Demystifying High Quality Submissions for IVPT Studies

Submission of In Vitro Permeation Test (IVPT) Data and Information in ANDAs for Topical Drug Products

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SBIA Generic Drug Form – April 13, 2023

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

Learning Objectives

1. Identify key components that constitute a high quality IVPT submission
2. Understand the key submission expectations for each key component
3. Clarify their organization within the electronic common technical document (eCTD) submission

1. Key Components of a High Quality IVPT Submission

Key Components

1. Development and optimization of IVPT methodology (IVPT-MD)
2. Validation of IVPT methodology (IVPT-MV)
3. Pivotal evaluation based on validated methodology (IVPT-PIV)

Key Components (contd.)

4. Validation of the analytical methodology (ANA-MV)
5. Sample analyses (IVPT-MV and IVPT-PIV)

2. Key Expectations of Information & Data

All IVPT studies

1. IVPT-MD
2. IVPT-MV
3. IVPT-PIV

4. ANA-MV
5. Sample analyses

All IVPT Studies

- **Each** experiment/set of reported results -
  - Objective
  - Parameters (see appendix B)
  - Procedures (see appendix B)
  - Operators involved
  - Conclusion

All IVPT Studies (contd.)

- **Each** IVPT experimental run -
  - Cells run in parallel (unique cell IDs)
  - Each dosed cell (replicate #)
  - Product lot #
  - Experimental run date(s)

All IVPT Studies (contd.)

- **Each** product lot -
  - Lot #
  - Product strength
  - Formulation
  - Batch size

All IVPT Studies (contd.)

- **Each** product lot – (contd.)
  - Assay potency
  - Container content uniformity
  - Manufacturing or expiration dates
  - Altered manufacturing process with details of alteration

All IVPT Studies (contd.)

- **Each** skin section –
  - Donor ID, age, race & sex
  - Supplier information
  - Anatomical site
  - Individual replicate measurements, mean & %CV
    - Skin thickness & barrier integrity

%CV: Percent coefficient of variation

All IVPT Studies (contd.)

- Handling of **each** skin section –
  - Receipt conditions (temperature, date & time)
  - Storage conditions (temperature range)
  - Each retrieval & restorage (date & time)
  - # of freeze thaw cycles
- Experimental observations & protocol/SOP deviations

