FDA Initiatives to Stimulate Innovation and Improve Patient Access to Generic Topical & Transdermal Products Part II

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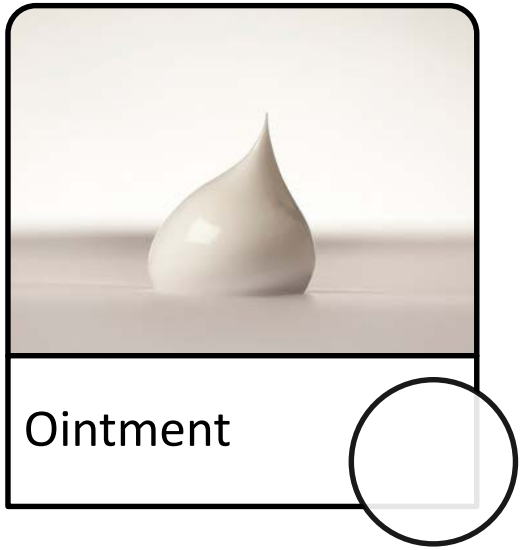
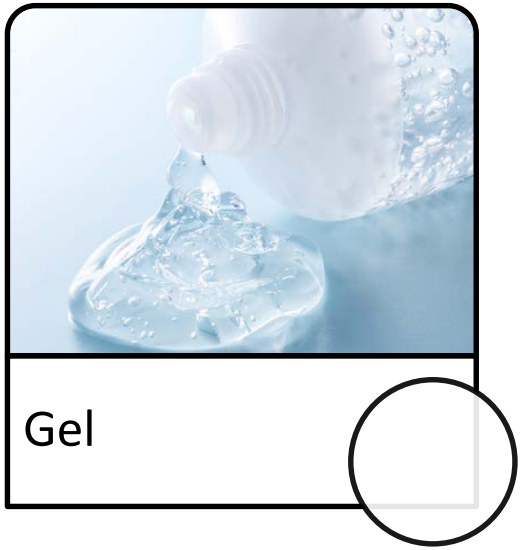
- This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

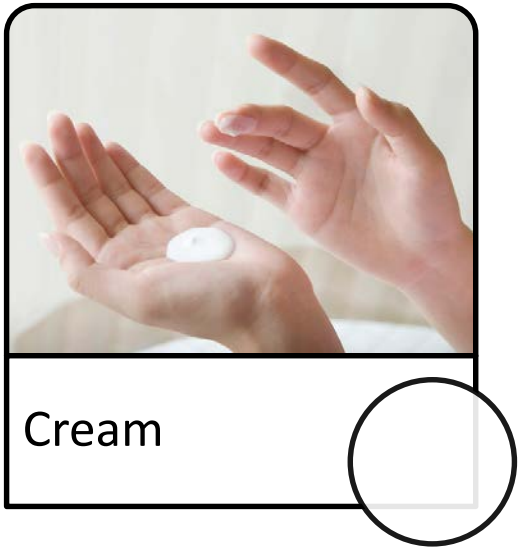
Topical Dosage Forms



Ointment



Gel



Cream

https://pharmaceutical.basf.com/en/Drug-Formulation

Topical Dosage Forms

Dermal	Ophthalmic	Otic	Rectal	Vaginal
Aerosol Foam	*Emulsion*	Solution/Drops	*Aerosol Foam*	*Cream*
Cream	*Ointments*	Suspension/Drops	*Gel*	*Gel*
Gel	Solution/Drops	Oil/Drops	*Suppository*	*Suppository*
Lotion	Suspension/Drops		Enema	Insert
Ointment			Powder	Ring
Patch			Solution	
Shampoo				
Spray				
Solution				
Suspension				

