Tergus Pharma

Think Topicals, Think Tergus

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TOPICAL DRUG DEVELOPMENT -- EVOLUTION OF SCIENCE AND REGULATORY POLICY

A presentation at

CERSI
University of Maryland

University of Maryland
School of Pharmacy

Topical drug development -Evolution of science and regulatory policy

The Use of IVPT as a Tool in Developing Topical Drug Products

Vijendra Nalamothu, Ph.D.,
Chairman & CEO, **Tergus Pharma**

The Use of IVPT as a Tool in Developing Topical Drug Products

- **Topics covered:**
  - **Skin Permeation**
  - **Product Development**
  - **Clinical de-risking**
  - **Regulatory Approvals**

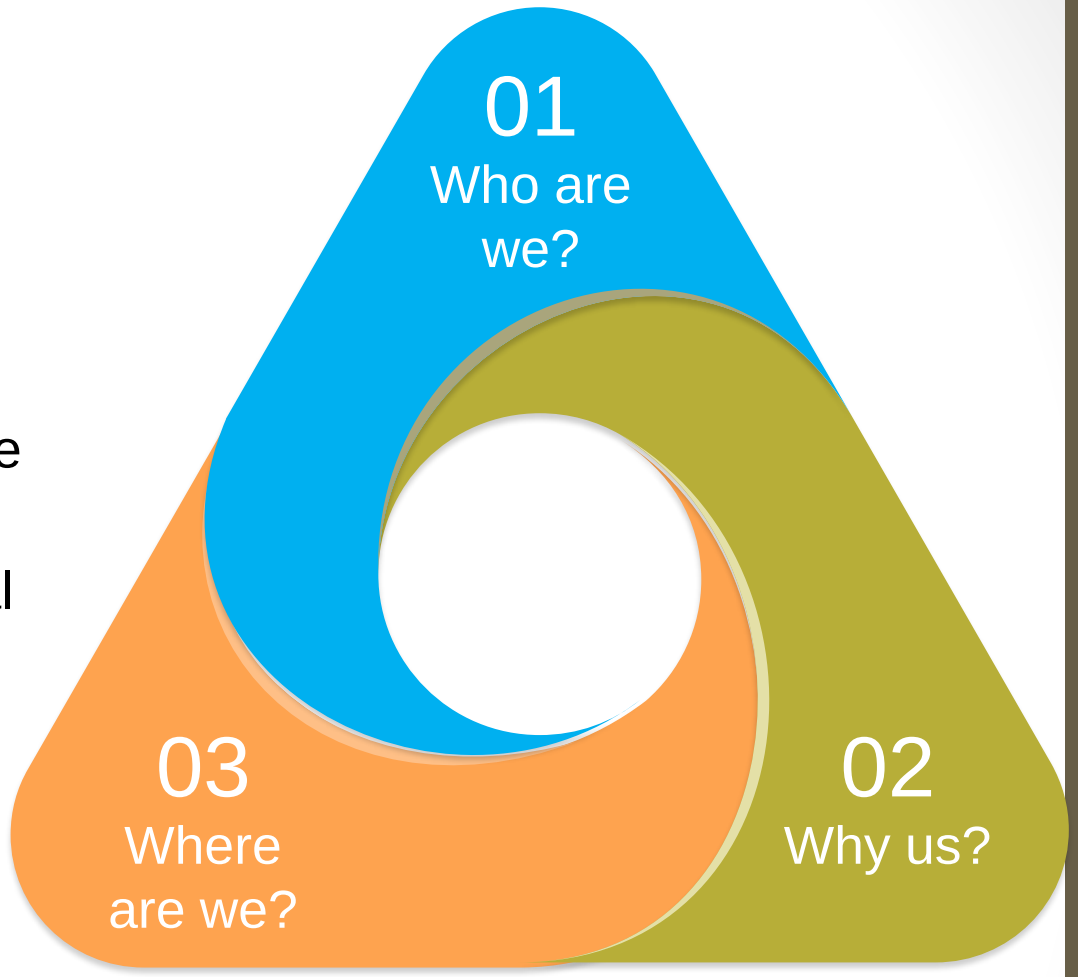
- **What you will learn:**
  - Begin with end in mind®
  - Understanding your product
  - Why systematic development matters?
  - Using the skin data properly
  - Pitfalls of IVPT
  - How will you use this data to go to clinic?

Who are we?

01 Leaders in the topical pharmaceutical industry with combined 250+ years of experience
We focus exclusively on our core expertise

02 One of the first CRO to use QbD for topical pharmaceuticals in the industry.
Ensure client and product success.
Ease technology transfer and scale up.
Hold an impeccable quality record.

03 Located in Research Triangle Park, NC with state-of-the-art 20,000 square-foot facilities and 75+ staff.
Globally, one of the largest IVRT and skin permeation cGMP compliant labs.



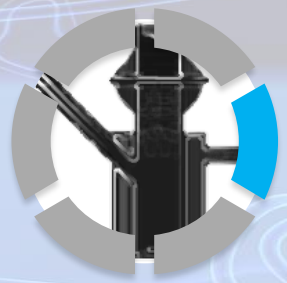
Leading Experts in Topicals

Full Contract Development Services

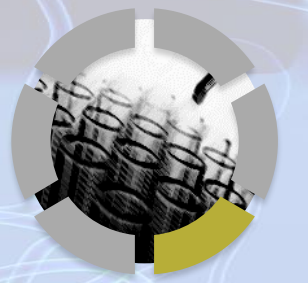
Formulation, Development

Analytical Research & Development

Skin Biology and Permeation Studies



In Vitro Release Testing (IVRT)



Clinical Supply Manufacturing

CMC logistics, Scale-up and Tech transfer Consulting

Development Services

Creams

Lotions

Ointments

Gels

Schedule drugs
Sexual Hormones
High Potent APIs

Nail Lacquers

Pastes

Suppositories

Foams

Tergus Collaboration

- **A one-stop shop to support**
  - NCE development incl. repurposing/repositioning
  - A generic equivalent of RLD
  - 2 men and a molecule companies to large pharma
  - Post-approval (SUPAC), marketing claims support
  - M&A assistance
  - Building platforms / portfolios for companies

- **Begin with end in mind®**
  - Next stage gate: tox / clinical / commercial
  - Type of dosage form / dossier
  - *In vitro* skin PoC or animal / disease models or straight to FIM / PoC
  - Clinical de-risking and reduce CMC surprises
    - Irritation / IID / Vehicle effect, permeation, scale-up, QbD, stability, phase-specific validations
  - Launch – ready products

Tergus Approach

- Type of formulation
  - Disease specific
  - Delivery kinetics
  - Unmet needs
- Type of Dossier
  - NDA – 505(b)(1)
  - 505(b)(2)
  - ANDA
    - Q1/Q2/Q3
- Pre-clinical concerns
- Clinical De-risking

