IVPT Studies During Topical Product Development

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

Best Practices and Scientific Considerations for ANDA Submissions

August 18th, 2021

Disclaimer

The views and opinions expressed in this presentation are mine and made in my individual capacity. They must not be construed as representing the views or opinions of my employer.

Agenda

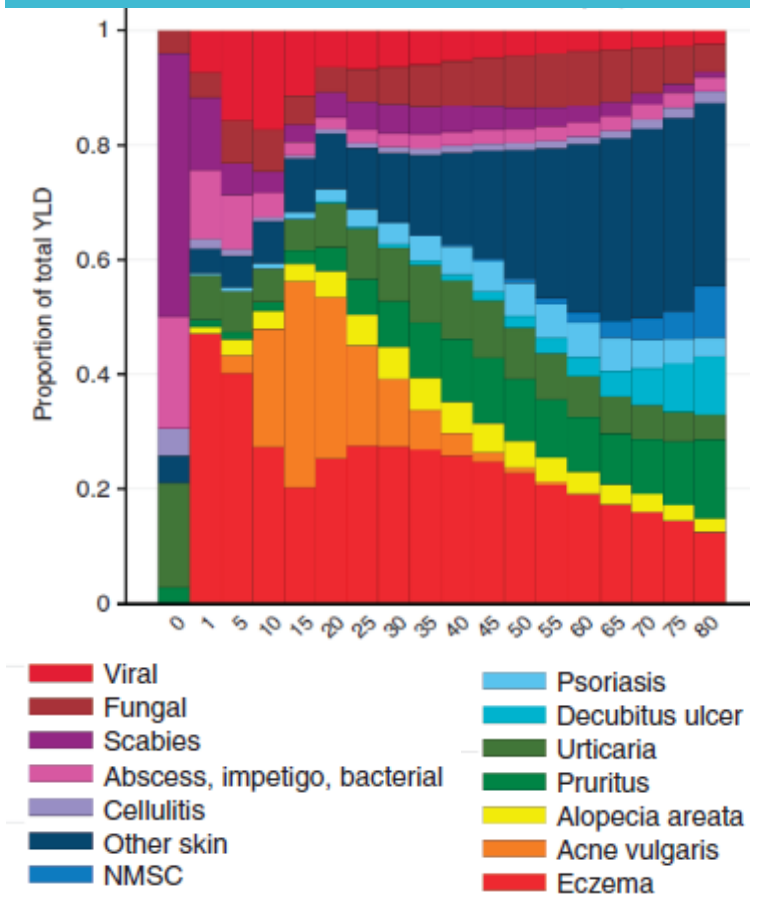
- Topical Drug Development and Innovation
- IVPT: A Versatile Technique
- IVPT Method Development/Validation Considerations
- IVPT General Recommendations

Skin Conditions, Quality of Life, and Cost

Years lost due to disability (YLD)[1]

Cause	Global YLDs	YLD rank
Low back pain	81M	1
Major depressive disorder	63M	2
Iron-deficiency anemia	43M	3
Skin conditions	**34M**	**4**
Neck pain	33M	5
Chronic obstructive pulmonary disease	29M	6

Skin condition, YLD composition by age[1]



Average cost (USD) per diagnosed person[2]

Disease	*Cost
Cutaneous lymphoma	$3,182
Ulcers	$1,754
Melanoma	$1,366
Non-melanoma skin cancer	$1,252
Connective tissue disease	$1,177
Bullous diseases	$925
Psoriasis	$462
Cutaneous infections	$452
Wounds and burns	$440

*Insured population (USA)

[1]Hay, R.J. et al. The global burden of skin disease in 2010: an analysis of the prevalence and impact of skin conditions. *J Inv Dermatol* 134, 1527-1534, 2014. DOI: 10.1038/jid.2013.446.
[2]Lim, H.W. et al. Contribution of health care factors to the burden of skin disease in the United States. *J Am Acad Dermatol* 76, 1151-1160, 2017. DOI: http://dx.doi.org/10.1016/j.jaad.2017.03.006.

Innovation in Topical Development

New Chemical Entities (NCEs)/repurposed topical drugs approved: 2010-2020

Active	Year	Classification	Dosage form; drug load	Indication
Ingenol mebutate	2012	NCE	Gel; 0.015% and 0.05%	Actinic keratosis
Brimonidine	2013	Repurposed	Gel; 0.33%	Rosacea
Luliconazole	2013	NCE	Cream; 1%	Tinea pedis
Efinaconazole	2014	NCE	Solution; 10%	Onychomycosis
Tavaborole	2014	NCE	Solution; 5%	Onychomycosis
Ivermectin	2014	Repurposed	Cream; 1%	Rosacea
Crisaborole	2016	NCE	Ointment; 2%	Atopic dermatitis
Oxymetazoline	2017	Repurposed	Cream; 1%	Rosacea
Ozenoxacin	2017	NCE	Cream; 1%	Impetigo
Glycopyrrolate	2018	Repurposed	Solution (cloth); 2.4%	Hyperhidrosis
Trifarotene	2019	NCE	Cream; 0.005%	Acne vulgaris
Abametapir	2020	NCE	Lotion; 0.74%	Head lice
Clascoterone	2020	NCE	Cream; 1%	Acne vulgaris
Delgocitinib	2020	NCE (Japan)	Ointment; 0.5%	Atopic dermatitis
Tirbanibulin	2020	NCE	Ointment; 1%	Actinic keratosis

