U.S. FOOD & DRUG ADMINISTRATION

FDA and Dermatology -

Topical Drug Products:

New Paradigm for Generics

IDEOM 2021

November 19, 2021

Markham C. Luke, MD PhD FAAD
Director, Division of Therapeutic Performance 1
Office of Research and Standards, OGD

Disclaimer

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

FDA – Most Relevant Centers for Dermatology

- **Center for Drug Evaluation and Research (CDER)**
  - **Office of New Drugs (OND)**
  - **Office of Generic Drugs (OGD)**
- **Center for Devices and Radiological Health (CDRH)**
- **Center for Biologics Evaluation and Research (CBER)**
- **Center for Food Science and Nutrition (CFSAN)**
  - **Office of Cosmetics and Colors**

New Dermatology Drug Approvals – 2020-2021 (Dermatology Division, OND)

- Xeglyze (abametapir) – For head lice infestations in patients 6 months of age and older
- Winlevi (clascoterone) – For the treatment of mild to moderate acne
- Rituxan (rituximab) – New indication for pemphigus vulgaris
- Dupixent (dupilumab) – Indication extended to patients 6 years of age and older
- Korsuva (difelikefalin) – For the treatment of moderate to severe chronic kidney disease associated pruritis (CKD-AP)

Korsuva (difelikefalin) Solution

- First-in-class approval of a kappa opioid agonist
  - No binding at mu receptors, the main target of opioid analgeisics
- First approval for treatment of CKD-AP.
- Physicochemical properties selected to prevent/minimize CNS penetration
  - Supported by in vitro and in vivo non-clinical studies

Korsuva (Difelikefalin) Efficacy

	Trial CLIN3102		Trial CLIN3103	
	Difelikefalin (N=189)	Placebo (N=189)	Difelikefalin (N=237)	Placebo (N=236)
≥3-point Improvement in WI-NRS				
Proportion	52%	31%	49%	38%
Difference (95% CI)	22% (12%, 32%)		11% (1%, 20%)	
Adjusted Proportion[3]	51%	28%	54%	42%
Odds Ratio (95% CI)[3]	2.7 (1.7, 4.3)		1.6 (1.1, 2.4)	
P-value[3]	<0.001		0.020	
≥4-point Improvement in WI-NRS				
Proportion	40%	21%	37%	26%
Difference (95% CI)	19% (9%, 28%)		12% (3%, 20%)	
Adjusted Proportion[3]	39%	18%	41%	28%
Odds Ratio (95% CI)[3]	2.9 (1.8, 4.8)		1.8 (1.1, 2.7)	
P-value[3]	<0.001		0.010	

[1] Intent-to-Treat (ITT) population: all randomized subjects. Missing data were imputed using multiple imputation (MI).

[2] Average over the 20 imputed datasets.

[3] LS mean, difference (95% CI), and p-value are based on ANCOVA with treatment, baseline score, region (only Trial CLIN3103), prior use of anti-itch medication (yes/no), and presence of specific medical condition (yes/no) as factors in the model.

[4] The SAP specified a sequential gatekeeping approach to control the Type I error rate. For Trial CLIN3103, the SAP specified testing change from baseline in Skindex-10 total score at Week 12 before testing change from baseline in 5-D total score at Week 12.

Source: Statistical Reviewer's Analysis (same results as Applicant's Analysis); ADFIVDMI.xpt, ADSKINMI.xpt

Korsuva (difelikefalin) Safety

Table 2: Adverse Reactions in ≥ 2% of KORSUVA-Treated Subjects with Moderate-to-Severe CKD-aP Undergoing HD and ≥ 1% Higher Than Placebo in Trials 1 and 2

Adverse Reactions	Placebo (N=424) n (%)	KORSUVA (N=424) n (%)
Diarrhea	24 (5.7)	38 (9.0)
Dizziness	16 (3.8)	29 (6.8)
Nausea	19 (4.5)	28 (6.6)
Gait Disturbances[a]	23 (5.4)	28 (6.6)
Hyperkalemia	15 (3.5)	20 (4.7)
Headache	11 (2.6)	19 (4.5)
Somnolence	10 (2.4)	18 (4.2)
Mental Status Change[b]	6 (1.4)	14 (3.3)

[a] Gait disturbances includes: preferred terms of falls and gait disturbances

[b] Mental Status Change includes: preferred terms of confusional state and mental status change.

Generic Drugs

- Why are generic drugs important to dermatology patients?
- What are specific considerations for “topical drugs” that are applied to the skin?

Patient Access to Generic Drugs

- Generic drugs must demonstrate bioequivalence (BE)
  - Per 21 CFR 314.3: *BE is the absence of a significant difference in the **rate and extent to which the active ingredient** or active moiety in pharmaceutical equivalents or pharmaceutical alternatives **becomes available at the site of drug action** when administered at the same molar dose under similar conditions in an appropriately designed study.*
- For systemically acting drug products, it is **efficient** to demonstrate BE by pharmacokinetics (PK) based studies
- For locally acting drug products, it has been **challenging** to directly assess the rate and extent to which the active ingredient becomes available at the site of action

Generic Drug Access

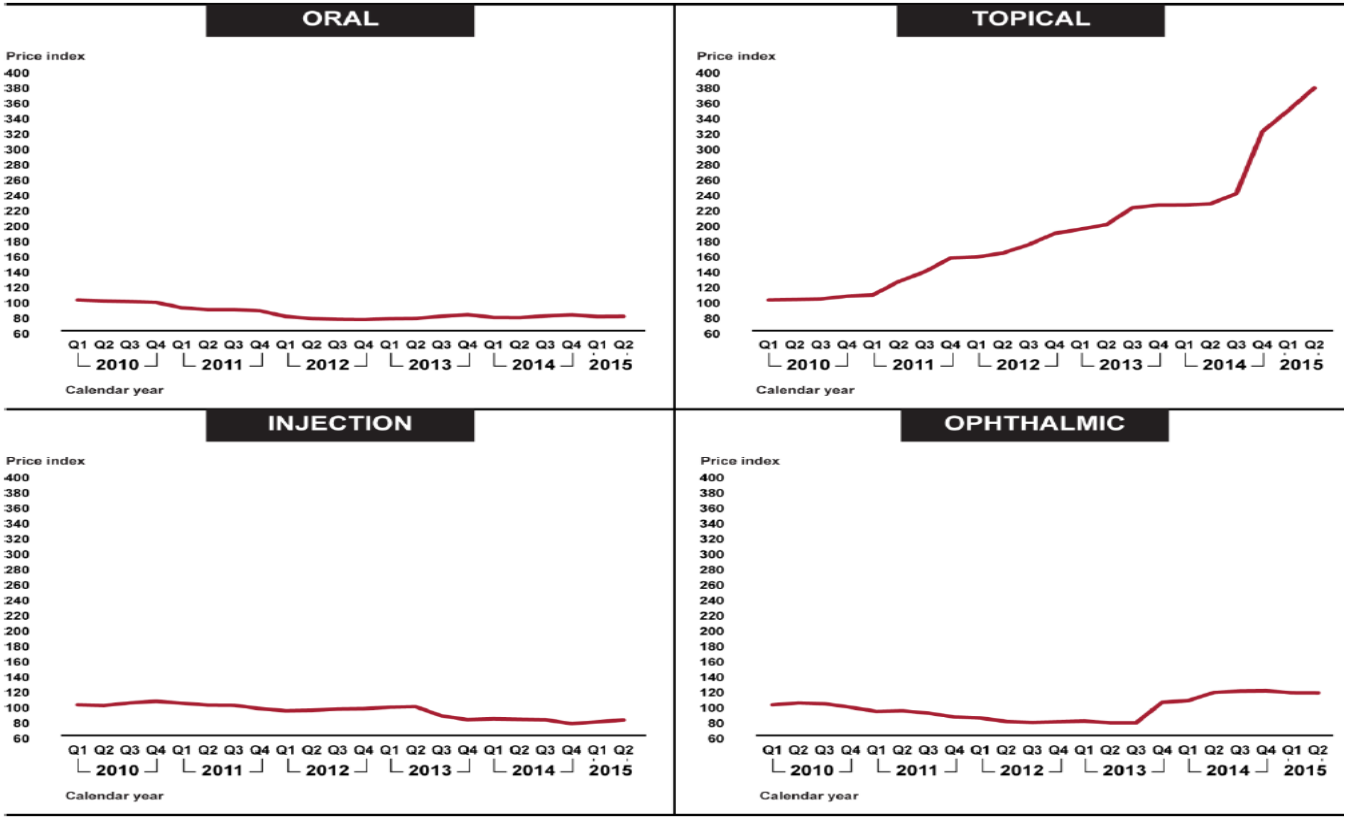
- The Association for Accessible Medicines (AAM) 2017[1] and 2020[2] Generic Drug Access & Savings Reports have documented the ***overall*** success of generic drugs
- **90%** of the of the prescriptions filled in the U.S. during 2019 were dispensed as generics, up from 89% in 2016
- **95%** of generic prescriptions were filled at ≤ $20, up from 90% in 2016; the average generic copay in 2019 was **$6.97**
- ***Overall***, this represented **exceptional patient access** to high quality, safe, effective, affordable medicines, even in 2016