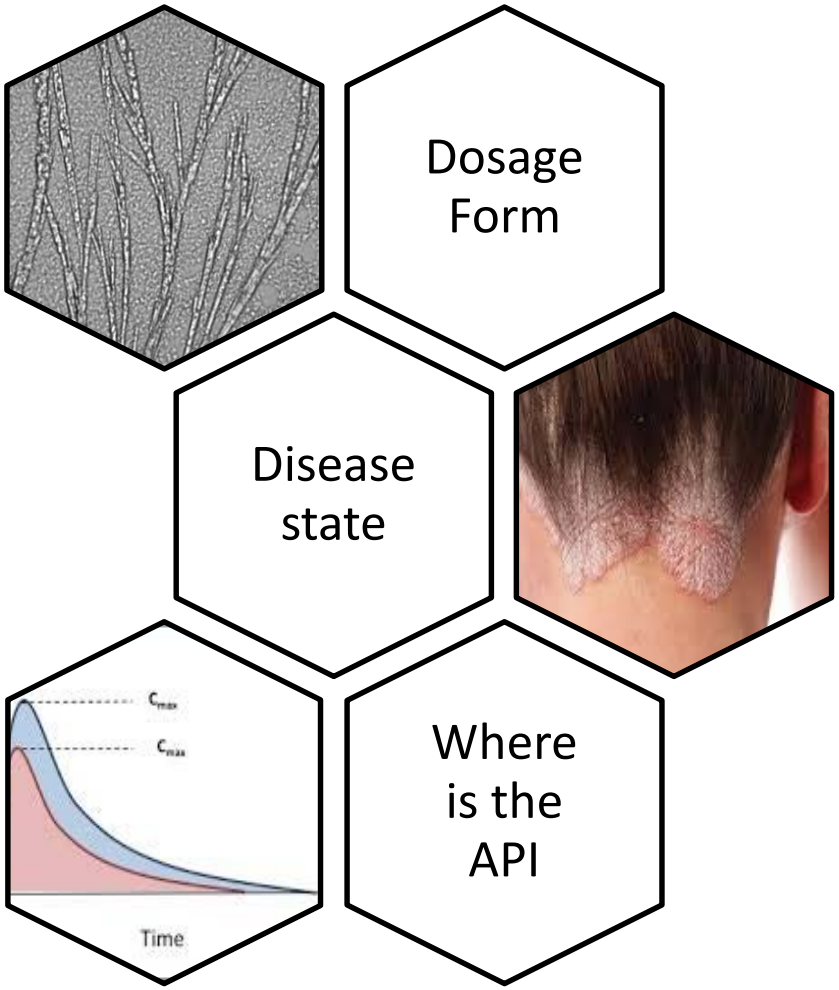
Bioavailability of Locally Acting Product

- A 2003 addition to the Federal Food Drug and Cosmetic Act at Section 505(j)(8)(A)(ii) indicates that–

  "For a drug that is not intended to be absorbed into the bloodstream, the Secretary may assess bioavailability by scientifically valid measurements intended to reflect the rate and extent to which the active ingredient or therapeutic ingredient becomes available at the site of drug action".

Adapted from Dr. Markham Luke, GDUFA Research Public Workshop May 3, 2017

Developing Efficient BE Methods

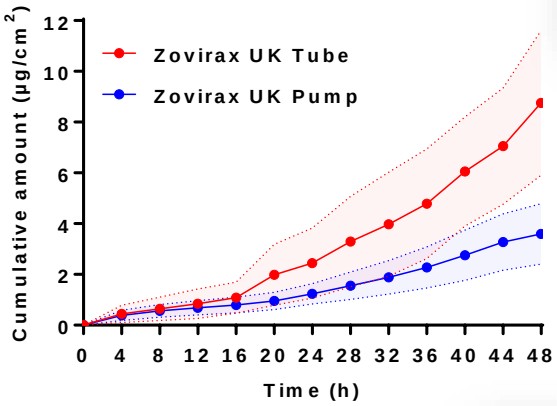


How can we adapt available techniques or methods to better understand these interrelated issues?