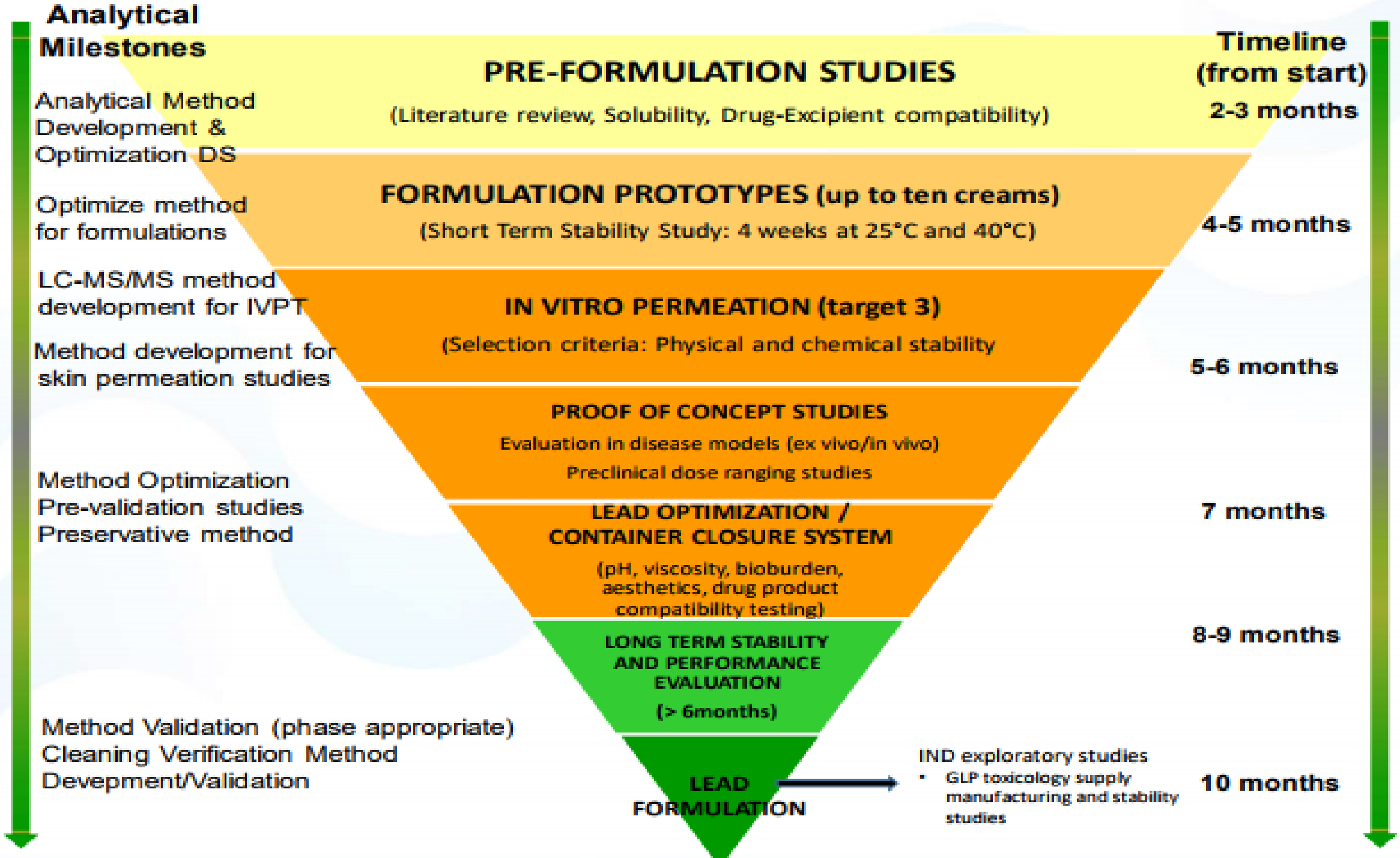
Development Snap Shot

- Skin Biology
  - Early Candidate Selection / Molecule Assessment

- Early Formulation Development
  - Concurrent Analytical Method Development

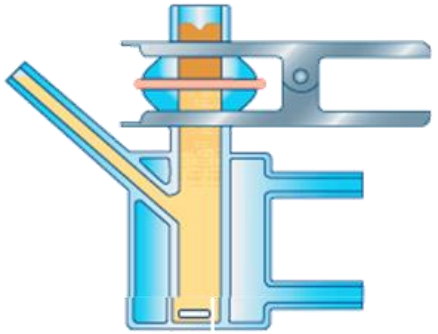
- Skin Permeation (PoC)
  - Other Proofs-of-Concept such as PK/PD assessment, target engagement

- Formulation Optimization
  - Mfg. process Development / Scale Up – Tox Supplies / Clinical Trial Materials
  - QbD / Risk Assessment / IVRT


Analytical Milestones
Timeline (from start)
PRE-FORMULATION STUDIES
(Literature review, Solubility, Drug-Excipient compatibility)
2-3 months
Analytical Method Development & Optimization DS
FORMULATION PROTOTYPES (up to ten creams)
(Short Term Stability Study: 4 weeks at 25°C and 40°C)
4-5 months
Optimize method for formulations
IN VITRO PERMEATION (target 3)
(Selection criteria: Physical and chemical stability
5-6 months
LC-MS/MS method development for IVPT
Method development for skin permeation studies
PROOF OF CONCEPT STUDIES
Evaluation in disease models (ex vivo/in vivo)
Preclinical dose ranging studies
LEAD OPTIMIZATION / CONTAINER CLOSURE SYSTEM
(pH, viscosity, bioburden, aesthetics, drug product compatibility testing)
7 months
Method Optimization
Pre-validation studies
Preservative method
LONG TERM STABILITY AND PERFORMANCE EVALUATION
(> 6months)
8-9 months
Method Validation (phase appropriate)
Cleaning Verification Method Devepment/Validation
LEAD FORMULATION
IND exploratory studies
GLP toxicology supply manufacturing and stability studies
10 months

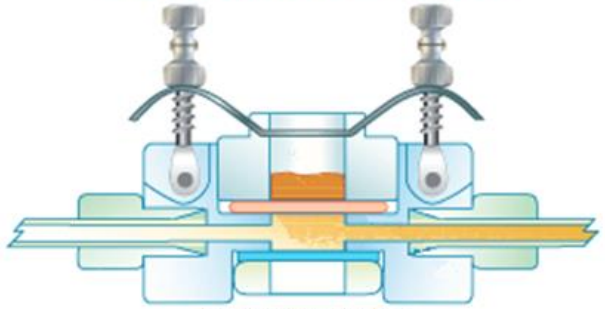
Skin Penetration – Static vs In-Line System

Franz Cells



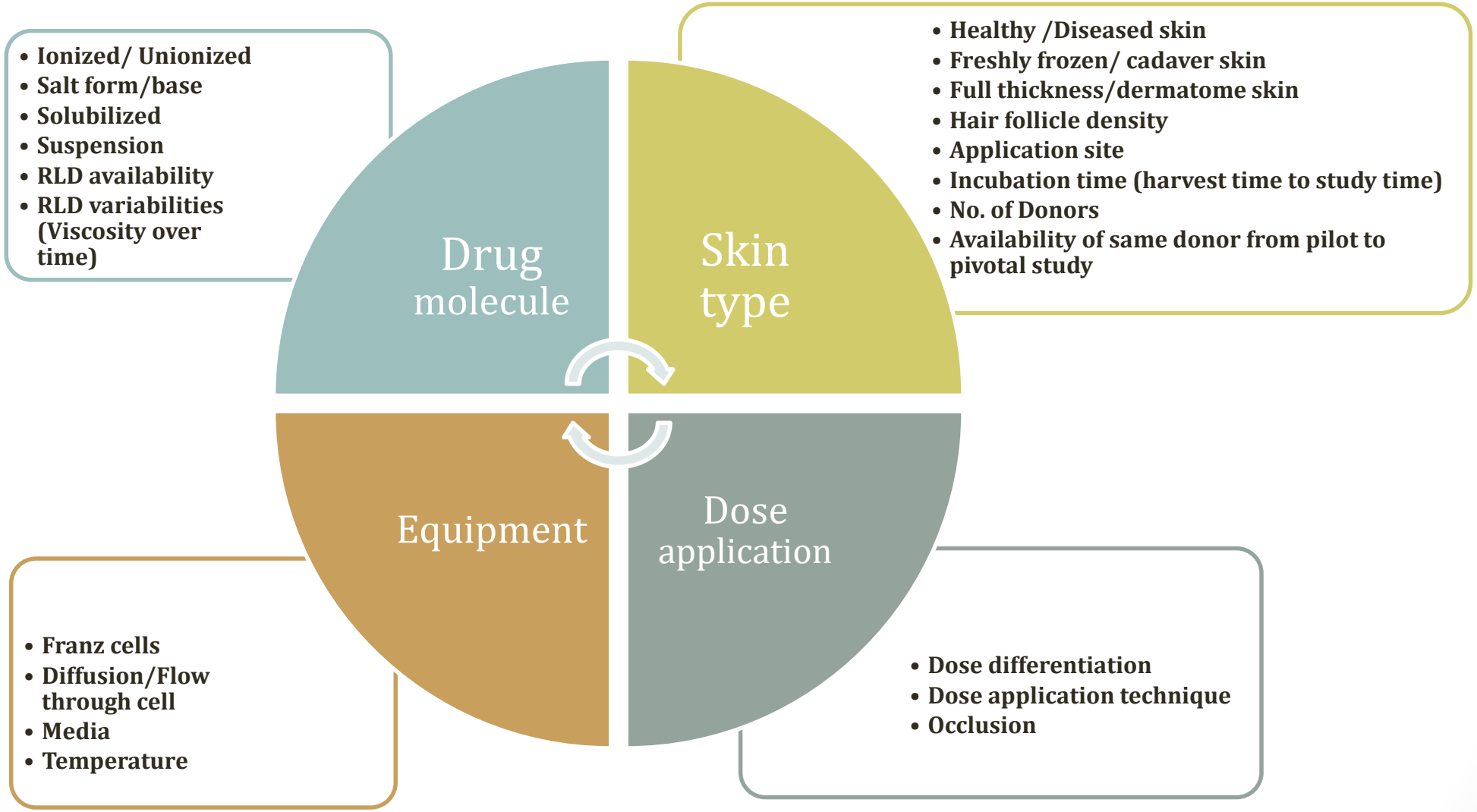
PermeGear, Inc

In-Line (flow through)



PermeGear, Inc

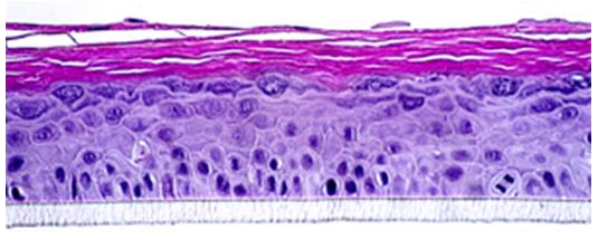
FACTORS TO CONSIDER



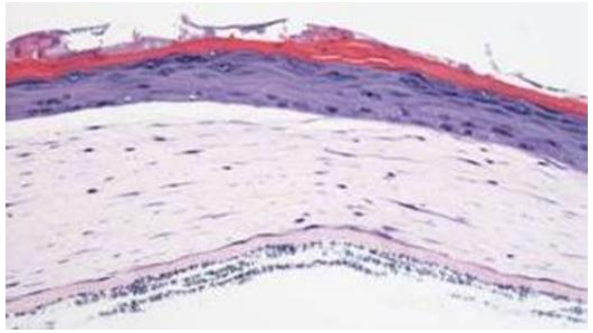
OTHER FACTORS

- Skin sourced from the location of body
- Type of Drug Product i.e., Target Product Profile
- Diseases / Disorder
  - Compromised Skin Barrier
- Variability of the skin / donors
- Quantitative techniques
  - LC-MS
  - Biochemical
  - Functional assay
- Fresh, frozen, flash frozen, freshly excised skin
- Reconstructed Human Epidermis (RHE) *i.e.* differentiated 3D tissue model
- RHE with psoriatic fibroblasts harvested from psoriatic lesions