[1] AAM Report: 2017 Generic Drug Access & Savings in the U.S. (https://accessiblemeds.org)
[2] AAM Report: 2020 Generic Drug & Biosimilars Access & Savings in the U.S. (https://accessiblemeds.org)

The GAO Report

- The U.S. Government Accountability Office (GAO) Report (GAO-16-706; August 2016) had analyzed a period spanning Quarter 1 of 2010 through Quarter 2 of 2015
- **57%** of the topical drug products experienced an extraordinary price increase in that period
- The average price of topical generic drugs was **276% higher** by the end of the period analyzed
- Manufacturers and other stakeholders reported that market **competition**, influenced by various factors, drives generic drug prices

The GAO Report (GAO-16-706)



Source: GAO analysis of Medicare Part D prescription drug event data. | GAO-16-706

Retail Prices for Topical Products

Drug	Type	Price, US $ 2009	2011	2014	2015	Absolute Change, 2009-2015	% Change, 2009-2015
Altabax, 15 g	I	92.50	106.18	168.75	196.86	104.36	112.82
Benzaclin, 50 g	A	166.79	205.80	451.29	503.85	337.06	202.08
Carac cream, 30 g	N	159.40	227.16	2939.68	2864.70	2705.30	1697.18
Clobex spray, 4 oz	S	389.57	500.29	827.11	958.01	568.44	145.91
Cloderm cream, 30 g	S	96.47	132.92	220.75	360.02	263.55	273.19
Cutivate lotion 120 mL	S	305.00	493.92	918.63	1067.25	762.25	249.91
Derma-Smoothe FS oil, 4 oz	S	45.70	47.23	247.84	322.67	276.97	606.06
Finacea, 50 g	A	124.42	185.42	288.92	284.30	159.88	128.51
Olux-E foam, 100 g	S	307.58	382.79	750.79	841.76	534.18	173.67
Oracea, 40 mg (30 tablets)	A	439.01	416.09	632.80	702.46	263.45	60.01
Oxistat cream, 30 g	I	76.50	119.25	399.00	544.66	468.16	611.97
Oxsoralen-Ultra, 10 mg (50 capsules)	P	1227.32	2150.49	4568.54	5204.31	3976.99	324.04
Retin-A Micro, 0.1%, 50 g	A	178.05	335.73	791.47	914.52	736.47	413.64
Solaraze gel, 100 g	N	442.89	618.56	1738.91	1883.98	1441.09	325.38
Soriatane, 25 mg (30 capsules)	P	757.75	958.50	1452.50	1595.27	837.52	110.53
Taclonex, 60 g	P	465.99	522.58	848.21	962.90	496.91	106.64
Targretin gel, one 60-g tube	N	1686.78	1787.97	15 708.40	30 320.12	28 633.34	1697.51
Tazorac cream, 0.1%, 60 g	A	266.18	464.96	656.20	722.27	456.09	171.34
Xolegel, 30 g	I	212.50	278.00	389.25	641.96	429.46	202.10

Abbreviations: A, acne and rosacea; I, antiinfective; N, antineoplastic; P, psoriasis; S, corticosteroid.

Source: Miranda E. Rosenberg, BA and Steven P. Rosenberg, MD (2016) *Changes in Retail Prices of Prescription Dermatologic Drugs From 2009 to 2015*. JAMA Dermatology. 152(2):158-163. doi:10.1001/jamadermatol.2015.3897

Patient Access to Topical Products

- Most topical dermatological drug products had fewer than three generic competitors; for many products no generics were available at all
- This may have been attributable to the historical challenges impacting the development of topical dermatological generic drug products, possibly including
  - Absence of efficient PK-based approaches by which to demonstrate BE
  - Inefficiency of high risk, costly, comparative clinical endpoint BE studies
  - The complex nature of topical formulations
- FDA conducts research to develop more efficient ways to demonstrate BE for complex generics, including topicals

Concept of BE for Topical Products

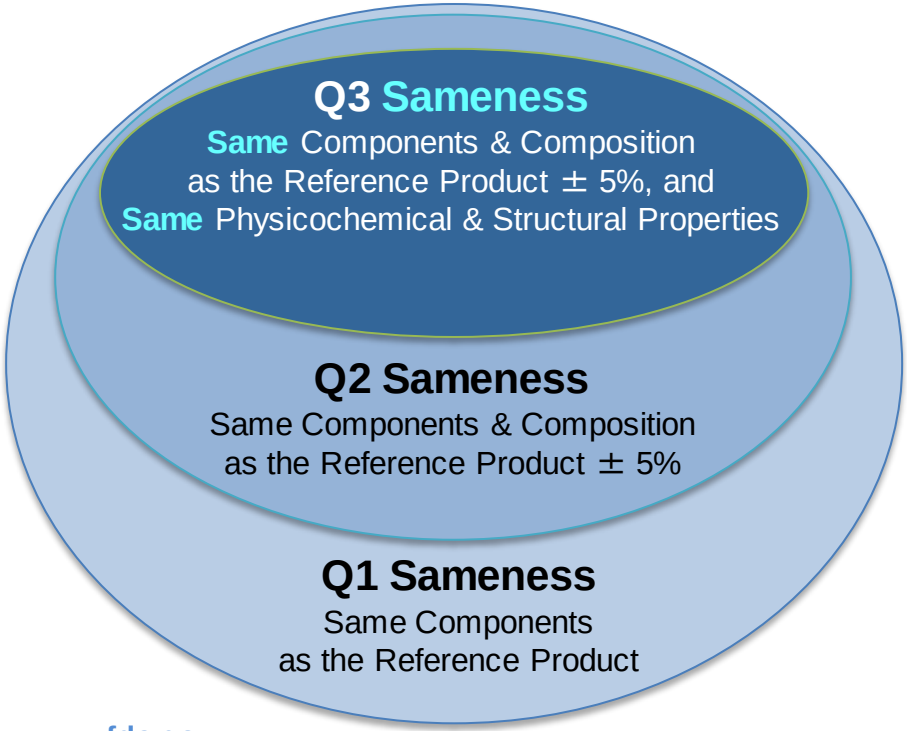
- **In Vitro** Methods to Support a Demonstration of BE
  - **Qualitative (Q1) and Quantitative (Q2)** Sameness or '*No Difference*'
  - **Physicochemical and Structural (Q3)** Sameness/Similarity
  - **IVRT** (In Vitro Release Test)
  - **IVPT** (In Vitro Permeation Test)
- **In Vivo/In Silico** Methods to Support a Demonstration of BE
  - **In Vivo Pharmacokinetic (PK)** Studies
  - **In Vivo Pharmacodynamic** (Vasoconstrictor) Studies
  - **In Vivo Comparative Clinical Endpoint BE** Studies
  - **In Silico** Quantitative Methods, Modeling and Simulation

