USP <1724> Prospective Scope and Content

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

Best Practices and Scientific Considerations for ANDA Submissions

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Agenda

- Key Changes
- Chapter Layout and IVRT *vs.* IVPT comparison
- Recommendations on IVRT and IVPT

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Main Changes

- Inclusion of IVPT subsections
- Use of generic diagrams for apparatuses
- Inclusion of subsections on equipment maintenance and qualification
- IVRT section layout change

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IVRT and IVPT: tentative section layout

IVRT

a. Theory

b. IVRT Method Development
   - i. Synthetic Membrane
   - ii. Equipment
   - iii. Analytical Method
   - iv. Experimental Design
     1. Dose
     2. Receptor Solution
     3. Experiment length and sampling
     4. Number of replicates
     5. Membrane temperature
     6. Data reporting

c. Application of IVRT in Scale-up and Post-approval change

IVPT

a. IVPT Method Development
   - i. Biological Membrane
   - ii. Equipment
   - iii. Bioanalytical Method
   - iv. Experimental Design
     1. Dose
     2. Receptor Solution
     3. Experiment length and sampling
     4. Number of replicates and donors
     5. Membrane temperature
     6. Membrane integrity
     7. Drug tissue distribution and mass balance
     8. Data reporting

b. IVRT versus IVPT comparison

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IVRT versus IVPT: Methodology Selection

Evaluation/goal	IVRT	IVPT
In vitro in vivo correlation assessment	Not recommended	✓
Ability of the compound/formulation to cross the stratum corneum and distribution of compound in epidermis and dermis, respectively		✓
Selection of a new chemical entity (NCE) for further development as a semi-solid formulation		✓
Compare in vitro kinetics of different semi-solid formulations (different composition of different presentation, such as solutions, gels, creams, ointments)		✓
Compare the rate and extent to which a topically administered compound becomes available in and/or through the skin from a reference versus a test semi-solid formulation		✓
Evaluate the effect of inactive ingredients on the rate of drug release from the formulation matrix	✓	Not recommended
Assess sameness of formulations with the same active and inactive ingredients and/or same levels of active/inactive ingredients	✓	
Compare the effect of critical manufacturing/process steps on the microstructure and associated performance (release rate) of semisolid formulations	✓	
Compare batch-to-batch variability of drug substance release rate at the time of manufacture, and during stability	✓	

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IVRT versus IVPT: Key Differences

Parameter	IVRT	IVPT
Membrane	Synthetic (e.g., mixed cellulose esters, nylon, polysulfone, polyethersulfone)	Biological; ex vivo human skin is typical, but other ex vivo epithelial tissues may be used (e.g., vaginal tissue, corneal tissue, nails, other mucosal tissues)
Receptor Solution	Aqueous and aqueous-organic combination, may include high percentages (≥30%) of organic solvents (e.g., ethanol, isopropyl alcohol, acetonitrile, etc.)	Aqueous, typically phosphate buffered saline; low levels (typically ≤5%) of additives may be added to allow sink conditions
Sampling	Small volume aliquots of the receptor solution at regular intervals	Larger volume sampling (e.g. entire content of the receptor solution replaced at every sampling time for VDCs). FDCs offer a different sampling methodology due to the continuous flow of receptor solution into the collection vials.
Apparatus	Vertical Diffusion Cells (VDC); Immersion Cells, USP Apparatus 4	VDC or flow-through diffusion cell (FDC)
Dose	Pseudo-infinite, occluded	Finite (typically ≤15 mg/cm^2), unoccluded
Experimental length	Typically, ≤ 6 hours	Typically, ≥ 24 hours
Receptor solution drug levels	µg to mg range	pg to ng range
Analytical technique	HPLC/UPLC with detection by UV, DAD, or FLD	HPLC/UPLC with mass spectrometric detection
Key data obtained	Release rate (slope)	Flux profile including peak flux (J_{max}) and cumulative amount permeated (AMT)