Active pharmaceutical ingredient (API)

Visualization of the Dosage Form

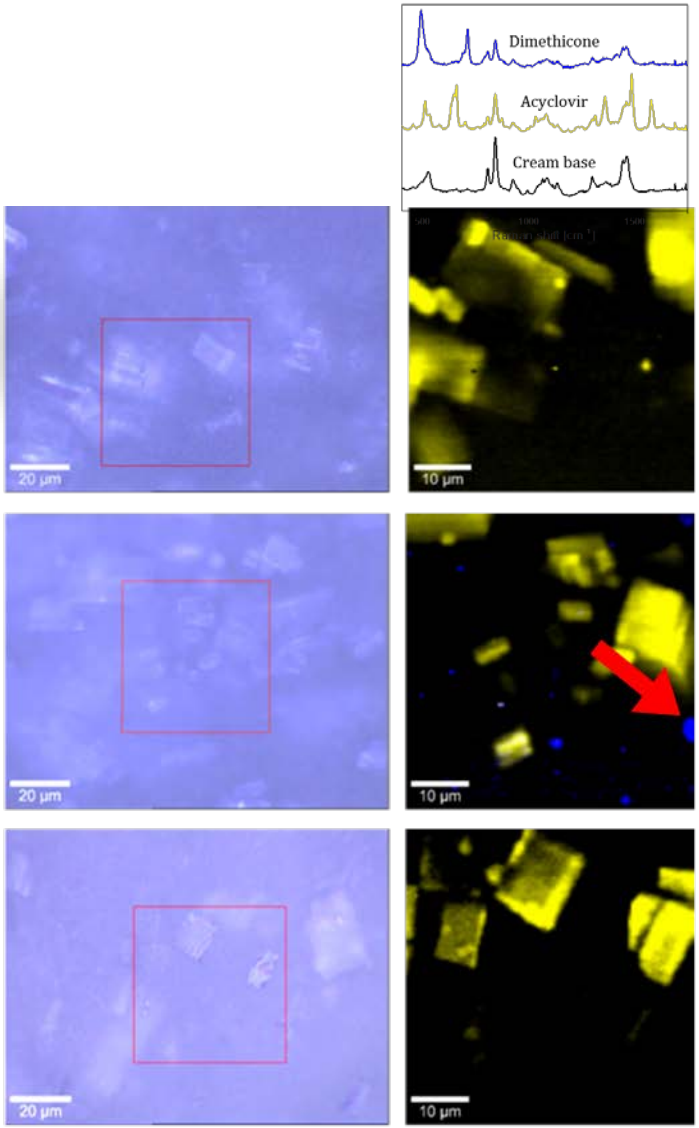
- Raman Spectroscopy



Zovirax® UK
Tube

Zovirax® UK
Pump

Zovirax® UK
Pump
(from inside container)



Prof. Michael Roberts FDA Award U01-FD005226

Visualization of the Dosage Form

- What other techniques can we use to expand our understanding of the dosage form?
  - Can we use imaging or other techniques to better understand the localization/ relative distribution of API within multiphasic systems?
  - Can we use imaging or other techniques to understand the localization of each API in systems containing multiple dispersed API's?
  - Can we use imaging or other techniques to understand the impact of dissolution of API on bioavailability?