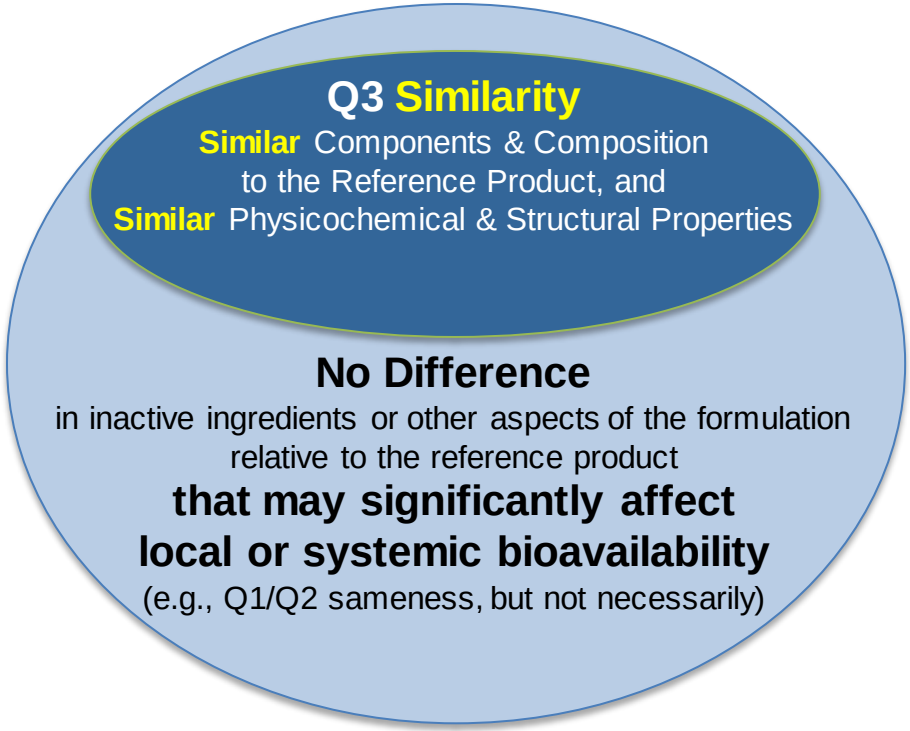
Topical Dermatological Formulations

- The components (Q1) and quantitative composition (Q2) of a topical product (and how it is manufactured) can modulate its physical and structural arrangement of matter (Q3)
- These Q3 characteristics influence molecular interactions that control the rate and extent of topical bioavailability
- One approach to developing generic topical products is to:
  - Characterize the complexity of the reference product
  - Match the Q1, Q2, and Q3 characteristics of the reference product

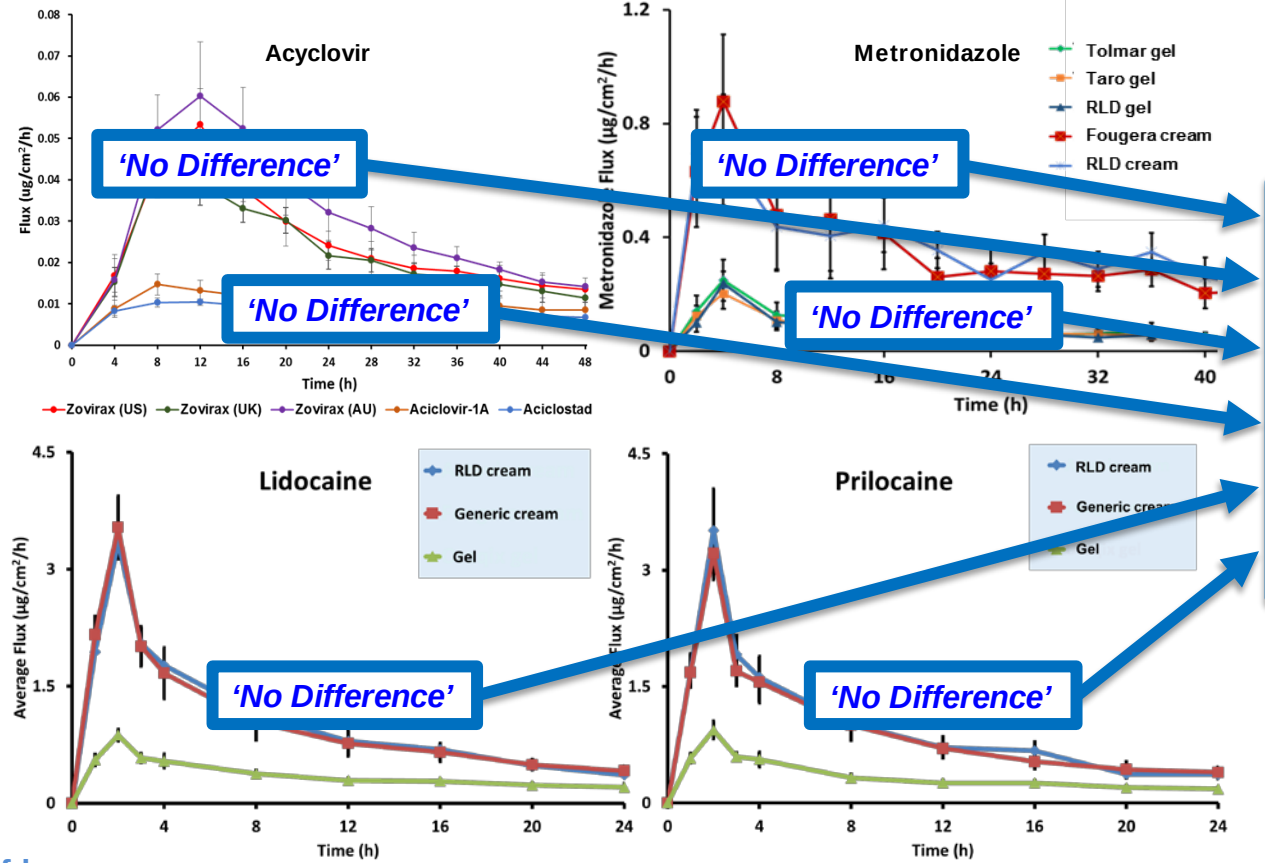
Q3 Sameness vs. Similarity

- An evolving concept *for topical dermatological products*





Q1/Q2 Sameness vs. 'No Difference'



Not necessarily
Q1 & Q2 the same

~

No significant impact on bioavailability

Data provided courtesy of Prof. Narasimha Murthy (University of Mississippi) ***FDA Award U01-FD005223***

Q1/Q2 Sameness vs. 'No Difference'

- Determining the suitability of proposed test product formulations to demonstrate BE by a characterization-based approach:
  - An assessment of 'No Difference' in formulation is based upon the same principles as assessing Q1/Q2 sameness, including tolerances of ±5%
  - An assessment of 'No Difference' for topical dermatological products evaluates whether certain components and compositions may be acceptable for a proposed generic product, based upon:
    - Information available to the Agency and/or
    - Evidence submitted in an abbreviated new drug application (ANDA)

      i.e., evidence that there is no difference between the test and reference products in the local or systemic availability of the active ingredient

Physicochemical Characterization

Physicochemical and structural (Q3) characterizations describe the essential properties of the product which may be critical to its performance.

- Q3 characteristics collectively represent the arrangement of matter in the dosage form
- Q3 characteristics may potentially be critical to product performance under relevant conditions

Comparative Q3 characterization between a test & reference topical dermatological product is critical

- to demonstrate that a test product and its reference product are the same dosage form
- to evaluate whether there are Q3 differences between the test and reference products that may affect BE.

Totality of Q3 characterization is critical to compare test and reference topical dermatological products.