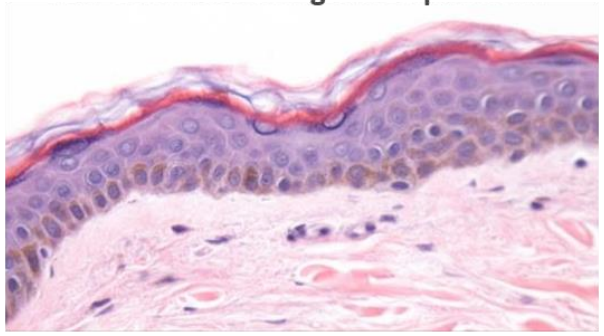
In Vitro & Ex Vivo Skin Models



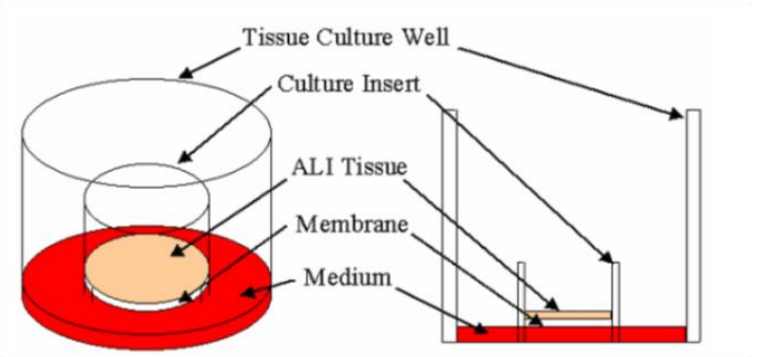
Reconstructed Human Epidermis

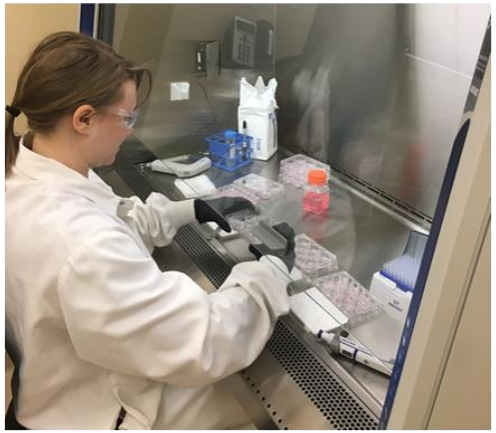


Full Thickness Living Skin Equivalent



Ex Vivo Human Skin Culture





Early Safety Screening
Drug Delivery
Drug Activity/Target Engagement

The Use of IVPT as a Tool in Developing Topical Drug Products

Applications & Case Studies

Applications of IVPT

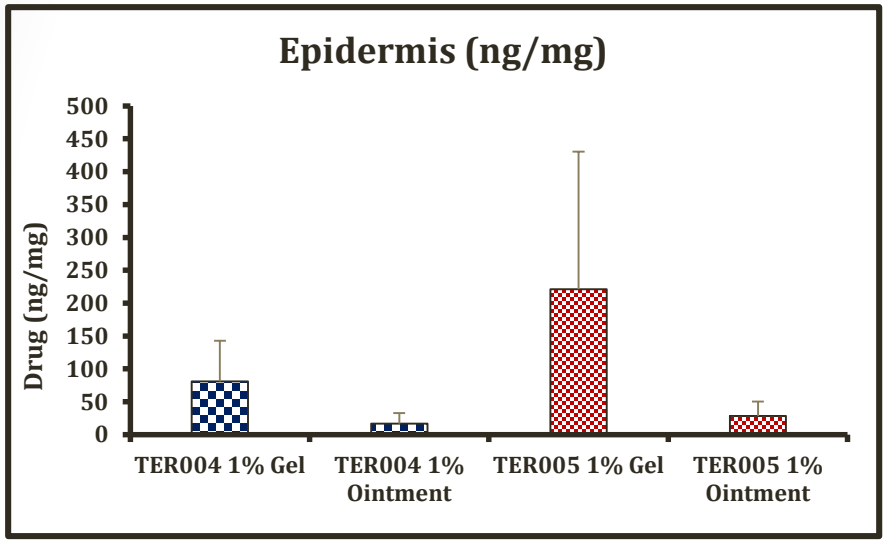
- Screening studies for new molecules
- R&D tool for formulation optimization of
  - Brand formulations
  - Generic – Innovator matching – formulations
- As a Quality-by-Design (QbD) tool
- Regulatory-required BA/BE studies
- Post-approval studies for product claims support
- PLE or Branding Strategy
- New techniques / Membranes comparison (evaluation) studies
- New drug-delivery platform technologies evaluation
- Will IVPT ever be a SUPAC-SS support study?

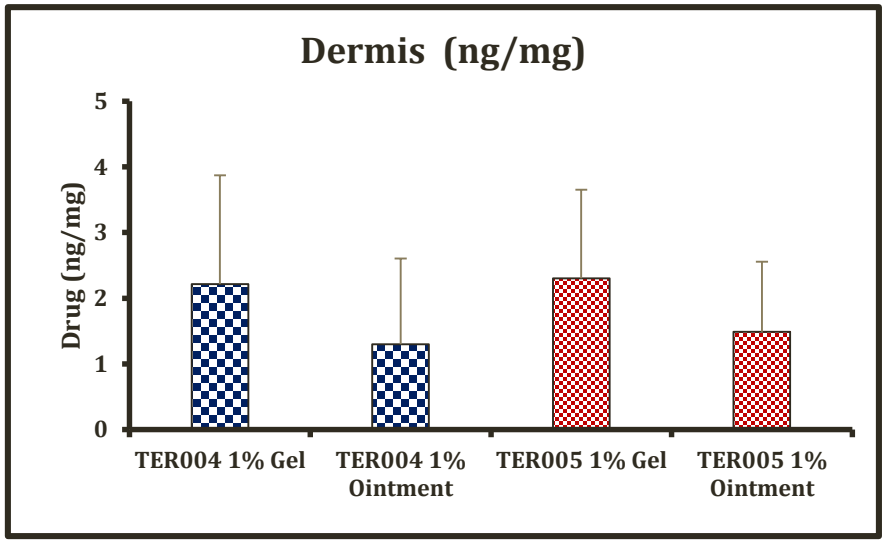
Applications of IVPT

Screening studies for new molecules:

- During the early stages of development
- Permeation should be evaluated in addition to the solubility and stability
- Helps narrow down the choices of molecules -> Lead Selection
- Helps understanding the permeation profiles of other forms and salts of Lead mol.
- A valuable tool when re-purposing or re-positioning a known molecule
- Helps medicinal chemists to modify the drug candidates (SAR)
- A powerful tool when used in conjunction with other *in-vitro* disease models
  - Psoriasis
  - Anti-inflammatory
  - Anti-fungal

Screening studies for new molecules





- Screening conducted on Two protein-tyrosine kinase inhibitors in two different dosage forms (Gel and Ointment) for same indication (TER004 and TER005)
- TER004 Gel, 1.0%w/w had a higher percentage delivery compared to the TER004 Ointment, 1.0%w/w
- TER005 Gel, 1.0%w/w had higher percentage delivery compared to the TER005 Ointment, 1%w/w
- Based on the intent of application, Gel formulations are better than Ointment formulations (Epidermis accumulation – choice of treatment)