Distribution of API

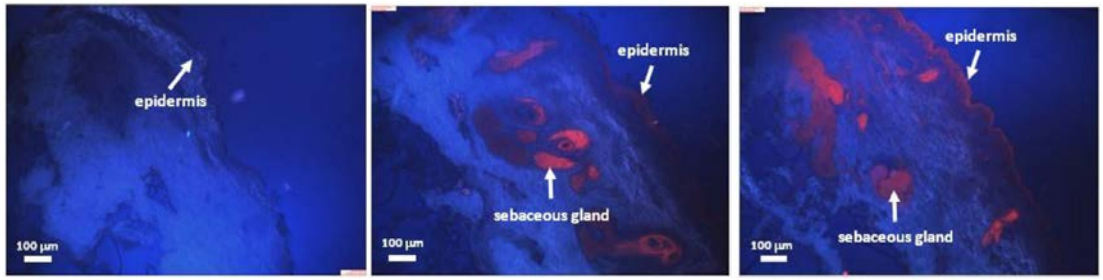
- Fluorescence Microscopy

Fluorescence microscopy images

Ex vivo human facial skin

- *Control*
- *1% BPX-01 (a topical acne gel)*
- *4% BPX-01 at 24 hours*

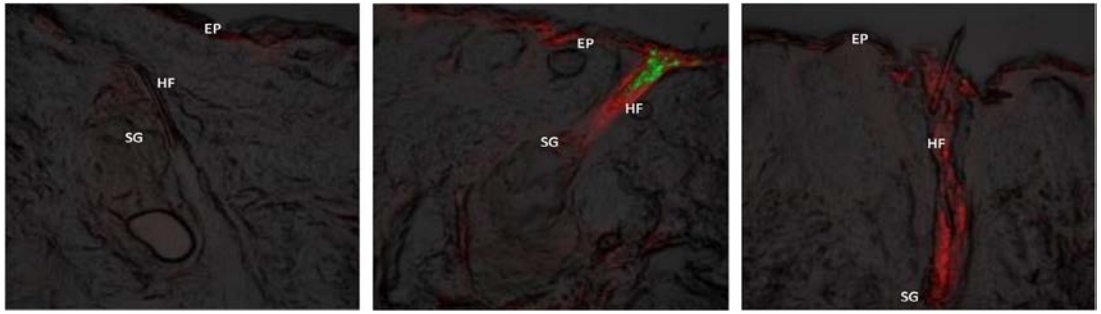
Minocycline fluorescence in red



Two-photon fluorescence microscopy

Ex vivo human facial skin

- *Control (endogenous fluorescence in the absence of minocycline in epidermis (EP), hair follicle (HF), and sebaceous gland (SG))*
- *1% BPX-01*
- *4% BPX-01 at 4 hours*

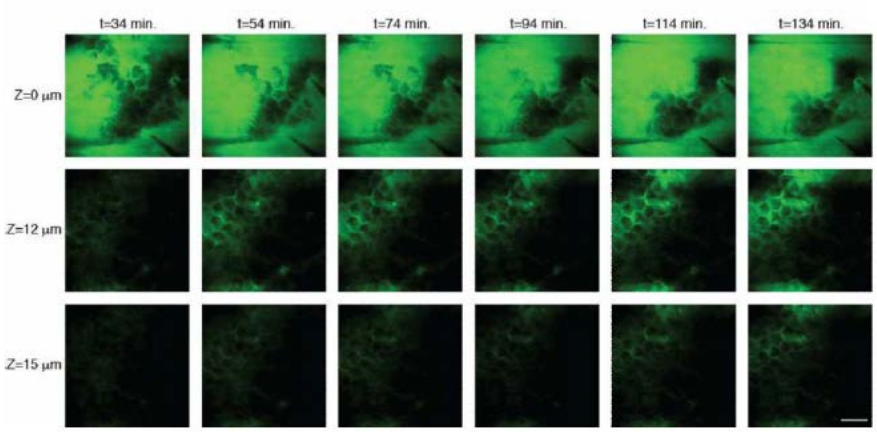


Evans Conor L. , Chan Kin F. , Prow Tarl and Osseiran Sam, **Visualizing and quantifying drug uptake in skin**, Biomedical Optics & Medical Imaging