Q3 Characterization in a Topical Dermatological Product ANDA

General recommendations on the characterizations:

1. Characterization of appearance and texture

2. Characterization of phase states – to support the drug is dissolved in the dosage form, and/or single-phase dosage form (as relevant)

3. Characterization of structural organization of matter – to assess particle size distribution and crystal habit, and/or emulsion globule size distribution (as relevant)

4. Characterization of polymorphic form(s) of the active ingredient(s)

5. Characterization of rheological behavior

- Complete flow curves (plotted as both, shear stress vs. shear rate and viscosity vs. shear rate) should consist of multiple data points across the range of attainable shear rates, typically until low or high shear plateaus are identified;
- Yield stress values should be reported if the material tested exhibits plastic flow behavior; and
- The linear viscoelastic response (storage and loss modulus vs. frequency) should be measured and reported.

Q3 Characterization in a Topical Dermatological Product ANDA

General recommendations on the characterizations –continued

6. Characterization of water activity and/or drying rate

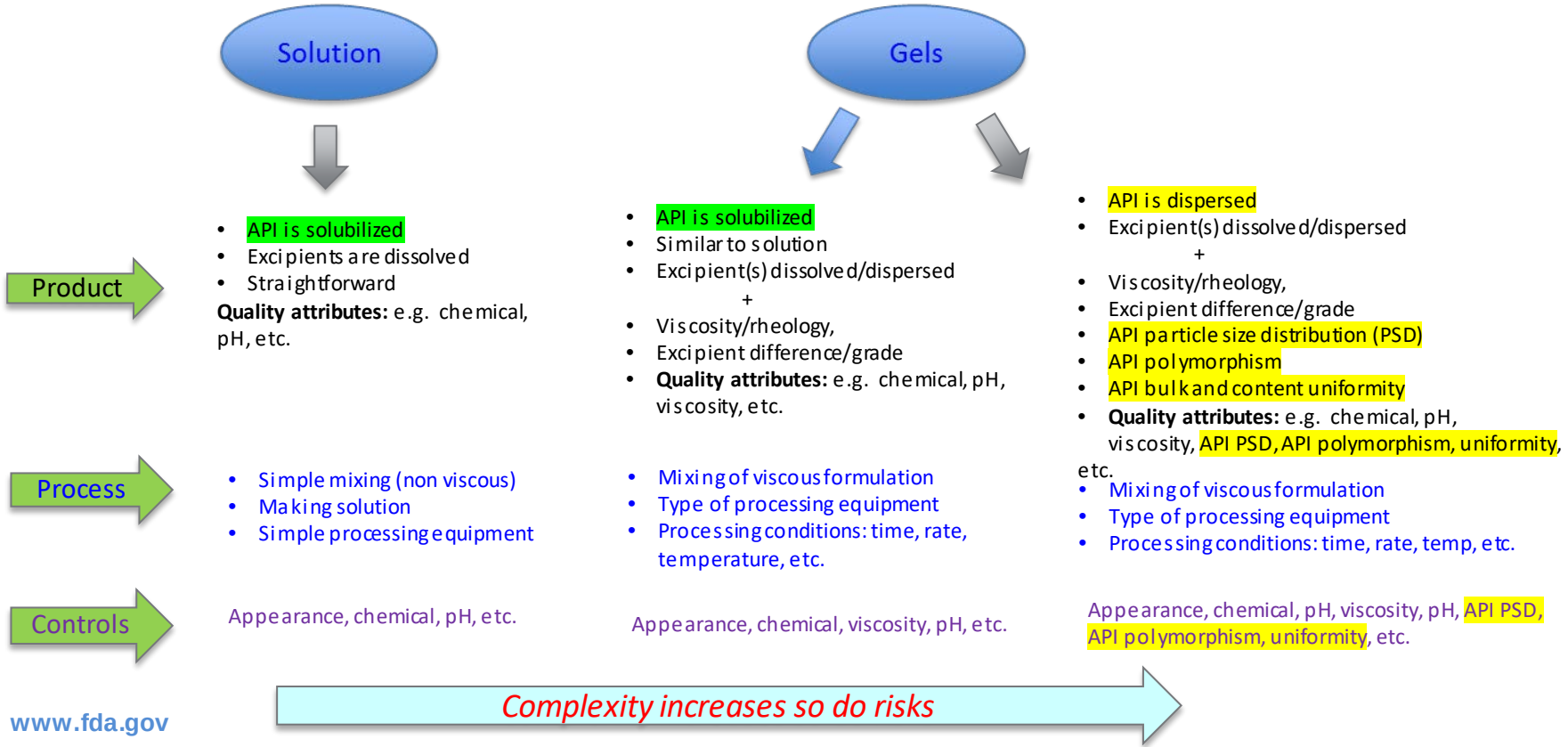
7. Characterization of pH and buffer capacity

8. Characterization of alkalinity and acidity

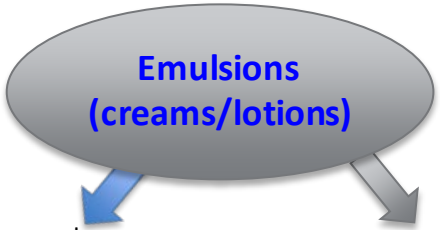
9. Characterization of specific gravity

10. Characterization of metamorphosis-related changes

Single/Multi Phase System (e.g., solution, gels)



Multi Phase System (Emulsions)



Product

- API is solubilized
- Excipient(s) dissolved/dispersed
  +
- Viscosity/rheology,
- Excipient difference/grade
- Globule size
- **Quality attributes:** e.g. chemical, pH, viscosity, globule size, etc.

Process

- Mixing of viscous formulation
- Type of processing equipment - emulsification
- Processing conditions: time, rate, temperature, etc.
- Impact of processing conditions on the quality attributes/product quality?

Controls

Appearance, chemical, viscosity, pH, globule size, etc.

- API is dispersed
- Excipient(s) dissolved/dispersed
  +
- Viscosity/rheology,
- Excipient difference/grade
- API PSD
- API polymorphism
- API bulk and content uniformity
- Globule size
- **Quality attributes:** e.g. chemical, pH, viscosity, API PSD, API polymorphism, uniformity, globule size, etc.

- Mixing of viscous formulation
- Type of processing equipment - emulsification
- Processing conditions: time, rate, temp, etc.
- Impact of processing conditions on the quality attributes/product quality?

Appearance, chemical, pH, viscosity, pH, API PSD, API polymorphism, uniformity, globule size, etc.

Complexity increases so do risks

Q3 Characterization in a Topical Dermatological Product ANDA – Points to Consider

It is recommended to perform Q3 characterization to demonstrate that a proposed topical dermatological product is pharmaceutically equivalent and/or bioequivalent to the reference product.

It is recommended that relevant comparative characterizations should be performed with a minimum of three batches of the test product and three batches (as available) of the reference product.

The particular Q3 characteristics that should be assessed for a specific proposed generic topical dermatological product will depend on the nature and complexity of its reference product.