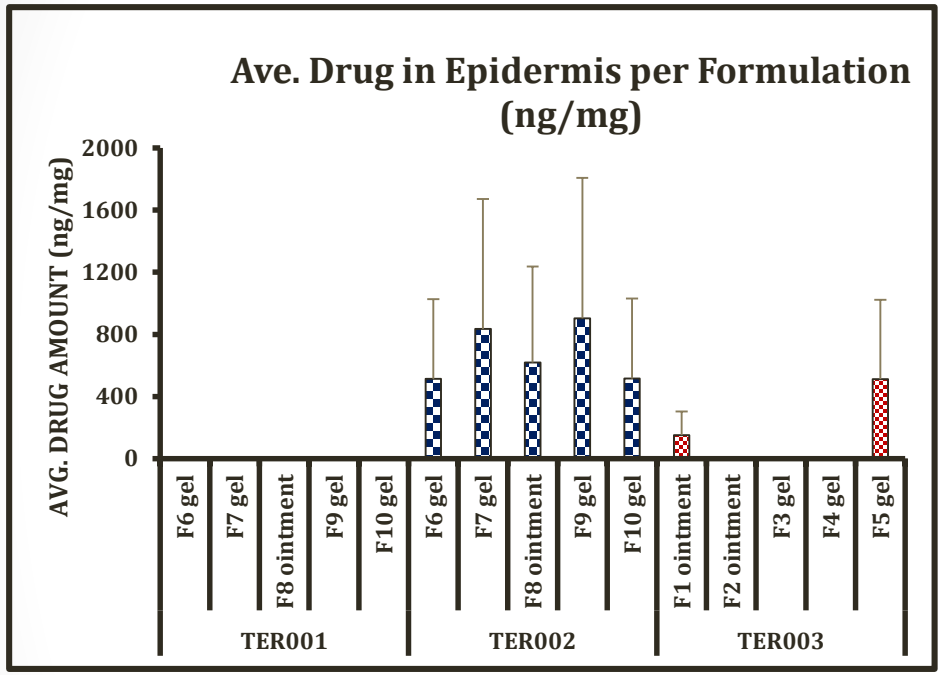
Applications of IVPT

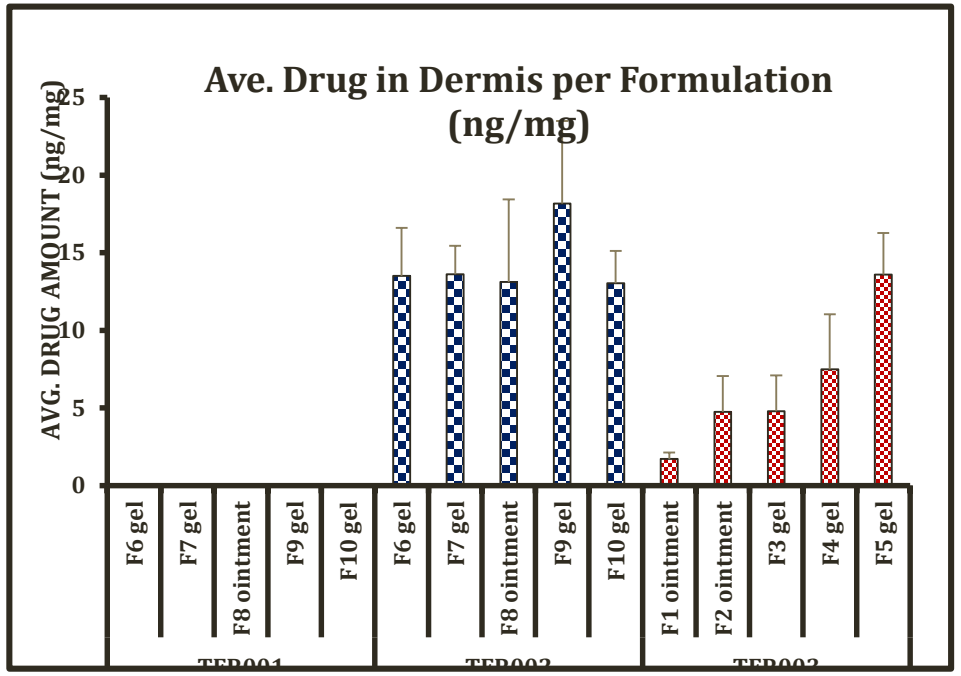
R&D tool for formulation optimization of Brand formulations:

- Helps in selecting a dosage form
- Helps in selecting right vehicle matrix
  - Excipients
  - Gelling agents
  - Chemical Penetration Enhancers (CPE)
  - Solvents, co-solvents
- Helps in understanding selecting the right dose
- Drug particle size *etc.*

Effect of Penetration enhancers

Different Drug Substances in Different Topical Dosage forms



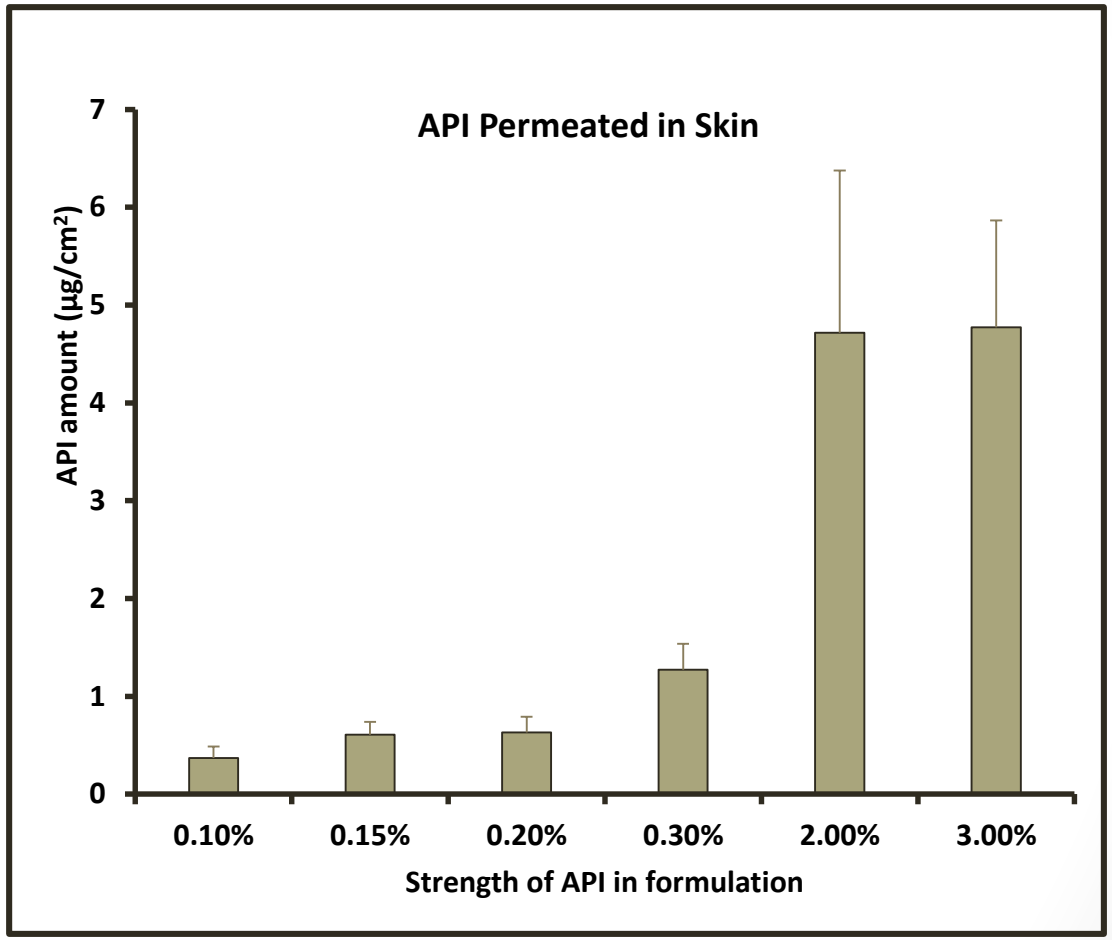


- Three actives (Uracil derivatives- indicated to treat skin cancers) were evaluated in two topical dosage forms (ointment and Gel) with different CPE's
- In this study CPE's (PEG's, Esterified glycols, Fatty acids and Fatty alcohols) significantly increased the permeation in Epidermis and Dermis with no to minimal RCF accumulation in TER002 (F9) /TER003 (F5) formulations respectively.
- With respect to formulation effect a cellulose based gel was found to be better than a PEG based ointment to aid in TER002/3 permeation.

Dose Selection - IVPT as a tool

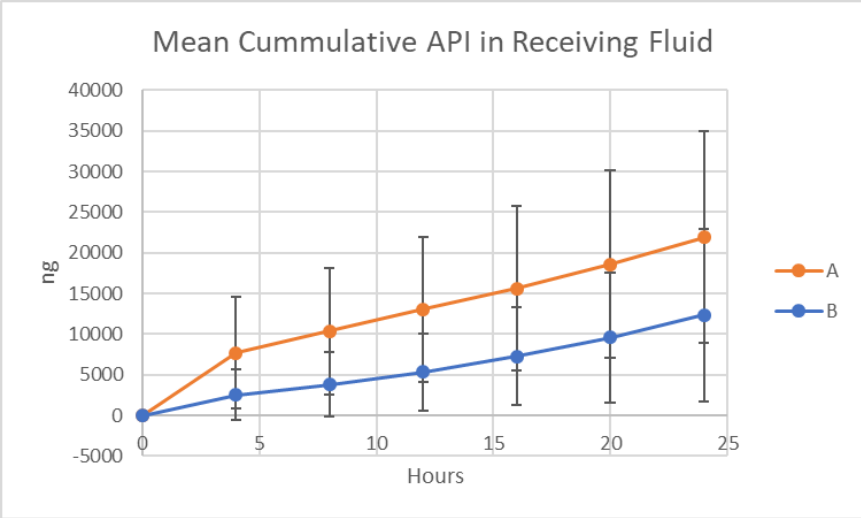
Dose ranging study -IVPT as a screening tool:

- Pharmaceutical maximum feasible conc achieved – 3.0%w/w for a model drug
- Varying %w/w strength of API
  - Manufactured different formulations using qualitative and quantitative similar excipients along with same manufacturing process parameters
- 2% conc was finalized as lead formulation for further CT studies

