # of donors and replicates per donor
- Stirring/flow rate

- Dose amount (unoccluded)
- Dose application method
- Dose duration

For the final IVPT method:

- Drug solubility in receptor solution, and skin integrity test acceptance criteria

J_{max} : maximum rate of drug permeation over the study duration

AMT: total cumulative amount of drug permeated into the receptor solution over the study duration

IVPT MD (cont'd)



- Detailed, well-organized documentation of the systematic efforts made to optimize the IVPT method:
 - Include details of each MD experiment corresponding to respective summary information (per above, as applicable)
 - Indicate the specific method parameters and experimental conditions / controls relevant to each set of data
 - For each IVPT run, specify which sets of diffusion cells (identified by unique cell IDs) were run in parallel
- In summary, all submitted information in the MD submission should assist in the understanding of
 - Why specific IVPT method parameters and procedures were utilized (including conventional as well as alternative methods, if any)
 - Whether the resulting IVPT method is suitably sensitive and reproducible



IVPT MV (Including Pilot) and Pivotal Studies

IVPT MV (Including Pilot) and Pivotal Studies



- In addition to detailed, and well-organized MV (including pilot) and pivotal study reports, summary information (separate table for each study) may be useful, such as, e.g.:

- Study #
- Study title
- Study objective
- Study dates
- Analytical dates
- Report #
- Report location
- Testing and analytical sites (name and address)

- Sampling time points (minimum of 8 non-zero time points)
- Sampling volume and study duration
- Receptor solution (molarity, and pH)
- Receptor solution sampling procedure
- Drug solubility in receptor solution
- Drug stability in receptor solution (exposed to underside of skin)**
- Anti-microbial agent and its concentration in receptor solution

**At the highest relevant temperature in receptor solution for the duration of study or for the longest interval between sampling time points for methods in which the entire receptor solution is replaced at each sampling time point.

IVPT MV (Including Pilot) and Pivotal Studies (cont'd)



- Summary information (cont'd), e.g.:

- Skin source
- Skin anatomical site
- Skin thickness
- Skin integrity test type
- Skin integrity test instrument
- Skin integrity test acceptance criteria
- Temperature at skin surface[@]

- Dose amount (unoccluded)
- Dose application method
- Dose duration

- Diffusion cell type
- Diffusion cell volume
- Diffusional area of orifice
- # of diffusion cells used
- # completed [# of donors and replicates/donor]
- Stirring/flow rate
- Environmental control (Temperature and humidity range)
- Sample storage duration and temperature^{^^} in receptor solution

- Randomization (for pilot and pivotal studies)

[@] Temperature maintained during MV (including pilot) and pivotal studies

^{^^} Storage stability should cover the duration from the first day of sample collection to the last day of analysis.

IVPT MV (Including Pilot) and Pivotal Studies (cont'd)



- Consider providing the following summary details for the test, reference, and the third product[#] as evaluated in the pilot study:
 - Intra- and Inter- donor values of mean and %CV for (i) Jmax and (ii) AMT
- For all IVPT sensitivity and selectivity studies, consider providing the following:
 - Complete flux profiles in tabular and figure formats
- Consider providing standard documents (e.g., protocols, and SOP/STPs) with coherent and chronological details of each IVPT study procedure along with how it would be controlled, and that clearly specify how evidence of such control would be monitored, recorded and reported.

[#]Product/formulation that is known or designed to be different from the reference product.

IVPT MV (Including Pilot) and Pivotal Studies (cont'd)



- IVPT method parameters (including the skin source, anatomical site and preparation) along with study conduct and control procedures, as well as any relevant acceptance criteria, that are consistent across the IVPT MV (including pilot) and pivotal studies
- All relevant method parameters and experimental conditions/controls that correspond with each set of IVPT results are clearly and consistently identified
- Adequate demonstration of consistent study procedure and method parameter control over the IVPT study duration. (See some examples on slide # 10.)

IVPT MV (Including Pilot) and Pivotal Studies (cont'd)



- Relevant documents that clearly indicate if the MV (including pilot) and pivotal study results were obtained using a validated ANA method
- For each diffusion cell used in the MV (including pilot) and pivotal studies
 - Details of diffusional area of the donor and receptor compartment orifices, and volume of receptor solution compartment in tabular format
 - Based on empirical measurements and manufacturer provided data (if available)
 - Each diffusion cell identified with a unique cell ID

IVPT MV (Including Pilot) and Pivotal Studies (cont'd)



- IVPT run summary with details relevant to each IVPT run such as:

- Date of IVPT run
- Diffusion cells in each run in parallel (identified by unique cell IDs)
- # of the corresponding analytical run

- Dosed and control cells (identified by unique cell IDs)
- Treatment/formulation dosed (for each dosed cell)