Note: 2010 and 2011: no NCE/repurposed topical molecule approved

15 approvals in 10 years

Challenges

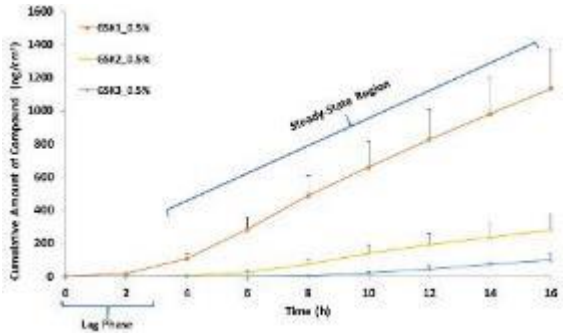
- Design and/or selection of an optimal molecule can be challenging
- Reliable nonclinical disease models not widely available
- Complex formulation development (unique expertise)
- Target disease can increase challenges to dermal delivery and to achieving therapeutic levels

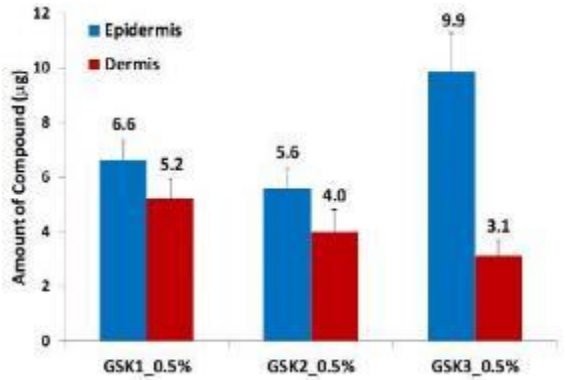
Santos, L.L.. et al. Developability profile framework for lead candidate selection in topical dermatology. *Int J Pharm* 604, 1-13, 2021. DOI: 10.1016/j.ijpharm.2021.120750.

IVPT Versatility

NCE Selection[1]

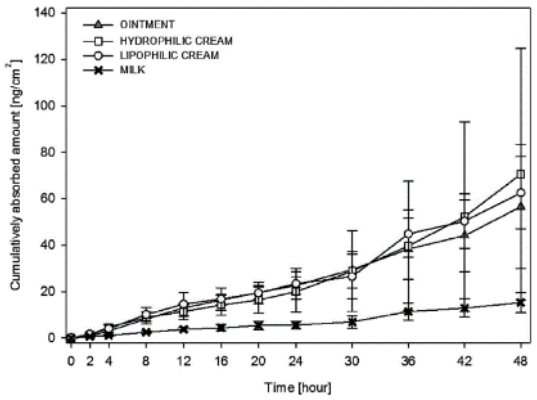
- Prototypical solvent system
- NCE ranking





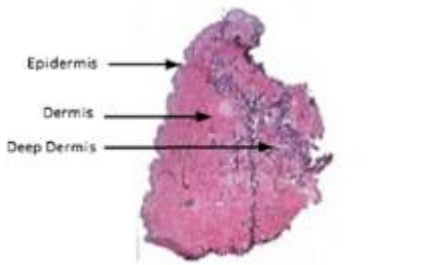
Formulation Selection[2]

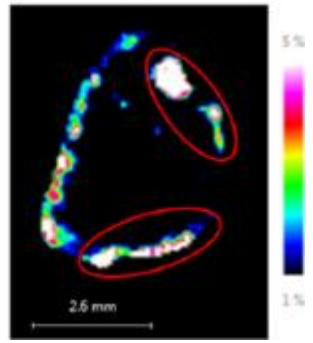
- Formulation optimization and/or selection (FTIH)
- Evaluate effect of formulation CQA's on dermal delivery



Imaging techniques[3,4]

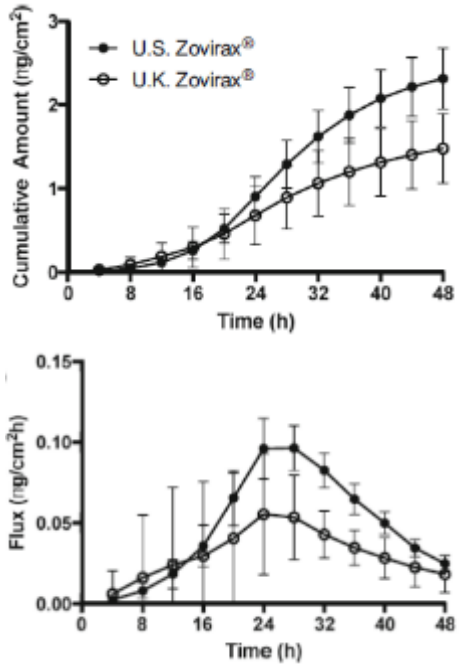
- Spatial distribution of drug, excipients, and biomarkers
- Concentration-depth profile





Bioequivalence[5]

- Demonstrate differences between Test and Reference formulations



[1]Santos, L.L., et al. In Vitro Permeation Test (IVPT) for Pharmacokinetic Assessment of Topical Dermatological Formulations. *Curr Prot Pharmacol* 91, e79, 2020. DOI: 10.1002/cpph.79.
[2]Gunther, C., et al. Comparison of in Vitro and In Vivo Percutaneous Absorption Across Human Skin Using BAY1003803 Formulated as Ointment and Cream. *Clin Pharm Drug Dev* 9, 582-592, 2020. DOI: 10.1002/cpdd.736
[3]Bonnel, D., et al. MALDI imaging facilitates new topical drug development process by determining quantitative skin distribution profiles. *Anal Bioanal Chem* 410, 2815-2828, 2018. DOI: 10.1007/s00216-018-0964-3
[4]Handler, A.M., et al. MALDI mass spectrometry imaging as a complementary analytical method for improved skin distribution analysis of drug molecule and excipients. *Int J Pharm*, 590, 2020. DOI: 10.1016/j.ijpharm.2020.119949
[5]Shin, S.H., et al. Cutaneous Pharmacokinetics of Acyclovir Cream 5% Products: Evaluating Bioequivalence with an In Vitro Permeation Test and an Adaptation of Scaled Average Bioequivalence. Pharm Res, 37, 2020. DOI: 10.1007/s11095-020-02821-z