IVRT Studies

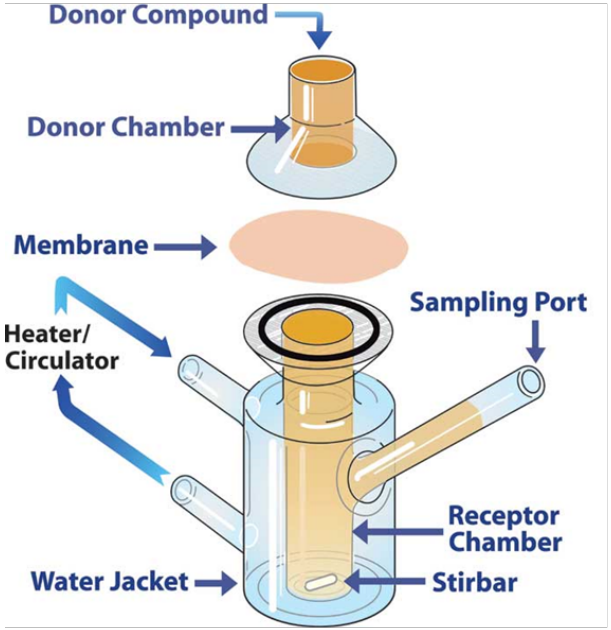
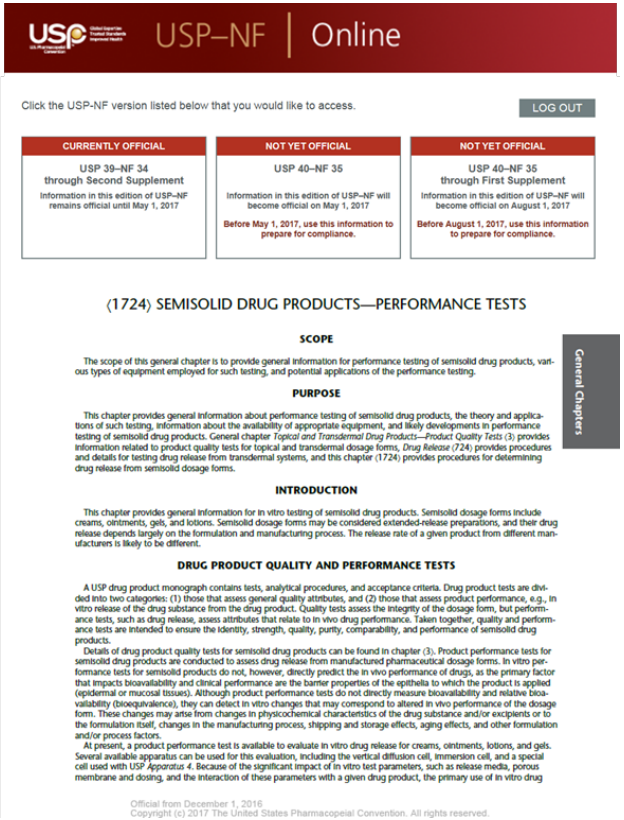


Image courtesy of PermeGear



USP–NF | Online

Click the USP-NF version listed below that you would like to access.

LOG OUT

CURRENTLY OFFICIAL	NOT YET OFFICIAL	NOT YET OFFICIAL
USP 39–NF 34 through Second Supplement	USP 40–NF 35	USP 40–NF 35 through First Supplement
Information in this edition of USP–NF remains official until May 1, 2017	Information in this edition of USP–NF will become official on May 1, 2017	Information in this edition of USP–NF will become official on August 1, 2017
	Before May 1, 2017, use this information to prepare for compliance.	Before August 1, 2017, use this information to prepare for compliance.

⟨1724⟩ SEMISOLID DRUG PRODUCTS—PERFORMANCE TESTS

General Chapters

SCOPE

The scope of this general chapter is to provide general information for performance testing of semisolid drug products, various types of equipment employed for such testing, and potential applications of the performance testing.

PURPOSE

This chapter provides general information about performance testing of semisolid drug products, the theory and applications of such testing, information about the availability of appropriate equipment, and likely developments in performance testing of semisolid drug products. General chapter *Topical and Transdermal Drug Products—Product Quality Tests* ⟨3⟩ provides information related to product quality tests for topical and transdermal dosage forms, *Drug Release* ⟨724⟩ provides procedures and details for testing drug release from transdermal systems, and this chapter ⟨1724⟩ provides procedures for determining drug release from semisolid dosage forms.

INTRODUCTION

This chapter provides general information for in vitro testing of semisolid drug products. Semisolid dosage forms include creams, ointments, gels, and lotions. Semisolid dosage forms may be considered extended-release preparations, and their drug release depends largely on the formulation and manufacturing process. The release rate of a given product from different manufacturers is likely to be different.

DRUG PRODUCT QUALITY AND PERFORMANCE TESTS

A USP drug product monograph contains tests, analytical procedures, and acceptance criteria. Drug product tests are divided into two categories: (1) those that assess general quality attributes, and (2) those that assess product performance, e.g., in vitro release of the drug substance from the drug product. Quality tests assess the integrity of the dosage form, but performance tests, such as drug release, assess attributes that relate to in vivo drug performance. Taken together, quality and performance tests are intended to ensure the identity, strength, quality, purity, comparability, and performance of semisolid drug products.

Details of drug product quality tests for semisolid drug products can be found in chapter ⟨3⟩. Product performance tests for semisolid drug products are conducted to assess drug release from manufactured pharmaceutical dosage forms. In vitro performance tests for semisolid products do not, however, directly predict the in vivo performance of drugs, as the primary factor that impacts bioavailability and clinical performance are the barrier properties of the epithelia to which the product is applied (epidermal or mucosal tissues). Although product performance tests do not directly measure bioavailability and relative bioavailability (bioequivalence), they can detect in vitro changes that may correspond to altered in vivo performance of the dosage form. These changes may arise from changes in physicochemical characteristics of the drug substance and/or excipients or to the formulation itself, changes in the manufacturing process, shipping and storage effects, aging effects, and other formulation and/or process factors.

At present, a product performance test is available to evaluate in vitro drug release for creams, ointments, lotions, and gels. Several available apparatus can be used for this evaluation, including the vertical diffusion cell, immersion cell, and a special cell used with USP *Apparatus 4*. Because of the significant impact of in vitro test parameters, such as release media, porous membrane and dosing, and the interaction of these parameters with a given drug product, the primary use of in vitro drug

Official from December 1, 2016

IVRT Studies

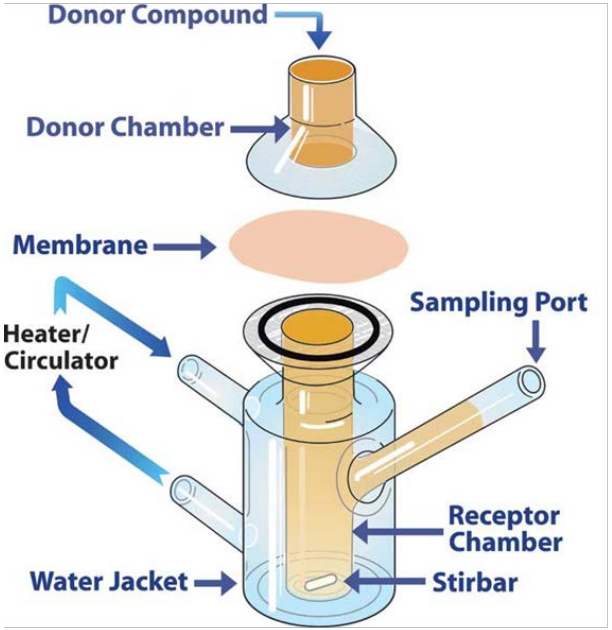
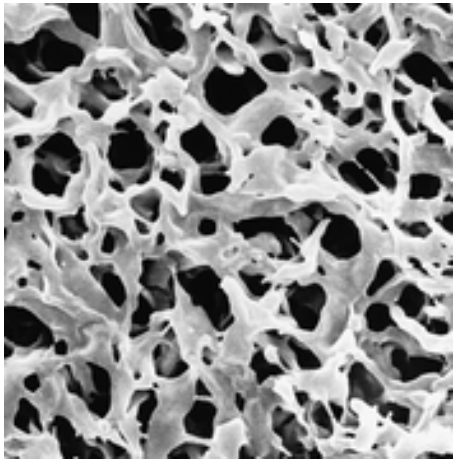
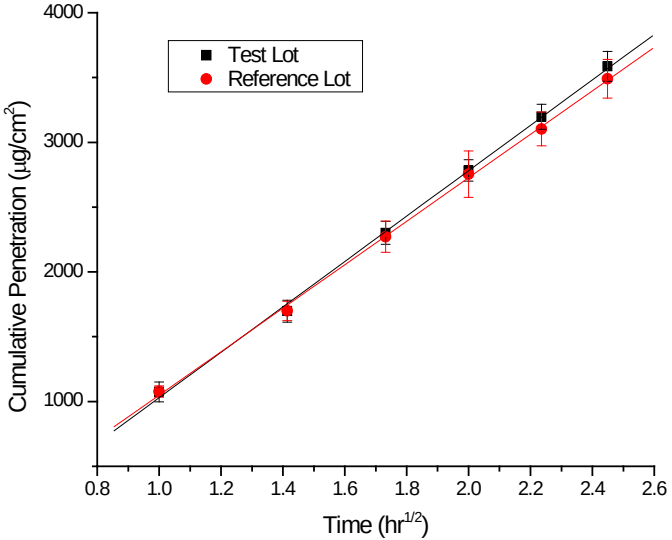