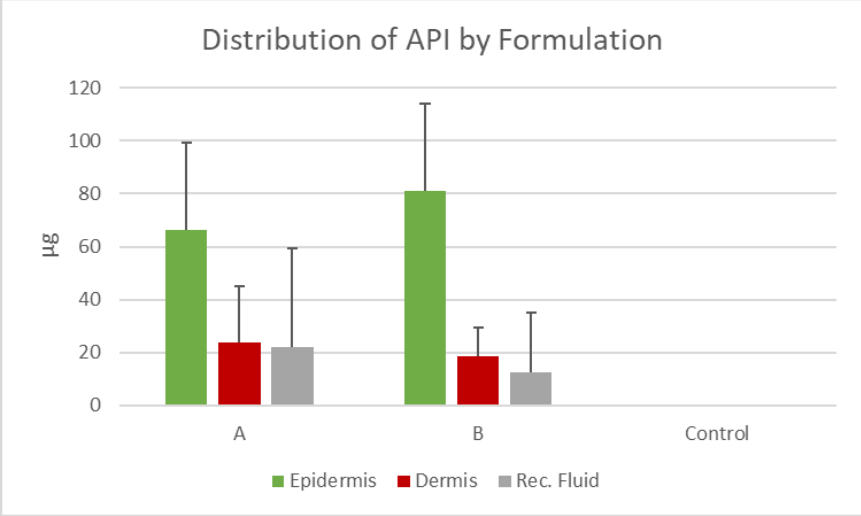


Skin Penetration Testing of two formulations

Skin Permeation



Skin Distribution



Statistical Comparisons Using =T.TEST(set1,set2,2,2) in Excel

T-test Epidermis

Form	Mean µg	St Dev	Comparison	T value	Significant Difference
A	66.43	32.69	A vs B	0.245	No
B	80.92	32.89			

T-test Dermis

Form	Mean µg	St Dev	Comparison	T value	Significant Difference
A	23.86	21.39	A vs B	0.399	No
B	18.49	11.13			

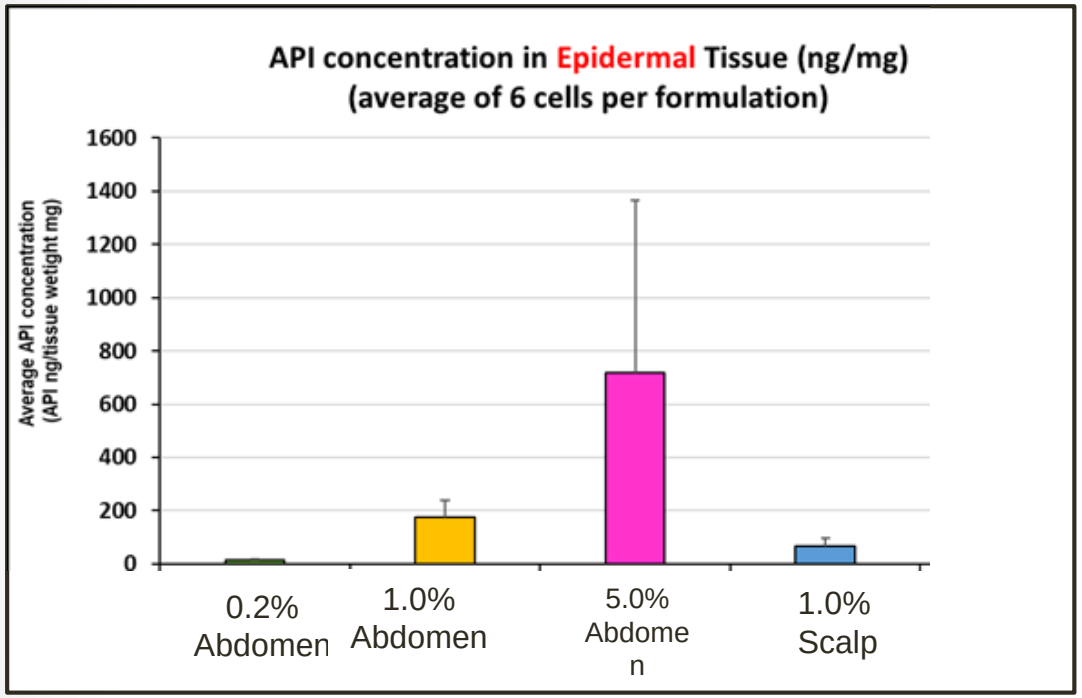
T-test Receiving Fluid

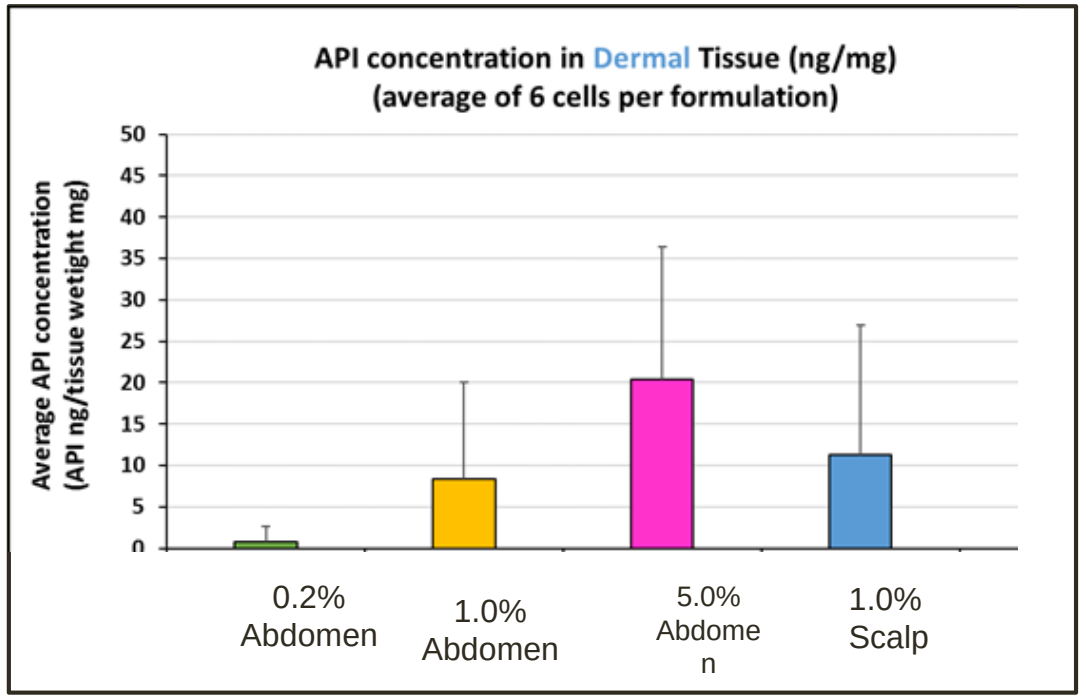
Form	Mean µg	St Dev	Comparison	T value	Significant Difference
A	21.91	37.66	A vs B	0.405	No
B	12.32	22.58			

T-test Total Mass

Form	Mean µg	St Dev	Comparison	T value	Significant Difference
A	117.32	56.92	A vs B	0.752	No
B	111.74	34.05			

Scalp Skin vs Abdomen Skin





- 1% Model drug formulation showed relatively higher permeation profile in Epidermis of Abdomen skin compared to Scalp skin
- Whereas, drug permeation was relatively higher in Dermis of Scalp skin compared to abdomen skin