IVPT Method Development and Validation

IVPT Method

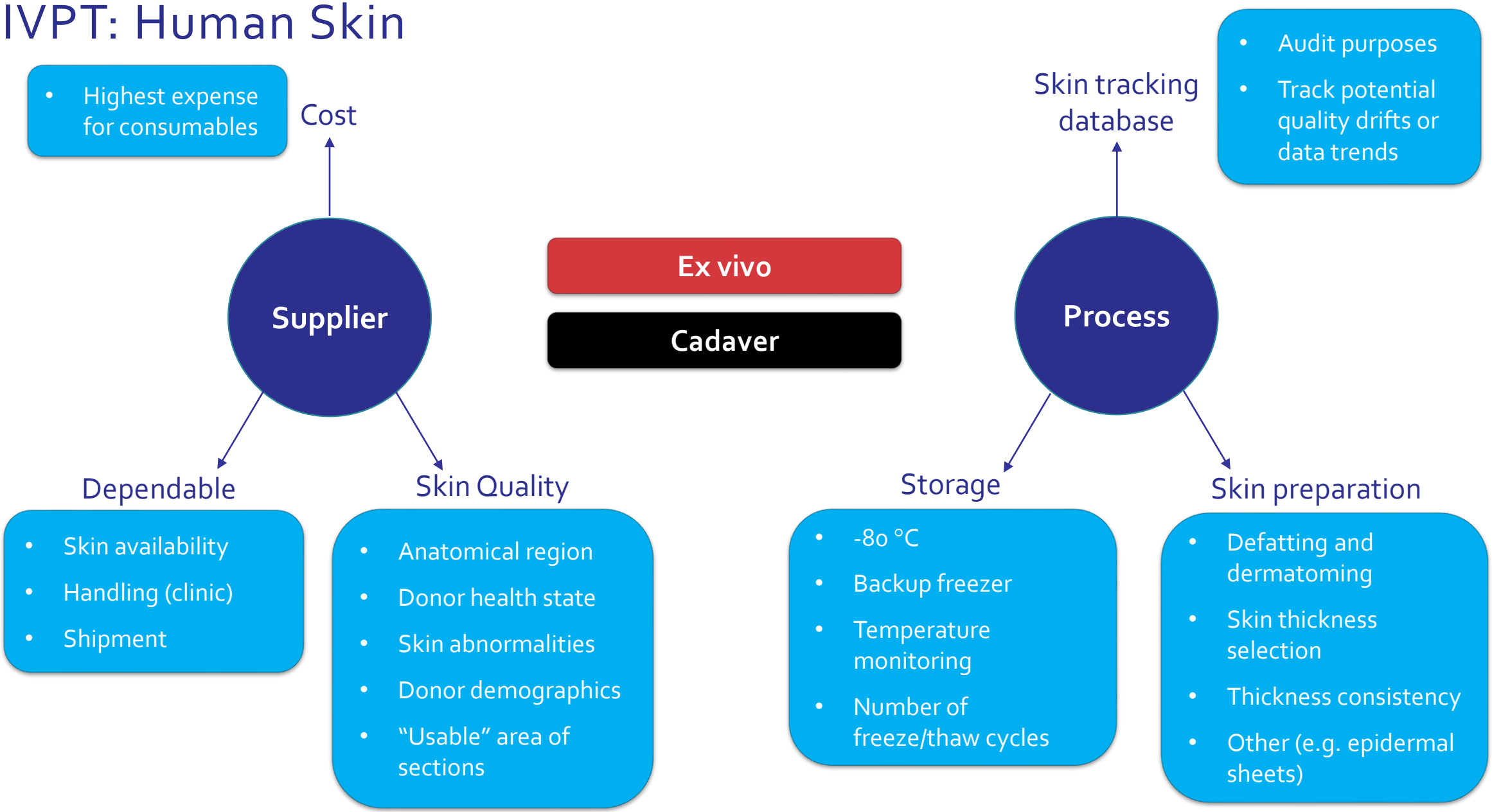
- **Membrane**
  - Source
  - Anatomical area
  - Thickness
  - Storage
- **Diffusion cell type**
  - VDCs
  - Flow-through
  - Other
  - Dosing area
- **Receptor solution**
  - Sink condition
  - Analyte stability
  - Compatibility with analytical method
- **Experimental conditions**
  - Number of donors/replicates
  - Duration
  - Dose
  - Sampling frequency
  - Membrane temperature
  - Mass balance
- **Data reporting**
- **Other**
  - Tissue distribution

Bioanalytical Method

- **Technique of choice:**
  - LC-UV/DAD/FLD
  - LC-MS
  - LC-MS/MS
  - Other (e.g. SPE-MS/MS)
- **Sample processing**
  - Concentration, extraction or dilution
- **Automation friendly**
  - Liquid handling

Santos, L.L., et al. In Vitro Permeation Test (IVPT) for Pharmacokinetic Assessment of Topical Dermatological Formulations. *Curr Prot Pharmacol* 91, e79, 2020. DOI: 10.1002/cpph.79.