Image courtesy of PermeGear



IVRT Study Results



Reference Product	Test Product	Lower Limit	Upper Limit	Pass/Fail
(Details Redacted)	(Details Redacted)	100.881 %	109.068 %	Pass

IVRT Studies

- Major IVRT Study Phases
  - IVRT method development
  - IVRT method validation
  - IVRT pivotal study
- Common misconceptions and/or development challenges
  - Pseudo-infinite dose kinetics
  - Steady state release rate for a suitably sustained duration
  - Appropriate linearity of steady state region
  - Misconceptions surrounding a dose depletion exceeding 30%
  - Issues related to specific apparatus and/or metamorphosis
  - Issues related to studies with certain synthetic membranes

IVPT Studies

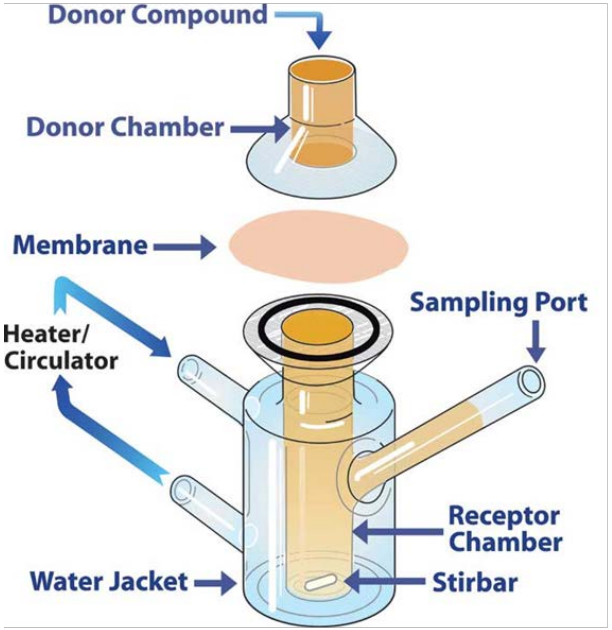
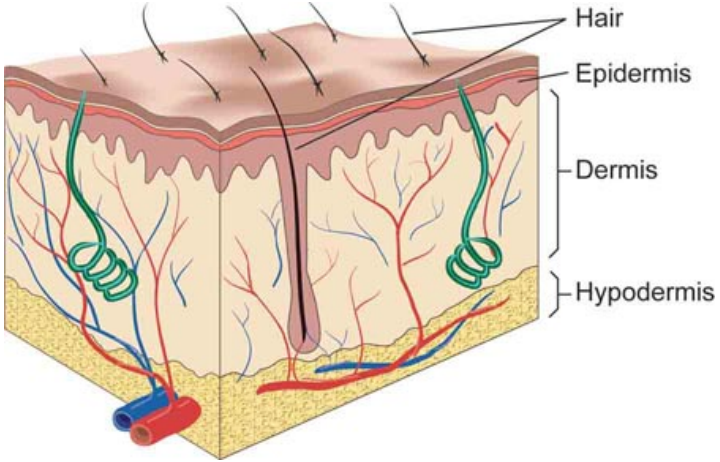
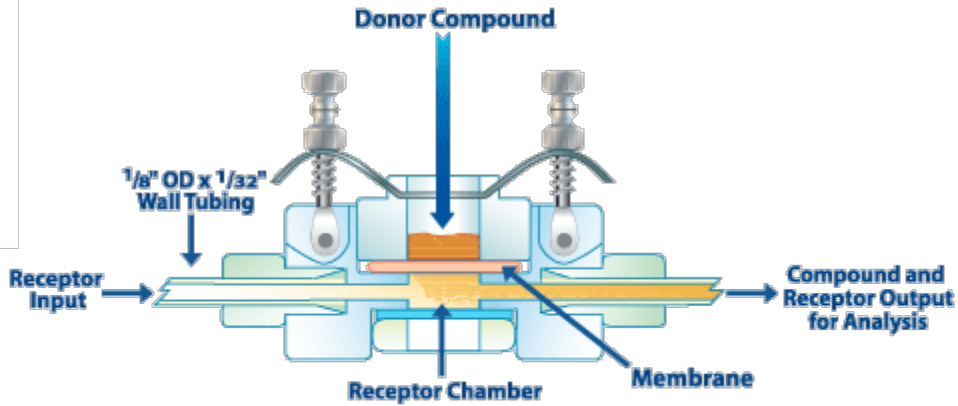


Image courtesy of PermeGear





IVPT vs. IVRT Studies

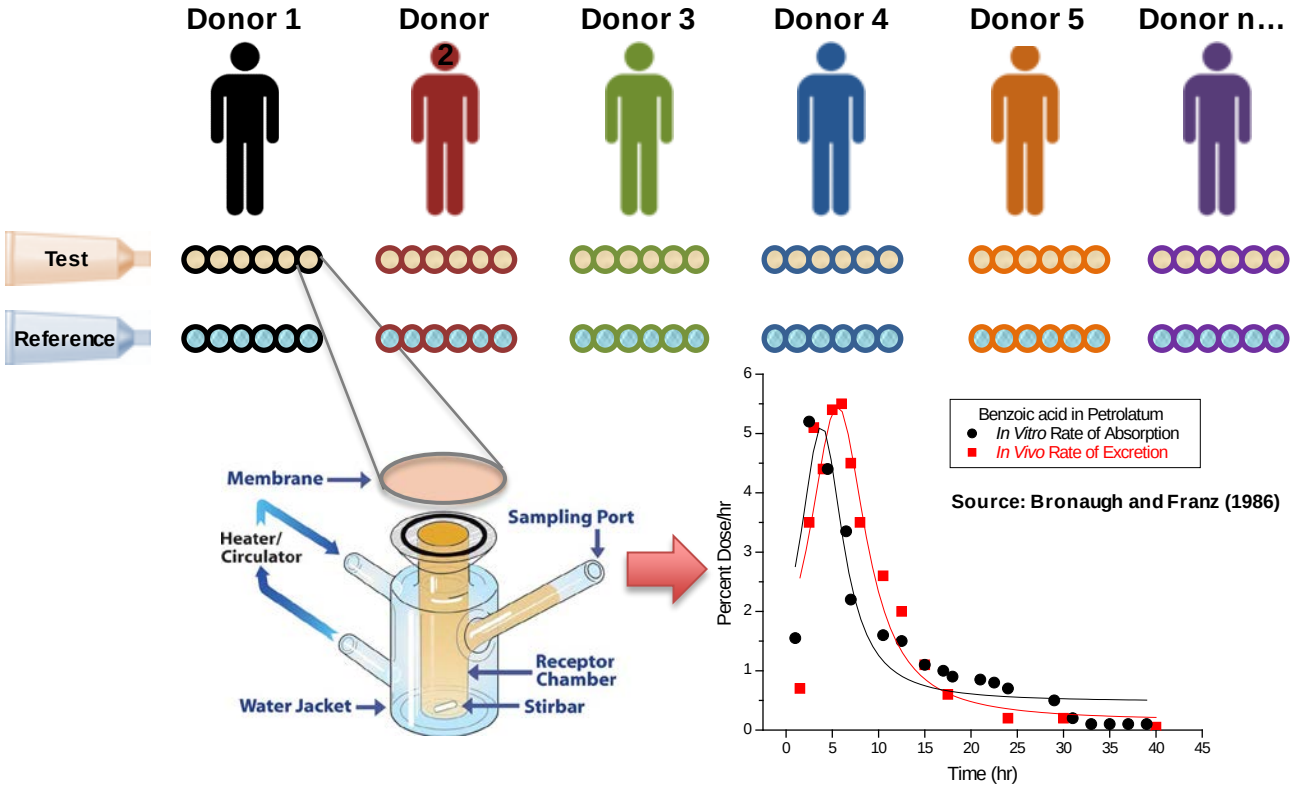
IVPT (Permeation)