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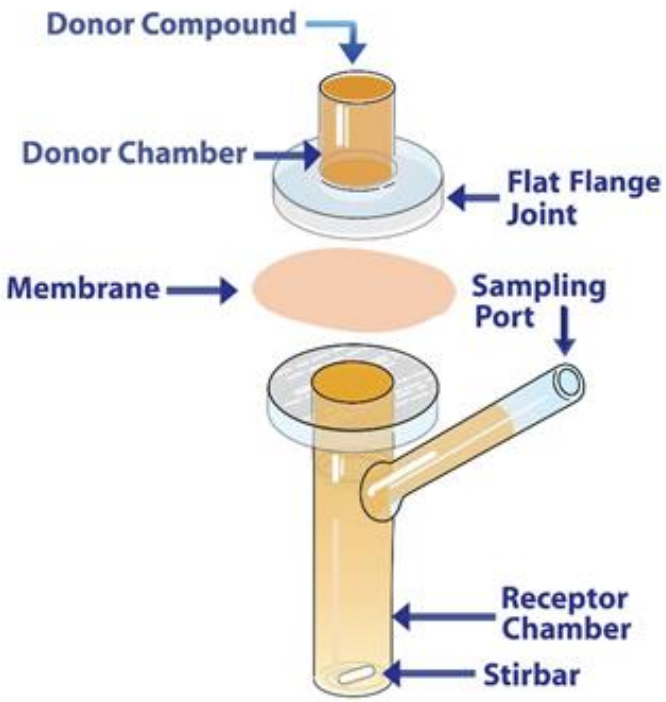
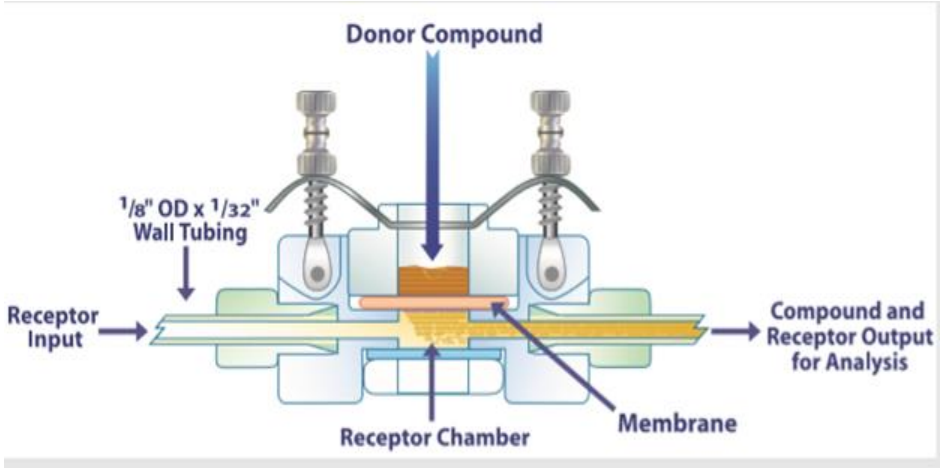
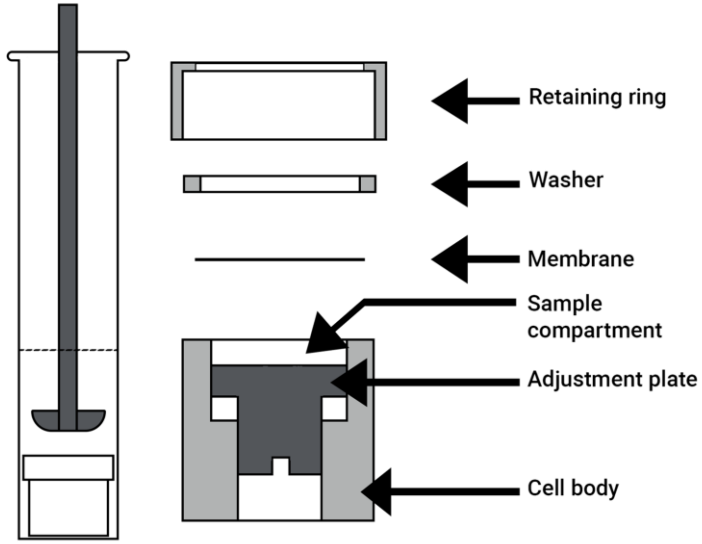
Examples of Generic Diagrams for Apparatuses







Vertical Diffusion Cell (VDC)

Flow-through Diffusion Cell (FDC)

Immersion Cell

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IVRT: General Recommendations

Membrane selection	<1002> chapter
Diffusion cell	VDCs (typical); immersion cells also used
Analytical method	LC-UV|DAD (typical); validation is encouraged
Dose	Pseudo-infinite, occluded; note on application methodology
Receptor solution	Aqueous / aqueous-organic; sink conditions; stirring; degas
Experimental length and sampling frequency	≤ 6 hs (typical); ≥ 5 sampling points (typical)
Number of replicates	≥ 6 (typical)
Membrane temperature	Membrane surface: 32 ± 1 °C (skin); 37 ± 1 °C (internal);
Data reporting	Release rate (slope)

Additional points:

- Sampling procedure / receptor solution temperature
- System equilibration

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IVPT: General Recommendations

Biological membrane	Human skin; dermatomed; ex vivo vs cadaver; anatomical area
Diffusion cell	VDCs; FDCs
Bioanalytical method	LC-MS (typical); validation is encouraged

Additional points:

- Sampling procedure / receptor solution temperature
- System equilibration

Dose	Finite (typically ≤15 mg/cm^2), unoccluded; application methodology
Receptor solution	Aqueous; additives may be needed; sink conditions; stirring;
Experimental length and sampling frequency	12-72 hs (typical); ≥ 8 non-zero time points (flux profile)
Number of replicates and donors	Minimum: ≥ 4 donors; ≥ 4 replicates /donor/treatment
Membrane temperature	Membrane surface: 32 ± 1 °C (skin);
Membrane integrity	TEWL; Electrical impedance; tritiated water
Drug tissue distribution and mass balance	Mass balance and epidermis /dermis splitting considerations
Data reporting	(J_{max}) and cumulative amount permeated (AMT)