IVPT: Human Skin



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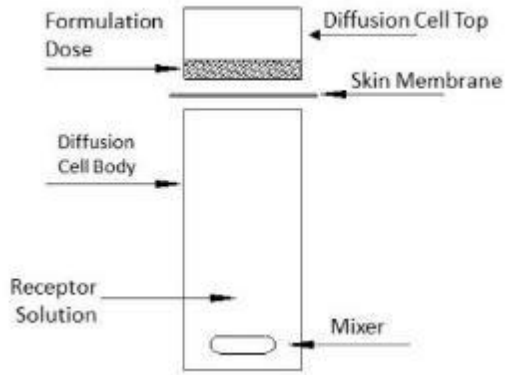
IVPT: Diffusion Cell Type

Receptor solution

More likely to require additives; concerns about bubbles over time (sampling)

Less challenging to ensure sink conditions



Bioanalysis

Less challenging (relatively higher analyte levels)

Requires more sensitive methods; concerns about non-specific binding and degradation

Receptor compartment volume

Diffusional area

Vertical Diffusion Cell (VDC)

Flow-through Diffusion Cell

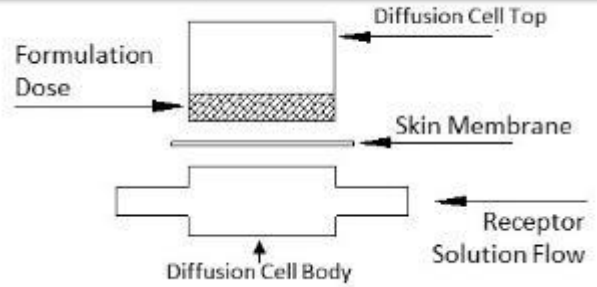
Stirring rate or flow rate control

Thermal regulation

Set up

Typically simpler; more common apparatus

Temperature control (long tubing) may be a challenge



Automation

Possible, but more challenging

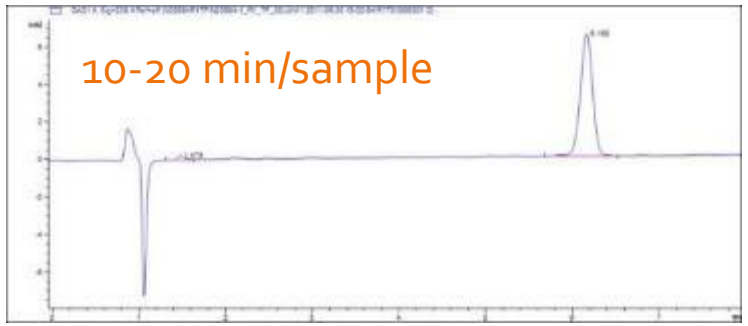
More automation friendly

Santos, L.L., et al. In Vitro Permeation Test (IVPT) for Pharmacokinetic Assessment of Topical Dermatological Formulations. *Curr Prot Pharmacol* 91, e79, 2020. DOI: 10.1002/cpph.79.

IVPT: Bioanalytical Method

FDA Guidance for Industry on Bioanalytical Method Validation

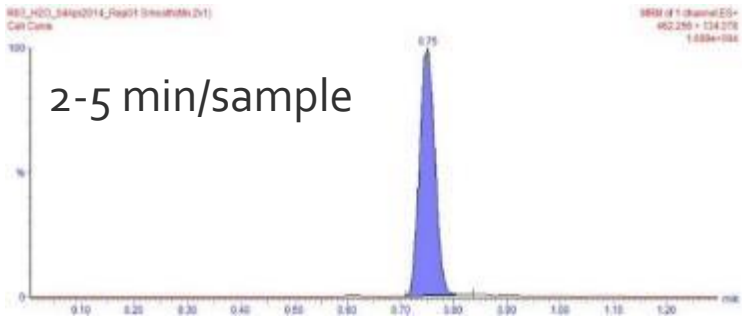
- Linearity
- Accuracy and Precision
- Sensitivity
- Selectivity
- Specificity
- Dilution integrity
- Analytical carryover
- Recovery
- Analyte Stability
  - In experiment (receptor solution temperature)
  - Sample preparation (extraction)
  - Autosampler (long analytical runs, >24 hr)
  - Storage



LC-UV (or DAD, FLD)

- Simpler training, maintenance and troubleshooting
- Adequate when sample throughput is not a bottleneck
- May not provide enough sensitivity for samples from flow-through experiments

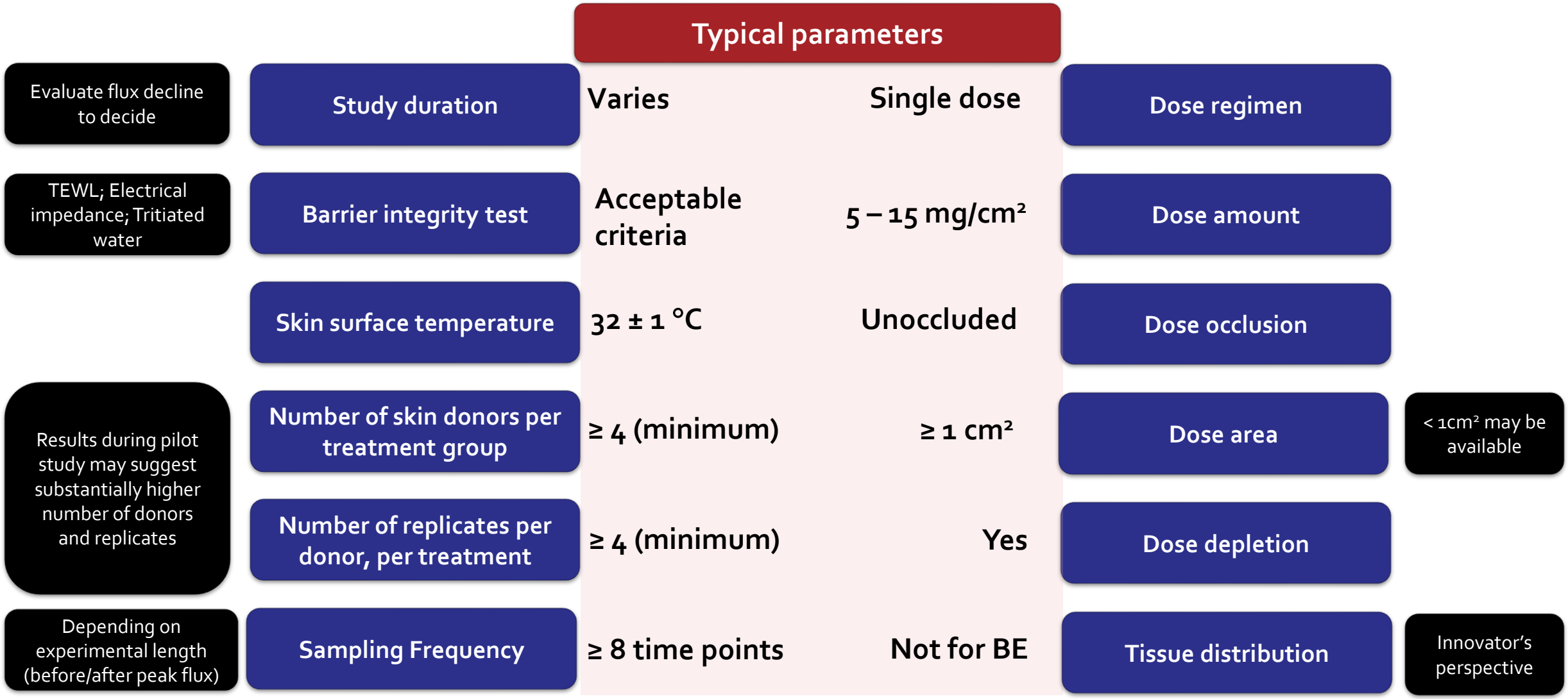
LC-MS (or MS/MS)