- Spreadsheet(s) containing complete concentration data with Jmax and AMT calculations (as applicable) such that:
 - Experiments to which each set of data belongs is clearly indicated
 - Cells are identified with unique cell IDs



IVPT Pilot and Pivotal Studies

IVPT Pilot and Pivotal Studies

- Complete SAS datasets and data definition files with units for the pilot and pivotal studies.
 - Concentration datasets should include details, e.g.:

- Treatment type
- Donor ID
- Sequence (1=ABAB[^] ... or 2=BABA ...)
- Replicate #
- Receptor volume
- Individual diffusion cell ID

- Dosed area of cell
- Actual dose amount applied
- Barrier integrity test value
- Thickness of skin section
- Randomization code

- Treatment/formulation group
- Actual sampling time points
- Receptor sample concentrations (corrected for dilution)
- Sampling type (aliquot or full replacement)
- Aliquot volume (if applicable)

[^]A and B = test and reference treatments, respectively

IVPT Pilot and Pivotal Studies (cont'd)



- Complete SAS datasets (cont'd):
 - PK datasets should include details, e.g.:

- Treatment type
- Donor ID
- Replicate #

- Treatment/formulation group
- Sequence (1=ABAB ... or 2=BABA ...)
- Individual diffusion cell ID

- Randomization code
- Jmax
- AMT

- Details of randomization, blinding, and unblinding procedures used in the IVPT pilot and pivotal studies

Analytical Method Validation (ANA MV)

ANA MV

- A suitable ANA method that includes a multi-point (6–8 concentration) Calibration Curve (CC) with suitable Quality Control samples (QCs) that is validated
- In addition to the detailed ANA MV report, consider providing the following summary information (for each analyte):
 - Data elements from Bioequivalence (BE) summary table #4[%] (as applicable) along with, e.g.:

- Report location
- Internal standard (ISTD) [if applicable]
- Recovery of ISTD (if applicable)
- Recovery of analyte

- Working solution stability
- Dilution integrity (if applicable)
- Experimental/in-process stability at the highest relevant temperature (specify) in receptor solution

ANA MV (cont'd)

- Summary information (for each analyte), e.g. (cont'd):
 - Brief descriptions for (i) sample preparation and analytical methods, and (ii) CC and QC preparation method(s)
 - Selectivity:
 - Indicate whether no interfering peaks were noted in blank matrix (exposed to underside of skin) for IVPT receptor solution in presence of antimicrobial agents (if applicable)
 - If peaks are noted, please comment
- *Reminder:* Validation of the ANA (e.g., HPLC/MS or UPLC/MS) method and validation of the IVPT method are separate, resulting in separate reports and standard documents
 - Details of each ANA MV experiment corresponding to the respective summary information (per above, as applicable)

Sample Analysis for IVPT Studies [MV (Including Pilot) and Pivotal]

IVPT Sample Analysis

- Summary information (CC/QC Data):
 - Provide per BE summary table #14% (as applicable)
 - Separate tabular details should be provided for IVPT MV (including pilot) and pivotal studies.
 - For precision and accuracy calculation, include all IVPT runs relevant to IVPT MV (including pilot) and pivotal studies
- It is important that CC and QC concentrations are adequately representative of the range of concentrations observed in the IVPT pilot and pivotal studies.
- It is generally recommended that all samples collected from the same donor should be analyzed in the same analytical run.

IVPT Sample Analysis

- 100% numerical raw data (all original, reinjected, repeated, and reintegrated analytical runs), along with 20% serially-selected representative chromatograms
- For any samples and/or runs that were rejected, repeat analyzed, reinjected and/or reintegrated, consider providing:
 - A summary of the original value, repeated/reinjection/reintegration value and the reported value
 - The detailed reason for sample/run rejection, repeat analysis, reinjection and/or reintegration, if applicable
 - The identification and reporting criteria for sample/run rejection, repeat analysis, reinjection and reintegration should be objectively pre-specified in SOPs that were effective at the time of study

IVPT Sample Analysis (cont'd)



- Consider providing summary details for all analytical runs involved in the IVPT MV (including pilot) and pivotal studies which include, e.g.:

- Analytical run #
- Analyte name
- Donor(s) #
- Extraction date

- Assay date
- Instrument #
- Status of the analytical run
- Brief description of the analytical run

Summary

- Today's presentation covers considerations for information to include in an IVPT submission.
 - Detailed data, rationale, and calculations in Module 5.3 can facilitate the Agency's assessment of the IVPT studies and associated calculations.
- A detailed, well-organized submission across each aspect of the submitted IVPT studies can potentially:
 - Reduce the number of deficiencies including those classified as major
 - Reduce the number of assessment cycles

For more information, please refer to the appropriate Agency guidance(s). Depending on the data submitted, additional information may be requested during the ANDA assessment.

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