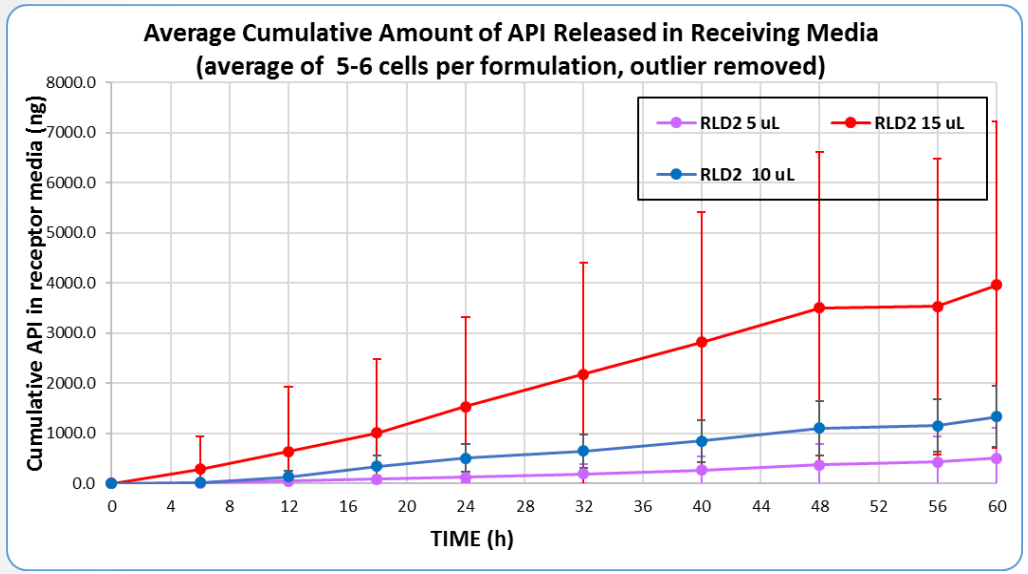
Applications of IVPT

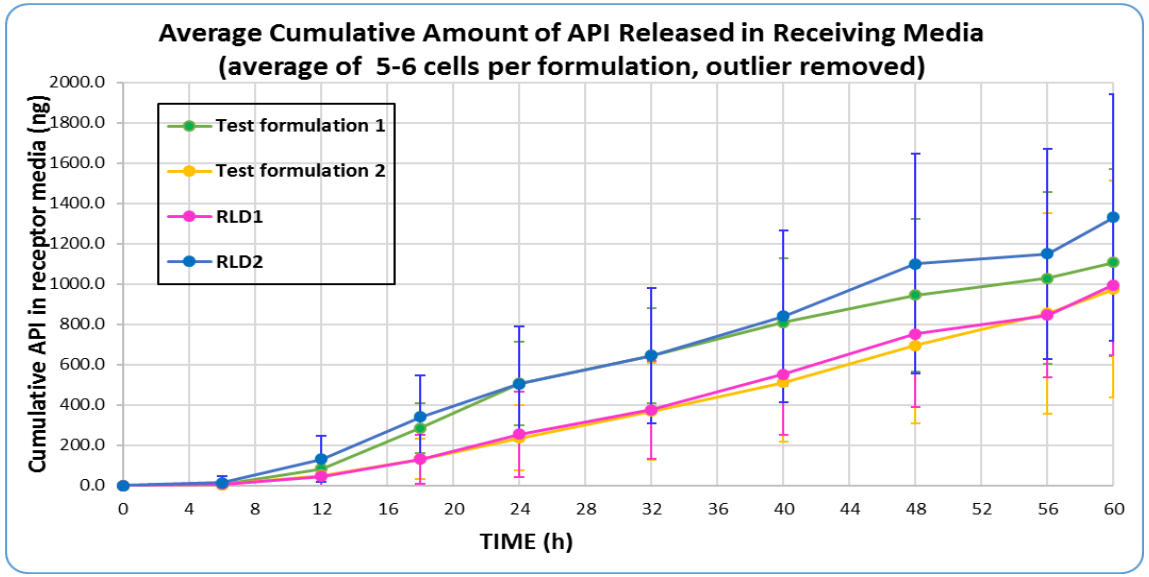
R&D tool for formulation optimization of Generic formulations:

- Generic – Innovator matching – formulations
- As a Quality-by-Design (QbD) tool
- Regulatory-required BA/BE studies

- Comparison of me-too generic equivalent with Reference Listed Drug (RLD)
- Effect of excipient grades
- Effect of excipient concentration
- Effect of Manufacturing process
- Other micro-structure related effects

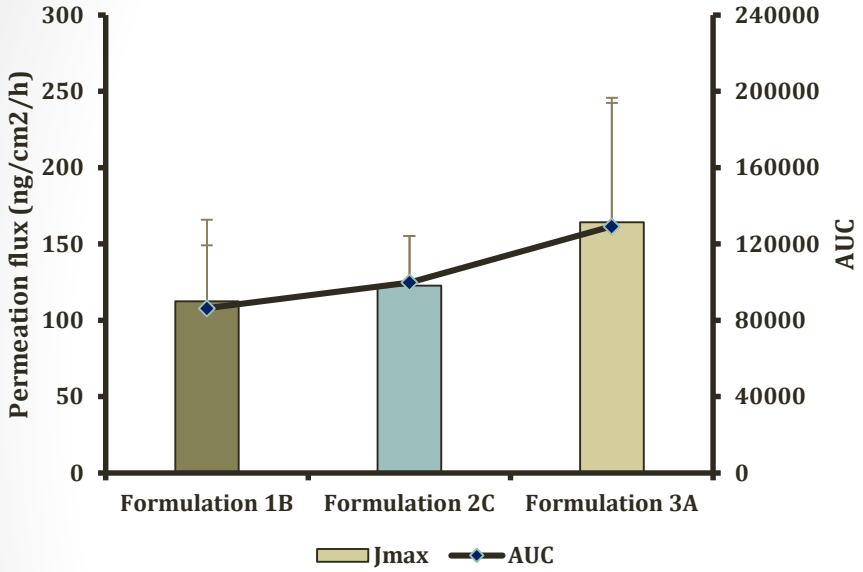
Generic formulation Comparison with Marketed drug product BA/BE Pilot study – Q2 variation

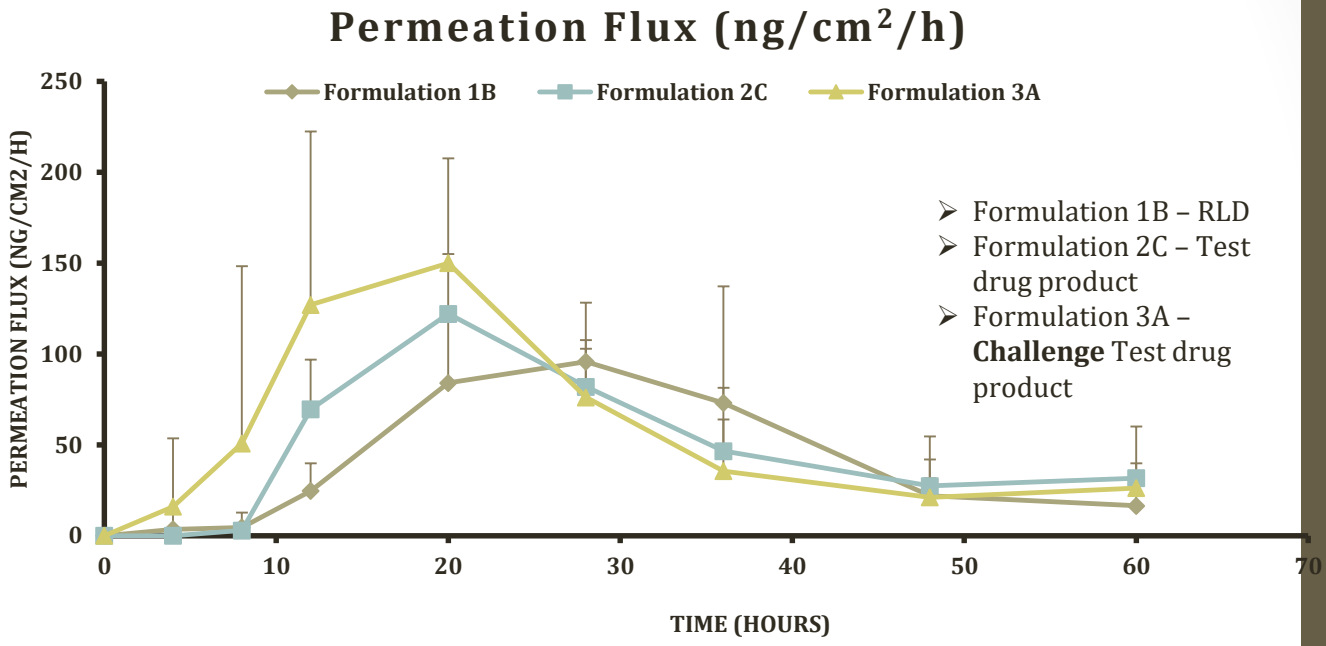




- The pilot study was conducted using two Test drug products and two RLD lots with three different skin donors. Additionally, the discernment of the test was assessed by applying different doses to the skin (Dose Discrimination established).
- Results of the study showed that one of the test lot matched with RLD and met the criteria to be bioequivalent with RLD.
  - The best comparison was found between Test formulation 2 and RLD 1, as %CV was small, and the Test-to-Reference ratios were close to 1 for both J_{max} and AUC.

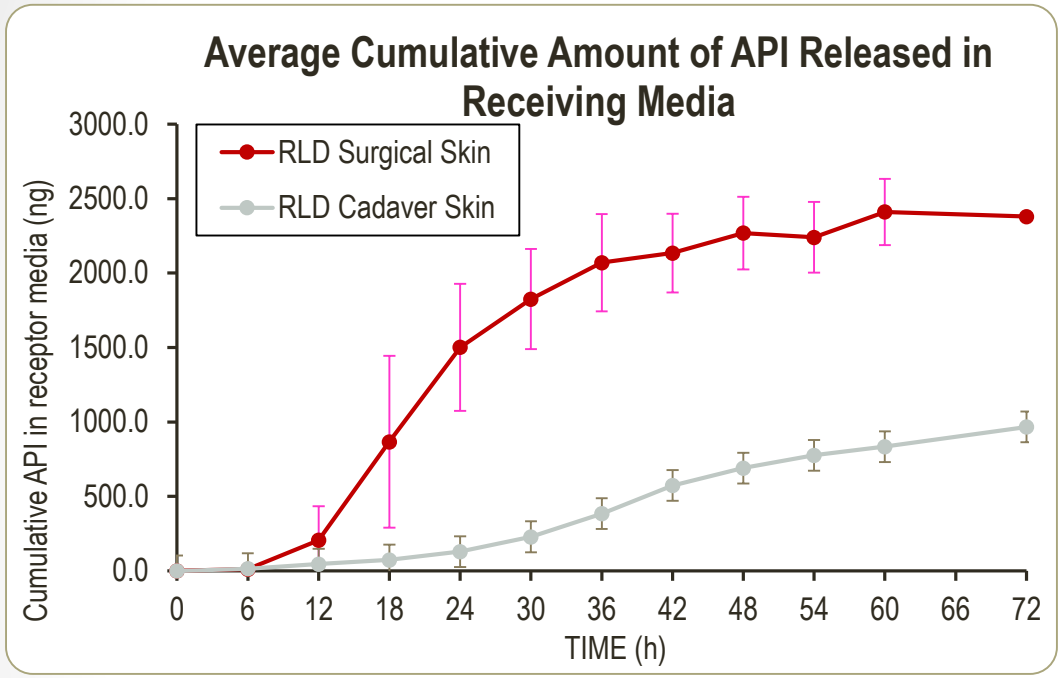
Generic formulation Comparison with Marketed drug product BA/BE Pilot study – Q3 variations