- Best sensitivity, selectivity, and specificity
- Allows faster run times
- Troubleshooting can be complex
- Substantial upfront investment (USD 500k+)

Santos, L.L., et al. In Vitro Permeation Test (IVPT) for Pharmacokinetic Assessment of Topical Dermatological Formulations. *Curr Prot Pharmacol* 91, e79, 2020. DOI: 10.1002/cpph.79.

IVPT: Experimental Design



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IVPT: Method Validation Considerations

Dose amount

- Dose Amount
- Dose Duration
- Dose Concentration
- Altered Formulation

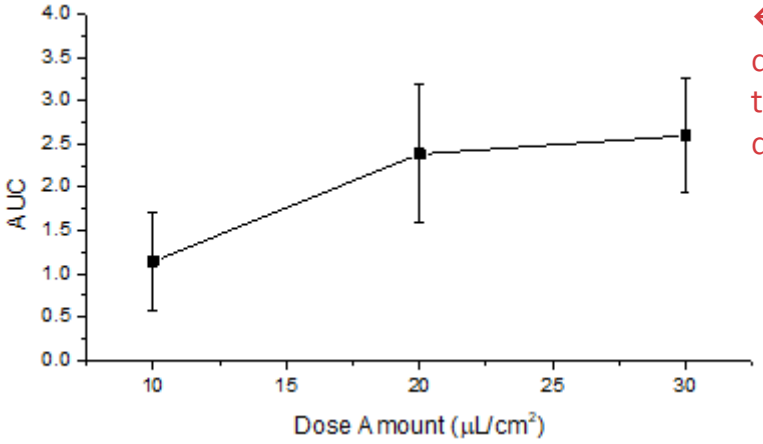
Suggested study design

- No less than 4 donors
- No less than 4 replicates per donor

Points for consideration

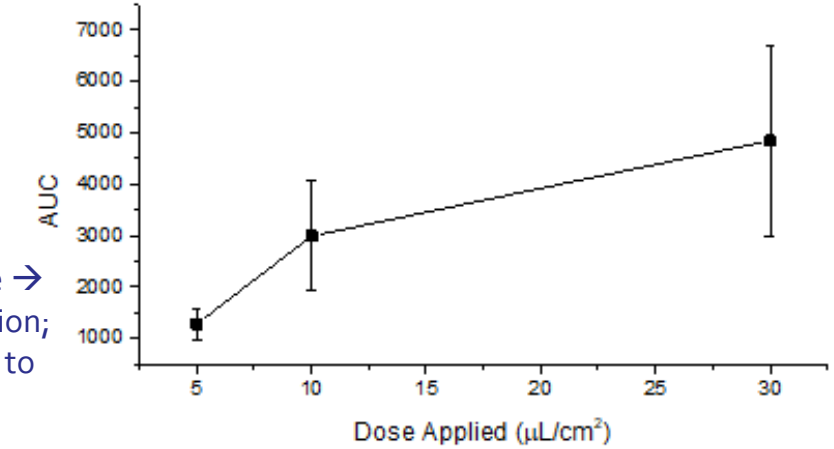
- Qualitative discrimination
- Sufficient sensitivity
- Sufficient selectivity
- Sufficient discrimination

Dose amount evaluation: AUC (µg/cm²) from multiple dose amounts (2 distinct experiments)

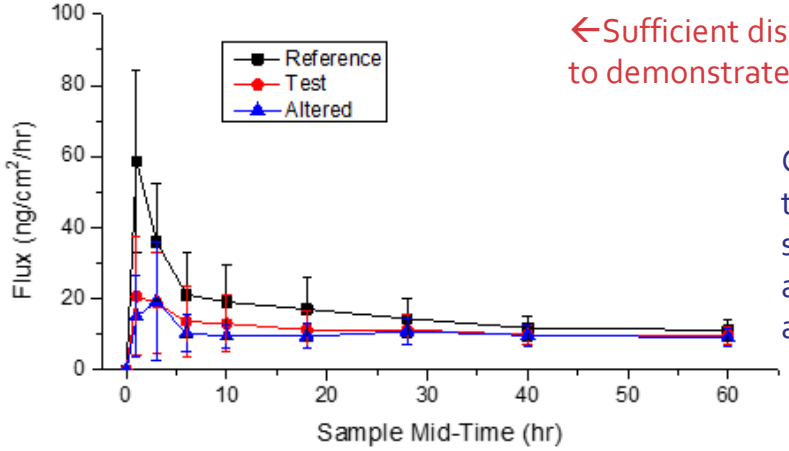


←Sufficient discrimination to use lower dose amounts?