- **Human Skin**
- Unoccluded Dose
- Finite Dose
- Flux Profile (J_{max}, etc.)
- Physiological Media
- pg to ng Range
- Product stays 'dry'
- *IVIV* Correlation
- Donor Variability

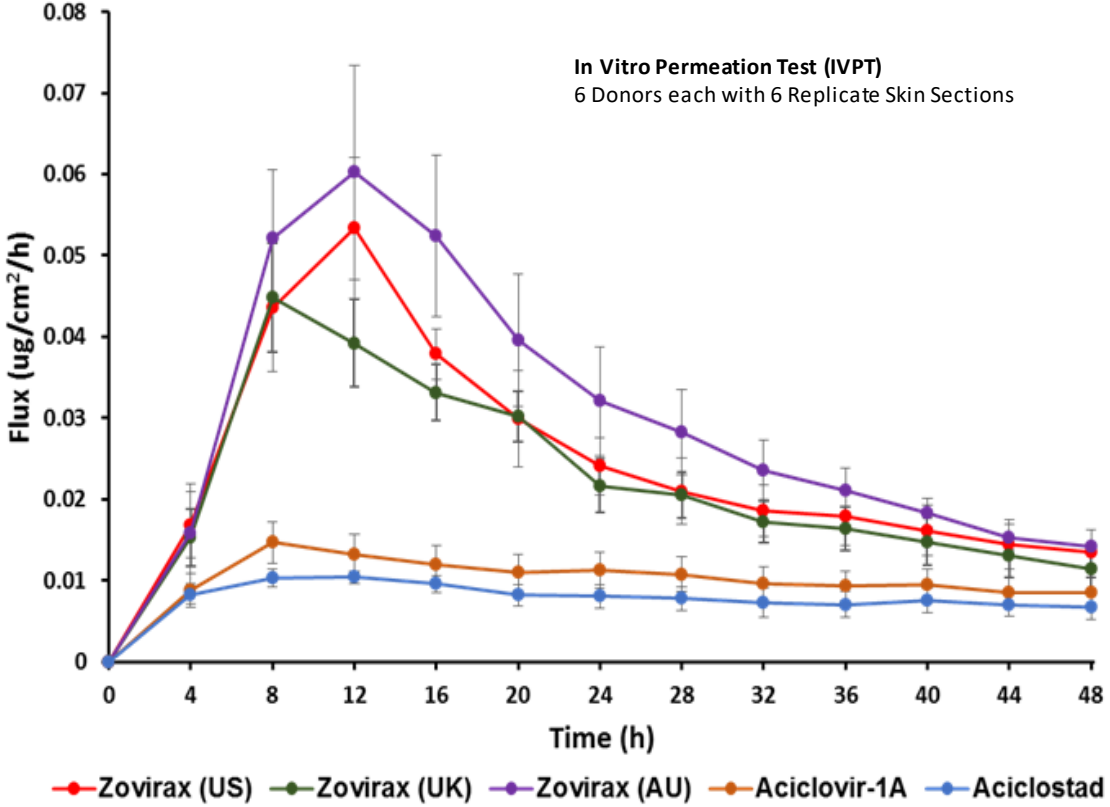
IVRT (Release)

- **Synthetic Membrane**
- Occluded Dose
- Infinite Dose
- Release Rate (slope)
- Alcoholic Media
- µg to mg Range
- Product-Media Interface
- Specific to the Formulation
- Relative Consistency

IVPT Study Design



IVPT Study Results



Data provided courtesy of Prof. Narasimha Murthy (University of Mississippi) ***FDA Award U01-FD005223***

IVPT Studies

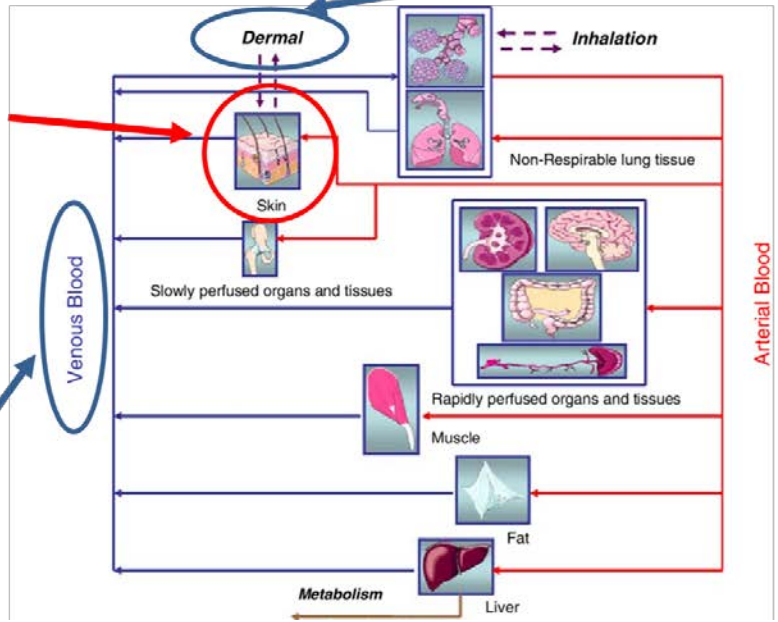
- Major IVPT Study Phases
  - IVRT method development
  - IVRT method validation (and pilot study)
  - IVRT pivotal study
- Common misconceptions and/or development challenges
  - Finite dose kinetics, dose depletion, and metamorphosis
  - Diffusion cell apparatus and sampling of the receptor solution
  - Considerations relating to skin type, preparation, and storage
  - Barrier integrity assumptions, testing, and acceptance criteria
  - Study designs and data analyses (appropriate to context of use)
    - Dose duration vs. study duration; number of donors vs. replicates
    - Questions/Issues related to “outlier” or aberrant data

Dermal PBPK Models

- Dermal PBPK models relate what we can measure to what we want to know

What we can measure:
-Formulation in vitro performance

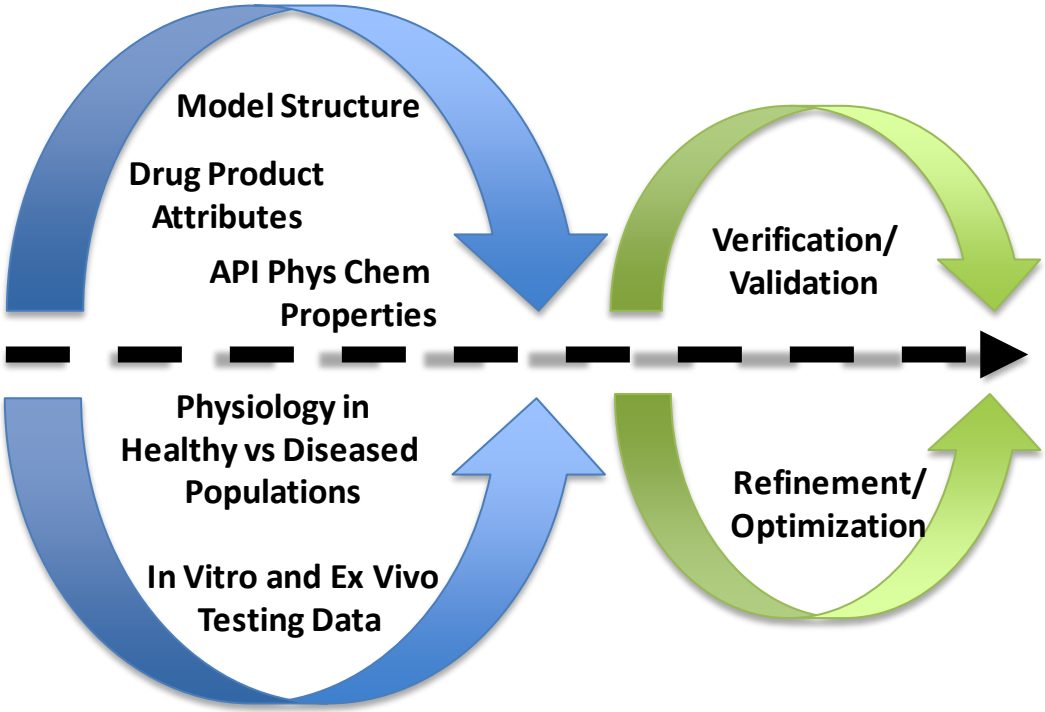
What we would like to know:
-local drug concentrations