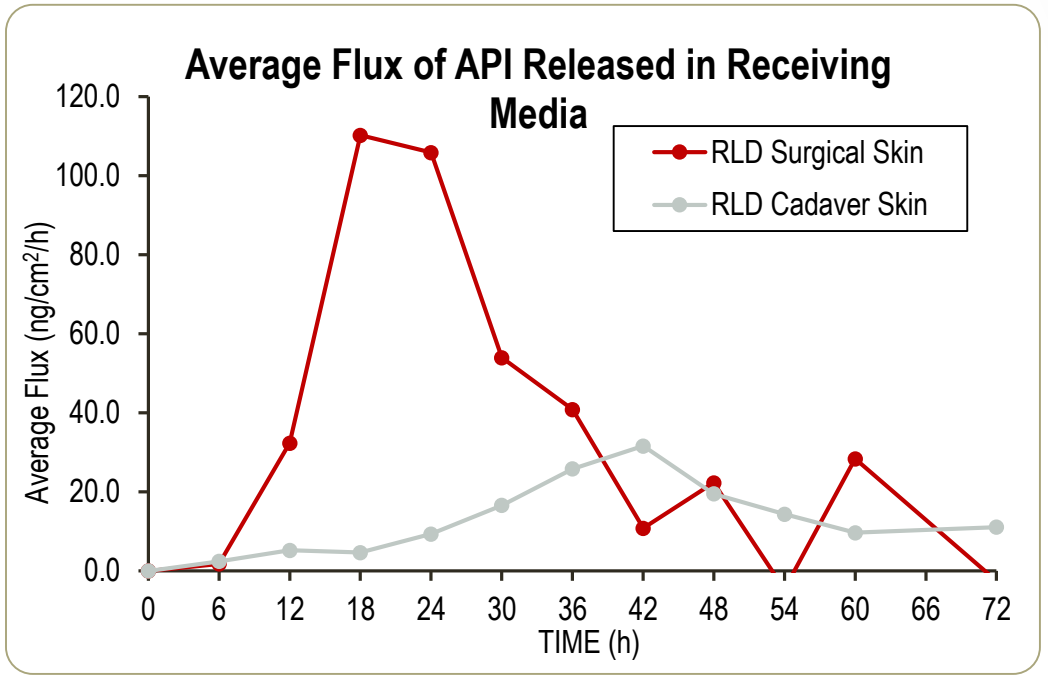




- Results of the study showed that the test drug product matched with RLD and met the criteria to be bioequivalent with RLD.
  - Whereas, Challenged test drug product failed to match RLD and test drug product
  - Flux (J_{max})and AUC for test and RLD found to equivalent

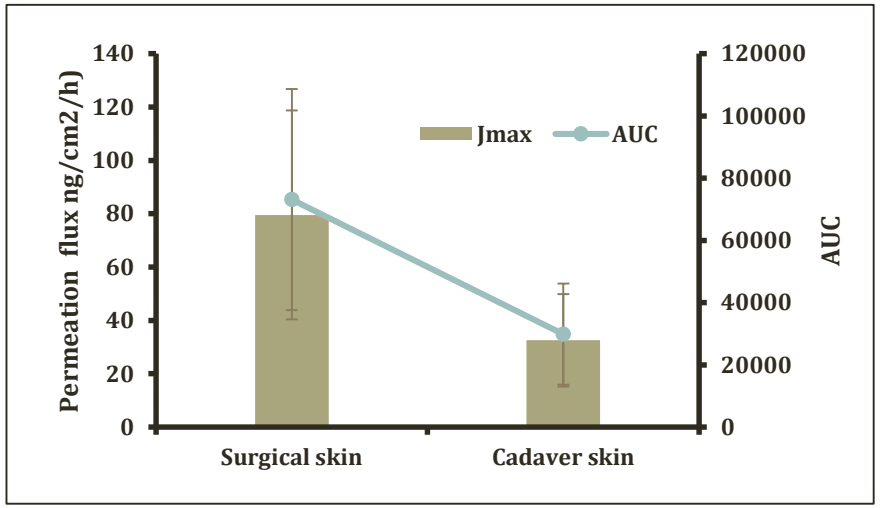
Comparing Human Cadaver vs Fresh Frozen Surgical Skin Using IVPT as a Tool - Case study-1

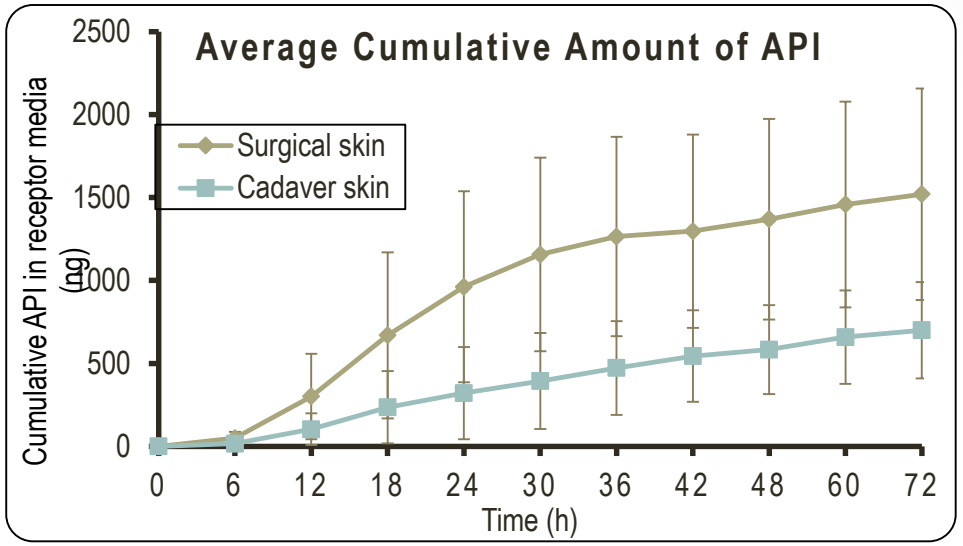


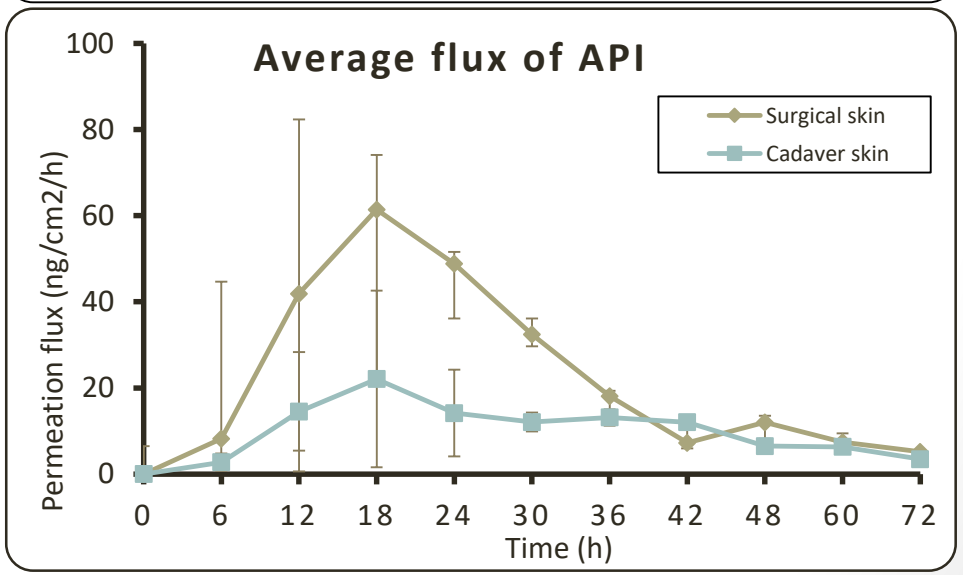


- The mean permeation of Model drug across 3 donors each of Cadaver skin and Ex Vivo Surgical skin that was processed within hours of harvest and frozen is shown above
- Results from this study proves fresh frozen surgical skin showed better permeation profiles than cadaver skin

Comparing Human Cadaver vs Fresh Frozen Surgical Skin Using IVPT as a Tool - Case study-2







- The mean permeation of Model drug across 2 donors each of Cadaver skin and Ex Vivo Surgical skin that was processed within hours of harvest and frozen is shown in this slide

- Results from this study proves fresh frozen surgical skin showed better permeation profiles than cadaver skin