Reasonable → discrimination; which dose to use?

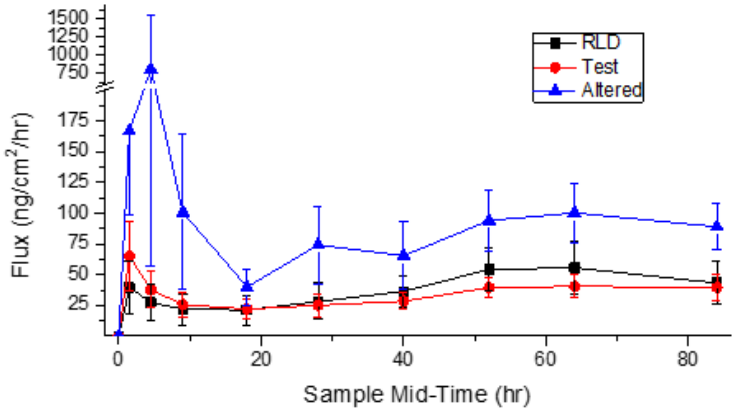


Altered formulation evaluation: mean flux (ng/cm²/hr) (2 distinct experiments)



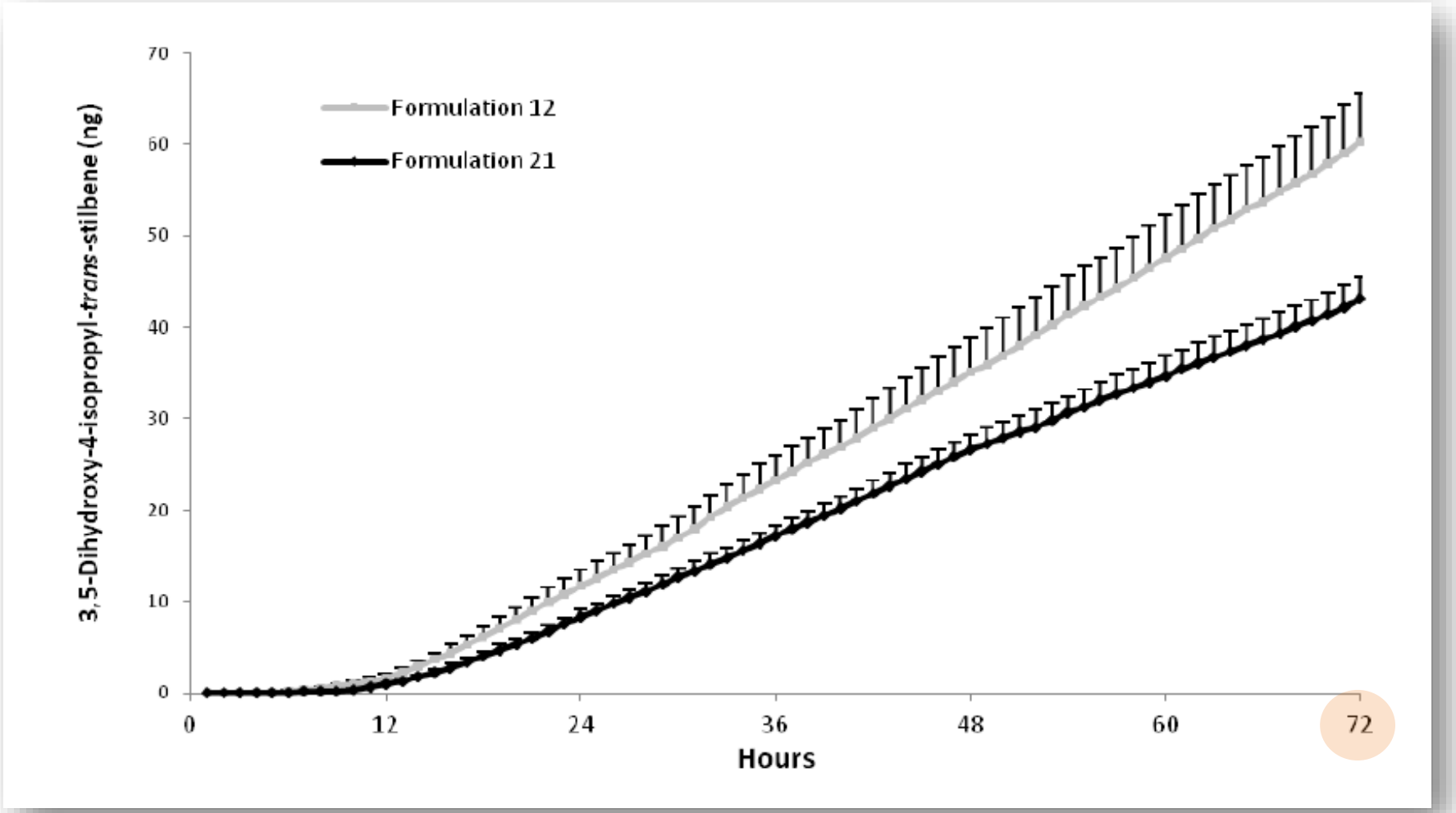
←Sufficient discrimination to demonstrate selectivity?