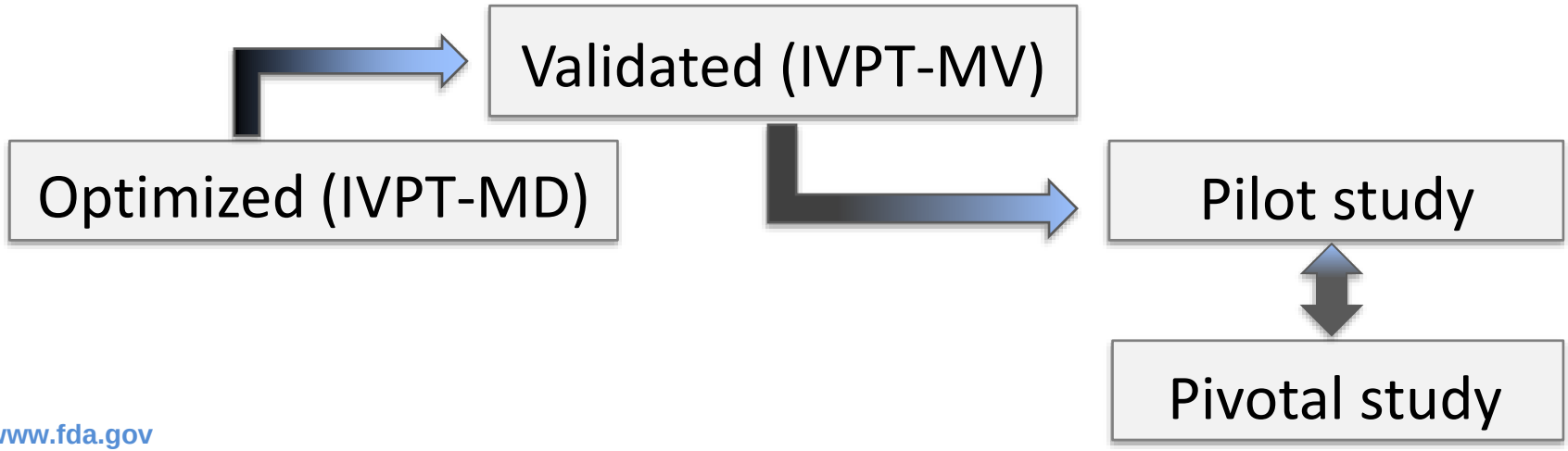
SOP: Standard operating procedure

IVPT-MD

- Recommendations per slides #8-13
- Complete & well-organized documentation
- Optimized & scientifically justified:
  - IVPT equipment
  - Method parameters
  - Controlled study procedures → Detailed SOPs
  - Acceptance criteria
  - Study conditions

IVPT-MD (contd.)

- Raw concentration & PK data with calculations (see appendix A for data format)
- IVPT Methodology:



IVPT-MV

- Specific qualification & controls:
  - Equipment qualification
  - Skin qualification
  - Receptor solution qualification
  - Receptor solution sampling qualification

IVPT-MV (contd.)

- Specific qualification & controls: (contd.)
  - Permeation profile & range (pilot study)
  - Precision & reproducibility (pilot study)
  - Dose depletion (pilot study)
  - IVPT selectivity (pilot study)
  - Environmental control

IVPT-MV (contd.)

- Specific qualification & controls: (contd.)
  - IVPT sensitivity
  - Robustness
- Recommendations per slides #8-13
- Detailed protocols & SOPs

IVPT-MV (contd.)

- Evidence:
  - Consistency of study procedures
  - Control of method parameters
- Raw concentration & PK data with calculations (see appendix A for data format)

IVPT-PIV

- Recommendations per slides #8-13
- Detailed protocols & SOPs
- Procedures:
  - Randomization
  - Blinding & unblinding

IVPT-PIV (contd.)

- Evidence:
  - Consistency of study procedures
  - Control of method parameters
- SAS raw concentration & PK data (see appendix A for data format)

ANA-MV

- Receptor sample analysis method & procedures
- Relevant protocols & SOPs
- **Each** study involved in ANA-MV
    - Linearity, recovery, accuracy & precision, etc.
    - Stability assessments & dilution integrity

Sample Analyses

- Detailed protocols & SOPs (sample analysis procedures)
- 100% numerical raw data
- Sample/run rejection, repetition, reinjection or reintegration, as applicable
- 20% serially-selected representative chromatograms

Sample Analyses (contd.)

- **Each** analytical run -
  - Run ID
  - Analyte
  - Extraction date
  - Assay date
  - Donor ID
  - Instrument ID
  - Run status
  - Run description

3. Organization within eCTD Submission

Organization is Key

Module 5.3.1.2

- IVPT-MD, IVPT-MV, & IVPT-PIV
  - Study reports, protocols, SOPs, study datasets, supporting documents, etc.
  - Simplified ts.xpt files (see appendix C)

Organization is Key (contd.)

Module 5.3.1.4

- ANA-MV
  - Study report, protocol, SOPs, etc.
- IVPT-MV & IVPT-PIV sample analyses
  - Analytical reports, 100% numerical raw data, 20% representative chromatograms, protocols, SOPs, etc.

Challenge Question

Validated IVPT methodology as used in the pilot study should be utilized (unchanged) in the subsequent pivotal study. A change in which of the following between the pilot and pivotal studies would not be considered as a change in the IVPT methodology:

A. Study procedures (such as those related to dosing, sampling, etc.)

B. Acceptance criteria (such as pertaining to skin section inclusion)

C. Formulations/products evaluated

D. Equipment (such as a vertical diffusion cell)

Summary

- A-B-Cs of high-quality IVPT Submissions

  A - Key components

  B - Key submission expectations for each key component

  C - Organization of information & data

Summary (contd.)