Applications of IVPT

As a Quality-by-Design (QbD) tool

- Critical Material Attributes (CMAs)
- Critical Process Parameters (CPPs)

- Using DoE approach, one can understand the formulation's behavior towards various influences much early on in development
- While other tests such as IVRT, Viscosity and Rheology are more helpful as Critical Quality Attributes (CQAs), IVPT is also a helpful tool
- Sometimes, it can help bridge the ongoing clinical formulation's changes

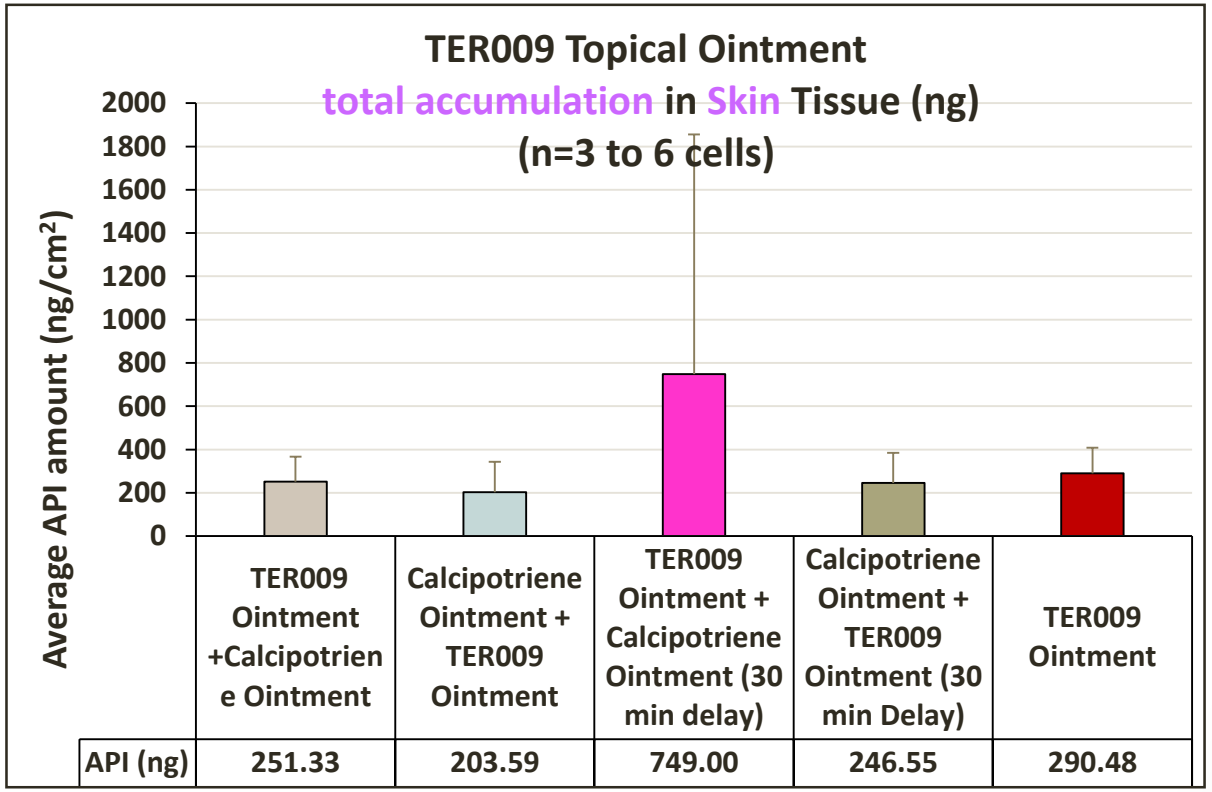
Applications of IVPT

Post-approval studies for product claims support

- Supports product's marketing claims
- Compares similarly marketed products
- Competitive comparison
- IP defense strategy
- IP claims support
- Helps in evaluating the impact of co-administered products

Marketed Drug Product Assessment – IVPT

- Four application schemes to determine the effect of simultaneously application of TER-009 topical ointment and marketed Calcipotriene ointment



Inference:

- There was a difference found between the "TER-009 Topical Ointment with Calcipotriene Ointment immediate application" vs. "TER-009 Topical Ointment with delayed Calcipotriene application"

Applications of IVPT

PLE or Branding Strategy

- Product Line Extensions (PLEs) can be developed using IVPT
- Helps in developing a me-too brands
- A useful tool in comparing a same Drug Class compounds with similar mechanism of action

Applications of IVPT

New techniques / Membranes comparison (evaluation) studies

- Excipients & Polymers
  - BASF
  - Gattefosse
  - Croda
  - Seppic
- Novel Skins
  - EpiSkin (pigmented, full thickness)
  - L'Oreal - Organovo 3-D Printing of human skin
- Pkg. innovations
  - Dual Chambers, novel applicators

Applications of IVPT

New drug-delivery platform technologies evaluation

- Platform Technologies
- Deuterated NCEs - **Deuterium Chemistry**
- Liquidia – PRINT Technology
- Confluence
- Botanix – Permetrex Technology
- Cage Bio – Ionic Liquids
- Leon Nanodrugs – Nano Technology
- Exicure – 3-D Spherical Nucleic Acid (SNA) Architecture
- Gold Nanoparticles
- Solid Lipid Nanoparticles (SLN)

Applications of IVPT

Will IVPT ever be a SUPAC-SS support study?

- With the advent of BA/BE Waiver approach using IVPT, it is possible to use this technique to approve product changes (post-approval) without the need for additional clinical studies.

Final Note on Delivery Kinetics

- Target Product Profile (TPP) may also shed some light on what is the ideal delivery profile
- Delivery to Stratum Corneum vs. Dermis dictates the selection of right formulation
- Need for a drug to stay in dermis vs. transdermal delivery into systemic circulation drives the choice of excipients
- Targeted delivery for pharmacological action
- Choose the right type of substrate
- Decide whether it is an R&D tool or for PoC or for regulatory approval
- Understand the product before venturing into IVPT evaluations

Begin with end in mind®

Acknowledgements

- Lynn Garcowski
- Brandon Holland
- Srikanth Manne
- Alon Mantel
- Purnendu Sharma
- Bethany Stewart
- JP Therrien

Tergus Pharma
Think Topicals, Think Tergus

Tergus Pharma is your one-stop-shop for concept to clinical topical formulation development.

Learn more about Tergus Pharma's capability and to schedule a teleconference please visit **TergusPharam.com »** .

The equation is simple: The Art + Science of Topicals = Tergus

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- Regulatory Support
- Preclinical Toxicology Support
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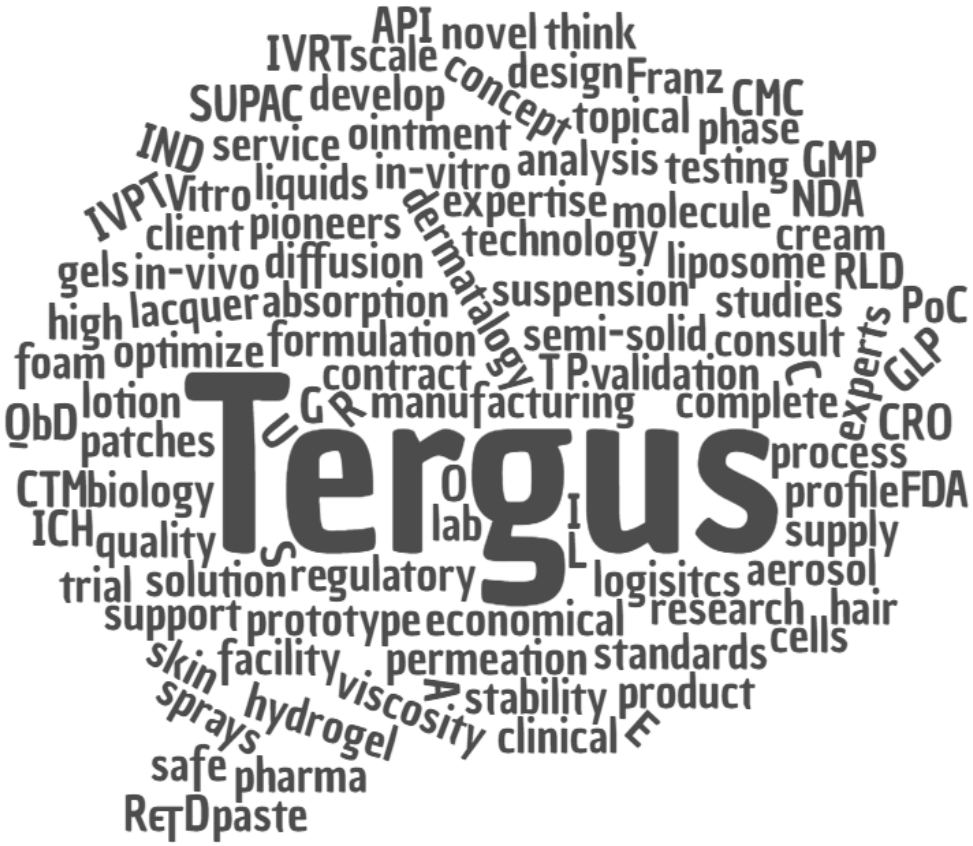

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