Good discrimination → to demonstrate selectivity, but due to an extreme vehicle alteration



Adapted from slide courtesy of Paul Lehman – email communication on July 26th, 2021

IVPT: Experimental Design Considerations

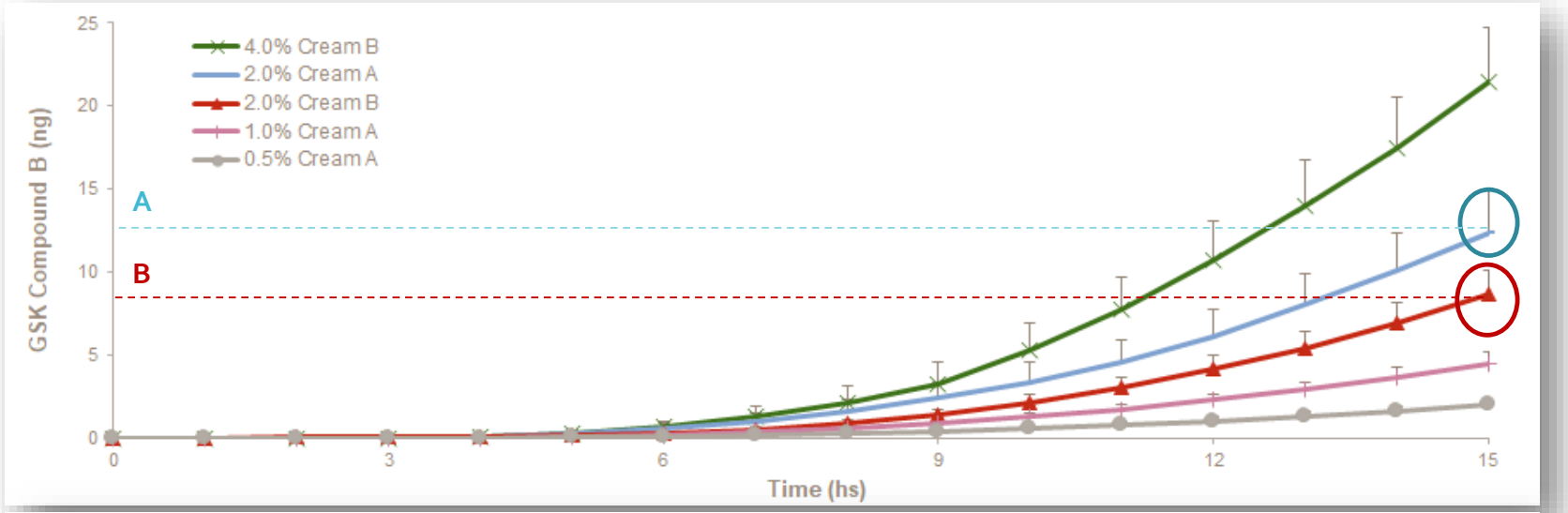


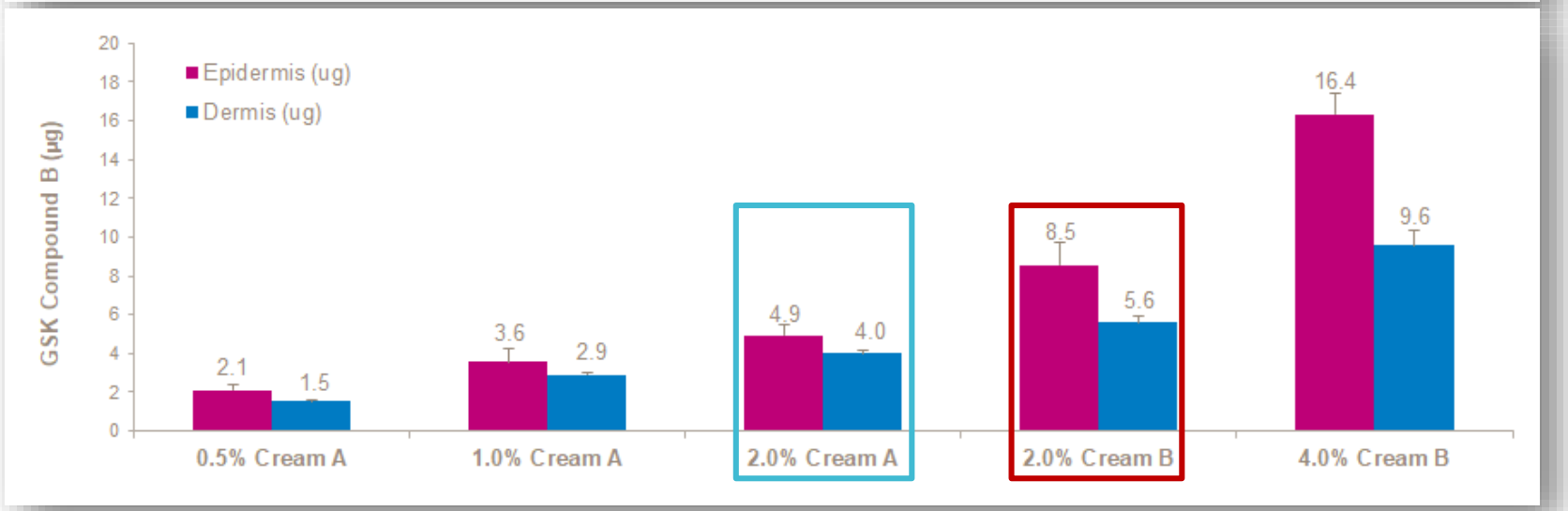
NCEs/formulations with very low skin flux (e.g. ≤ 1 ng/cm²/hr) may not display a **flux decline** (within a reasonable time) even in finite dosing

- **Flux plot**, instead of cumulative amount, should be used to better visualize the data

Figure adapted from US Patent 10,195,160. Sonti, S; Thomas, J.R.; Lenn, J.; Santos, L.; Whiteman, J.; Doherty, M.Q.; Bedard, M.; Jain, P. Topical pharmaceutical compositions. February 5th, 2019.