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Equipment Maintenance and Qualification

VDCs

Maintenance of all components, and requalification every 6-12 months

- Diffusion cell size and volume measurements – orifice diameter and cell volume
- Heating systems
- Stirring device (rate/speed)
- Flow rate
- Sampling devices and accuracy assessment

FDCs

Similar recommendations from VDCs; further:

- Tubing length must be the same for all diffusion cells
- Peristaltic pump/tubing unclamped at the end of test
- Tubing replacement during regular intervals
- Tubing alignment for proper sample collection

Immersion cells

Similar recommendations from VDCs; further:

- Due to the uniformity in manufacturing immersion cells, individual identification of the cells and components is recommended, but not required

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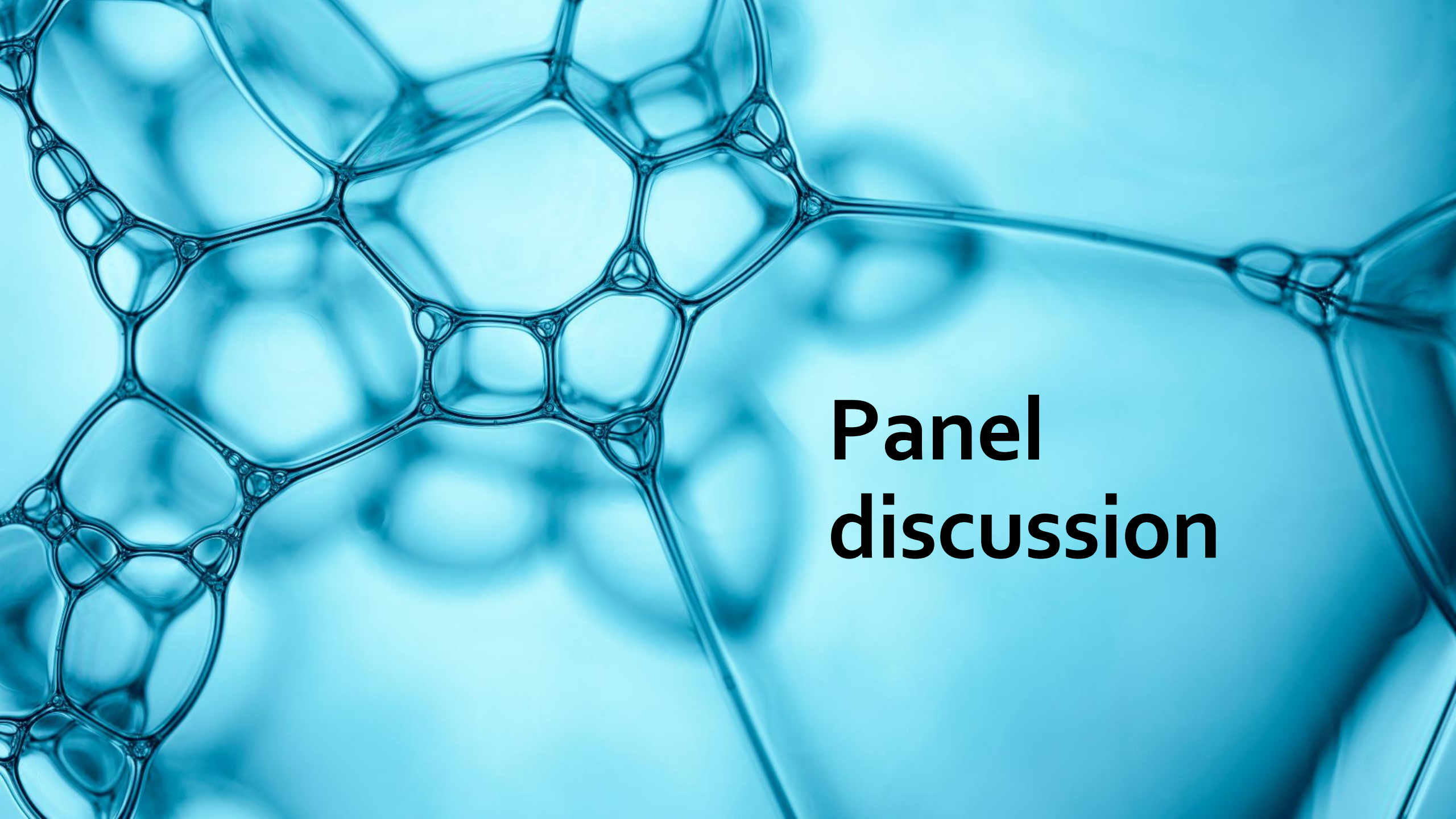

Panel discussion