- For comprehensive information, always consult relevant Agency guidances -
  - Guidance for Industry: In Vitro Permeation Test Studies for Topical Drug Products Submitted in ANDAs (October 2022)
  - Product-specific guidances on topical products

It’s Go Time

High-quality IVPT submissions

High-quality IVPT studies

Go <u>high-quality</u> all the way

- Developments & optimizations
- Validations
- Pivotal evaluations
- **Submissions to Agency**

Questions?

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APPENDICES

(For Reference Purpose)

APPENDIX A

Data Format for Calculation Spreadsheets or SAS Datasets

Data Format

Raw Measurement (Concentration) Data																			
RANDCODE	TRT	PRODUCT	DONOR	SEQ	REP	CELL	AREA	VOLUME	DOSE	BARRIER INTEGRITY	THICKNESS	C1	C2…	Cn	T1	T2…	Tn	SAMPLING	ALIQUOT

Definition Table for SAS Transport Dataset of Raw Measurement Data

Variable Name	Variable Label	Variable Type	Content	Notes
RANDCODE	Randomization Code	Character/ Alphanumeric/Numeric	Blinded Treatment Code	Unique randomization code
TRT	Treatment/Formulation Group	Numeric	1 or 2 or 3	1 = Test; 2 = Reference; 3 = Control which is a non-dosed control diffusion cell. See guidance for additional details.
PRODUCT	Treatment Type	Character	TEST or REFERENCE or CONTROL	
DONOR	Donor Identifier	Alphanumeric/Numeric	Donor identification code	Unique identifier for donor
SEQ	Sequence	Numeric	1 or 2	1 = ABAB...; 2 = BABA…
REP	Replicate number	Numeric	1,2, 3, 4, etc.	At least four replicates recommended
CELL	Individual diffusion cell identifier	Alphanumeric/ Numeric	Cell identification code	Unique diffusion cell identifier
AREA	Dosed area of cell	Numeric	Minimum two or three decimal places	Area in square centimeter (cm^2)

Data Format (contd.)

Definition Table for SAS Transport Dataset of Raw Measurement Data (contd.)

Variable Name	Variable Label	Variable Type	Content	Notes
VOLUME	Receptor volume	Numeric	Minimum one or two decimal place(s)	Receptor volume in milliliter (mL)
DOSE	Actual amount of dose applied	Numeric	Minimum one or two decimal place(s)	Actual amount of dose applied in milligram (mg)
BARRIER INTEGRITY	Barrier Integrity Test Value	Numeric	Minimum one or two decimal place(s)	Measured value of barrier integrity test for skin section in appropriate units
THICKNESS	Thickness of skin section	Numeric	Minimum two or three decimal places	Measured value of skin section thickness in millimeter (mm)
C1, C2, Cn, etc.	Receptor sample concentration	Numeric	**Corrected for dilution** Data provided should contain as much precision as is reasonable in terms of decimal points for a given measurement.	Receptor sample concentration in nanogram per milliliter (ng/mL)
T1, T2, Tn, etc.	Sampling time point	Numeric	Actual time points	If there are deviations in sampling time points, provide actual time points.
SAMPLING	Sampling type	Character	ALIQUOT or FULL REPLACEMENT	
ALIQUOT	Aliquot volume	Numeric		Aliquot volume in mL if sampling type is Aliquot.

Data Format (contd.)