IVPT: Experimental Design Considerations





- **For NCEs**, certain aspects, such as tissue distribution, may be relevant.
- **Example:** Cream B appears to demonstrate preferential delivery to dermis (site of action) compared to receptor solution
- **Time-course** evaluating epidermis/dermis levels is ideal, but resource-consuming

Adapted from oral presentation: Santos, L. Topical Drug Development – Evolution of Science and Regulatory Policy, July 30th, 2019. IVPT: Practical Considerations in Its Method Development and Implementation

IVPT: General Recommendations

- **Provide hands-on training for new hires, and evaluate experimental proficiency**
  - Choose a formulation in which skin flux profile is well characterized by the lab
  - New hires should perform all study steps with minimal supervision, and able to do data reporting/discussion

- **Ensure a standard "check list" is completed prior to starting an experiment**
  - *Check for air bubbles before and during the experiment;*
  - *Ensure receptor solution is flowing through the tubing;*
  - *Ensure circulating water baths are working properly, etc*

- Have a reference document with troubleshooting tips for both IVPT and the bioanalytical equipment of choice – some examples:
  - **IVPT – problem example:** *Receptor solution leaking into donor compartment*
    - **Possible cause(s):** *Perforation in skin section; skin improperly secured in diffusion cell*
    - **Possible solution(s):** *Exclude or replace replicate*

  - **LC-MS/MS – problem example:** *High background signal at analyte retention time*
    - **Possible cause(s):** *Contaminated solvents (with analyte or otherwise) or matrix interferents*
    - **Possible solution(s):** *Utilize fresh, high-purity solvents, alter chromatography in attempt to separate analyte and matrix interferents, and/or utilize alternative MS/MS transitions*

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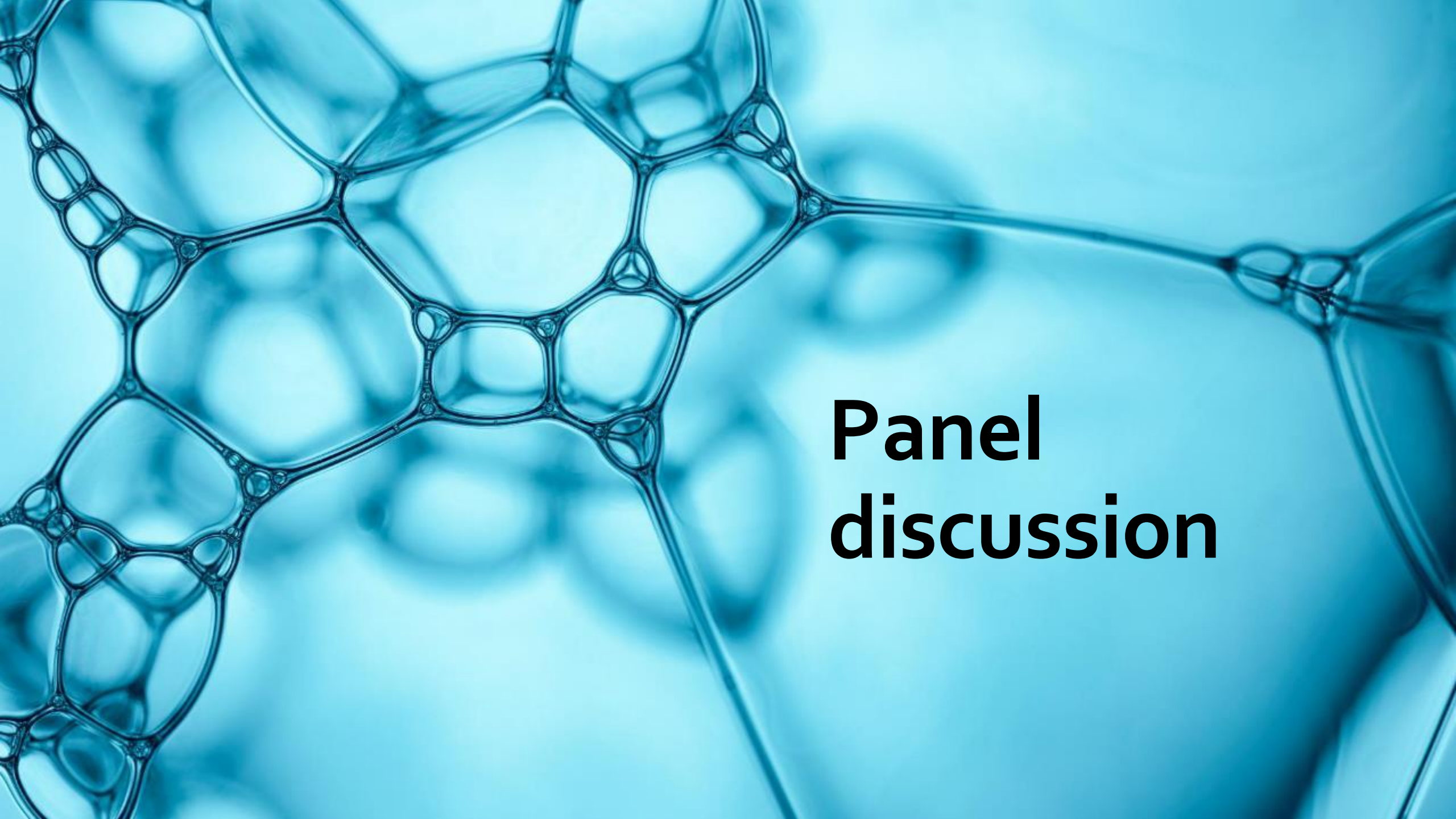

Panel discussion