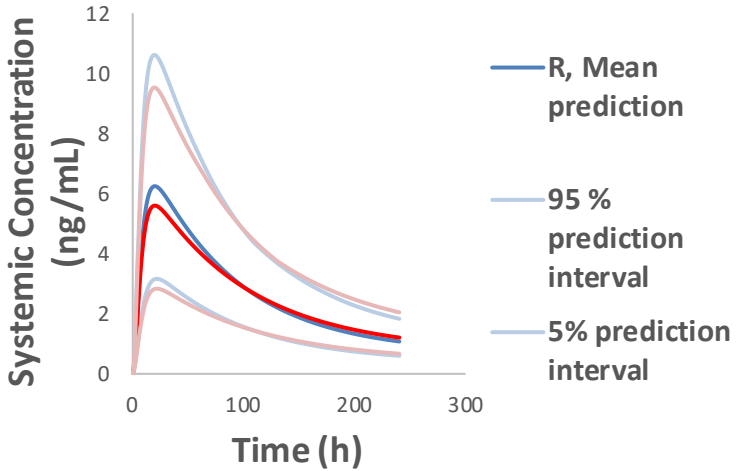


What we can measure:
-Systemic drug exposure

Source: Environ Geochem Health (2009) 31:165–187

PBPK Modeling for Generic Locally-acting Drugs to Support a Regulatory Decision





Are R and T bioequivalent?

R: Reference, T: Test

Utility of Dermal PBPK Models

- Generic drug development
  - Estimate impact of variations in product quality on product performance
  - Define a design space for critical quality attributes of topical formulations
  - Guide the selection of in vitro and/or in vivo study design parameters
- Generic drug approval
  - Support a demonstration of BE and regulatory decision-making
  - Extrapolate BE assessments from healthy to diseased subpopulations

Dermal PBPK Models

- Challenges of dermal PBPK models for regulatory decision-making
  - Need to develop and refine quantitative modeling tools that adequately describe formulation attributes, drug properties, skin physiology and/or disease states
    - Knowledge gaps currently exist
  - Need to verify/validate dermal PBPK models by utilizing observed local (skin) and systemic concentrations of the drug
    - It may not always be feasible (or ethical) to determine local concentrations
    - No correlation may be evident in many cases
  - Need to verify/validate dermal PBPK models that capture inter- and intra-subject variability under a fit-for-purpose modeling strategy
    - Leverage data on local concentrations from literature/FDA-funded research sources

Formulation of the Test Product

- **Test Product = Candidate Generic Drug**
- Steps to identifying an appropriate formulation
  - Deformulation (reverse engineering) of the reference product
  - Understanding limitations of information in the reference listed drug (RLD) labeling and FDA's inactive ingredient database (IID)
  - Developing a thorough understanding of the product by characterizing multiple (fresh and aged) batches of the reference product
  - Formulating the test product to match the reference product, determining critical quality attributes (CQAs), and failure modes for BE

Deformulation and Characterization

- Hypothetical RLD:

- Topical cream with two drug molecules
- Oil in water emulsion
- In the finished product ardamethacin is completely dissolved and tanasone is partially dissolved
- The pH of the finished product is 5.5
- The RLD is available in tubes and non-metered pumps

Reverse engineering of the RLD

Ingredients	Function	% W/W
Tanasone,	Active ingredient	0.1
Ardamethacin,	Active ingredient	0.5
White Petrolatum	Emollient, oil phase	15.0
Mineral Oil	Emollient, oil phase	2.0
CetoStearyl Alcohol	Stiffening agent, emulsifier	12.5
Propylene Glycol	Solvent, humectant	10.0
Ceteareth-30	Emulsifier	1.8
Sodium Phosphate Monobasic Dihydrate,	Buffering agent	0.30
Sodium Hydroxide	pH adjuster	0.002
Phosphoric Acid	pH adjuster	0.006
Benzyl alcohol	Preservative	1.00
Purified water	Vehicle	57.79

Seeking Acceptability of a Formulation

Assessment of qualitative (Q1) and quantitative (Q2) sameness

✓ Assessment of acceptability of a test formulation for the proposed BE approach

- When the product-specific guidance (PSG) recommends that test product should contain no difference in inactive ingredients or in other aspects of the formulation relative to the reference product that may significantly affect the local or systemic availability of the active ingredient.
  - Via a controlled correspondence
- When there is no PSG for the RLD.
  - Via a pre-abbreviated new drug application (pre-ANDA) meeting request in parallel with proposing a specific BE approach

Acceptability of a Test Formulation

- Is the following formulation acceptable for the in vitro BE approach?
  - May not be acceptable

Test Formulation	
Ingredients	% W/W
Tanasone, USP	0.10
Ardamethacin, USP	0.50
Petrolatum, USP	15.00
Mineral Oil, USP	**1.70**
CetoStearyl Alcohol, NF	**12.5 (The IID limit is 12%)**
Propylene Glycol, USP	10.00
Ceteareth-30	1.80
Sodium Phosphate Monobasic Dihydrate, USP	0.30
Sodium Hydroxide, NF	**0.004 (QS to target pH 5.5)**
Phosphoric Acid, NF	0.006
Benzyl alcohol, NF	1.00
Purified water, USP	56.10

RLD Formulation	
Ingredients	% W/W
Tanasone, USP	0.10
Ardamethacin, USP	0.50
White Petrolatum, USP	15.00
Mineral Oil, USP	**2.00**
CetoStearyl Alcohol, NF	12.00
Propylene Glycol, USP	10.50
Ceteareth-30	1.80
Sodium Phosphate Monobasic Dihydrate, USP	0.30
Sodium Hydroxide, NF	**0.002**
Phosphoric Acid, NF	0.006
Benzyl alcohol, NF	1.00
Purified water, USP	57.00

Acceptability of a Test Formulation

- Quantitative nominal amount for each (and every) ingredient in the composition table.
- Quantitative nominal amount specified to the same number of decimal places as the RLD.
- The correct compendial grades and names of each excipient should be specified.

Ingredients	Function	% W/W
Tanasone, USP	Active ingredient	0.10
Ardamethacin, USP	Active ingredient	0.50
White Petrolatum, USP	emollient, oil phase	15.00
Mineral Oil, USP	emollient, oil phase	2.00
Cetyl alcohol plus stearyl alcohol (Stenol® I665)	stiffening agent, emulsifier	12.00
Propylene Glycol, USP	solvent, humectant	10.00
Ceteareth-30 (EUMULGIN® B 3)	Emulsifier	1.77
Sodium Phosphate Monobasic Dihydrate, USP	buffering agent	0.35
Sodium Hydroxide, NF	pH adjuster	0.003^
Phosphoric Acid, NF	pH adjuster	0.006^
Benzyl alcohol, NF	preservative	1.00
Purified Water, USP	Vehicle	58.00
^ QS to pH 5.5		

Concluding Summary

- FDA serves the U.S. dermatology patient community by –
  - Facilitating development of new products to treat dermatologic disease
  - Improving access to high-quality generic drug products
- These efforts involve applying knowledge gained from research and a practical approach to regulation

Acknowledgements

U.S. Food & Drug Administration

- Priyanka Ghosh, PhD
- Tannaz Ramezanli, PhD
- Sam Raney, PhD
- Liang Zhao, PhD
- Robert Lionberger, PhD

- Kendall Marcus, MD

- Jonathan Wilkin, MD


FDA
U.S. FOOD & DRUG
ADMINISTRATION