PK Parameter Data								
RANDCODE	**TRT**	**PRODUCT**	**DONOR**	**SEQ**	**REP**	**CELL**	**JMAX**	**AMT**

Definition Table for SAS Transport Dataset of Individual PK Parameter Data

Variable Name	Variable Label	Variable Type	Content	Notes
RANDCODE	Randomization Code	Character/ Alphanumeric/Numeric	Blinded Treatment Code	Unique randomization code
TRT	Treatment/Formulation Group	Numeric	1 or 2 or 3	1 = Test; 2 = Reference; 3 = Control which is a non-dosed control diffusion cell. See guidance for additional details.
PRODUCT	Treatment type	Character	TEST or REFERENCE or CONTROL	
DONOR	Donor identifier	Alphanumeric/Numeric	Donor identification code	Unique identifier for donor
SEQ	Sequence	Numeric	1 or 2	1 = ABAB...; 2 = BABA…
REP	Replicate number	Numeric	1,2, 3, 4, etc.	At least four replicates recommended
CELL	Individual diffusion cell identifier	Alphanumeric/Numeric	Cell identification code	Unique diffusion cell identifier
JMAX	Jmax	Numeric	Minimum two or three decimal places	Maximum flux in nanogram per square centimeter per hour (ng/cm^2/hr). See guidance for additional details.
AMT	Total cumulative amount	Numeric	Minimum two or three decimal places	Total cumulative permeation in ng/cm^2. See guidance for additional details.

APPENDIX B

Non-exhaustive Lists of IVPT Method Parameters & Study Procedures

Method Parameters

- Temperature at skin surface (assessed at multiple points over the IVPT study duration)
- Time duration for dosing (includes dispensing, spreading/application) per cell
- Temperature of the receptor solution (assessed at multiple points over the IVPT study duration) **Note:** Experimental API stability as validated should cover (validation and pivotal study) experimental range of receptor solution temperatures.

Method Parameters (contd.)

- Skin source (e.g., cadaver)
- Skin anatomical site (e.g., posterior torso)
- Skin storage conditions and number of freeze thaw cycles to which subjected
- Skin preparation (e.g., dermatomed)
- Skin barrier integrity test acceptance criteria (e.g., < 15 $g/m^2/hr$)
- Skin thickness
- Skin barrier integrity test (e.g., trans-epidermal water loss (TEWL) measurement)

Method Parameters (contd.)

- Ambient temperature and humidity (ranges within which maintained)
- IVPT equipment (e.g., a vertical diffusion cell (VDC)),
- Sample volume or flow rate
- Stirring/flow rate
- Study duration (e.g., 48 hours)
- Time duration for sampling per cell
- Receptor solution (composition, molarity and pH |antimicrobial agent and its concentration)

Method Parameters (contd.)

- Receptor solution sampling times (e.g., 1, 2, 4, 6, 8, 12, 16, 20, 118 and 24 hours)
- Sampling method
  - automated v. manual sampling
  - complete v. partial (aliquot) volume replacement
- (Applied) topical product dose amount (e.g., 15 mg/cm2)
- Dose duration (e.g., 6 hours)

Study Procedures

- Equipment
  - Empirical qualification (e.g., measuring diffusional areas of the donor and receptor chamber orifices, and cell volumes)
- Skin
  - Preparation of skin sections
  - Mounting on diffusion cells
  - Measuring skin thickness
  - Measuring skin barrier integrity

Study Procedures (contd.)

- Sampling
  - Performing of sampling and replenishment
  - Handling and storage of samples
- Dosing
  - Dosing application technique including dispensing and spreading

Study Procedures (contd.)

- Measurement of pre-dose concentrations for all cells to help identify potential contamination associated with each skin section and/or diffusion cell
- Use of control cells across all IVPT studies which can facilitate the periodic monitoring and reporting of temperature control at skin surface and in the receptor solution during the study

APPENDIX C

Resources

Resources

- Please refer to FDA's Study Data Technical Conformance Guide for further details including an example of a simplified ts.xpt file/dataset for a nonclinical study (see appendix G). To access FDA's Study Data Technical Conformance Guide, first click on the link provided under reference #7 (see page 8 of 15) in the Guidance for Industry titled 'Providing Regulatory Submissions In Electronic Format — Standardized Study Data', June 2021, available at https://www.fda.gov/media/82716/download. Then, click on the link titled 'Study Data Technical Conformance Guide' under the section titled 'Quick Links'.