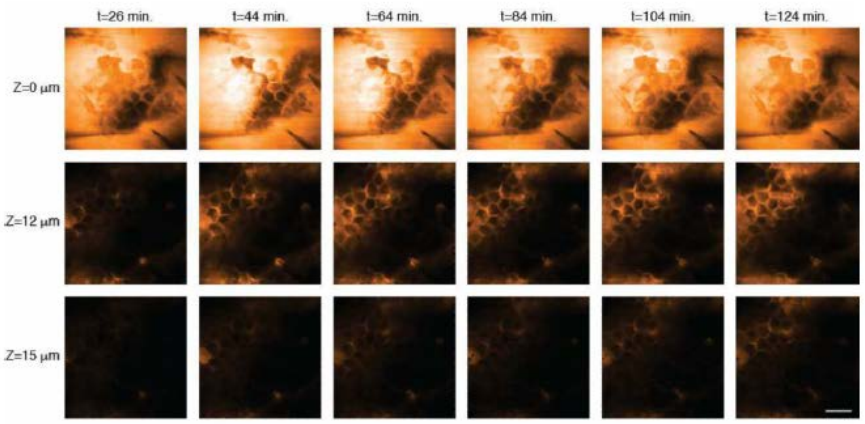
Distribution of API/Excipients

- Raman Spectroscopy

Ketoprofen



Propylene Glycol (deuterated)



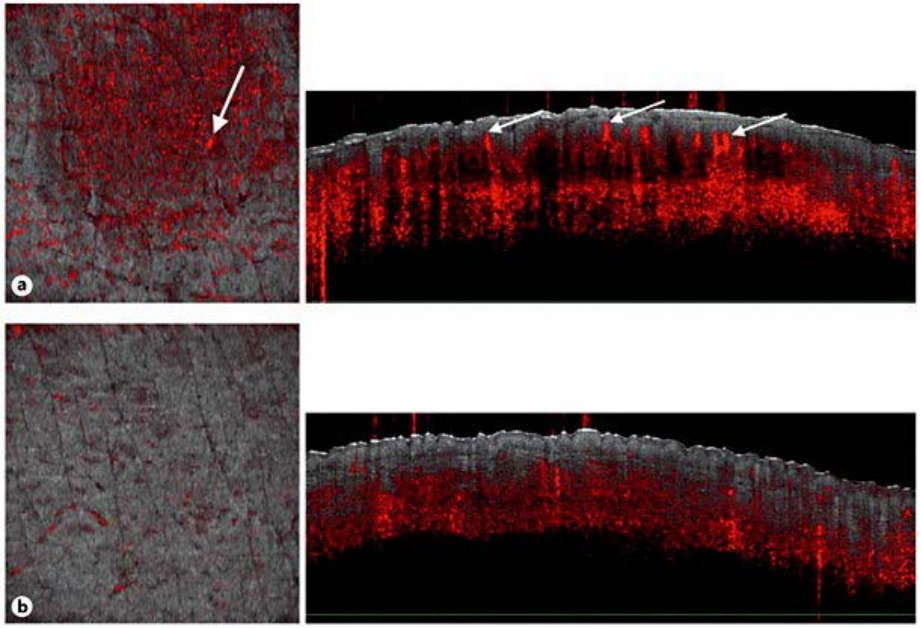
Saar Brian G. , Contreras-Rojas L. Rodrigo , Xie X. Sunney , and Guy Richard H. **Imaging Drug Delivery to Skin with Stimulated Raman Scattering Microscopy** Molecular Pharmaceutics **2011** 8 (3), 969-975

Distribution of API

- What other techniques can we use to expand our understanding of rate and extent of availability of API?
  - Can we use alternate techniques for (semi) quantitative assessment of drug at or near the site of action?
  - For imaging, most techniques appear to require modifications to the API (e.g., deuteration for detection/ quantification). Are specific techniques (more) suitable for specific classes of molecules?
  - How can we resolve challenges related to signal attenuation, depth profiling, temporal resolution, etc., when evaluating rate and extent of drug availability?

Changes in Skin Morphology

- Normal vs. diseased (psoriatic) skin



Optical Coherence Tomography

(a) Healthy (adjacent) skin

(b) Psoriatic skin- Despite marked morphological differences (thickened and bright stratum corneum, acanthosis), the number of blood vessels is increased in psoriasis. Especially in the upper stratum papillare, loops of dilated capillaries are present (arrows)

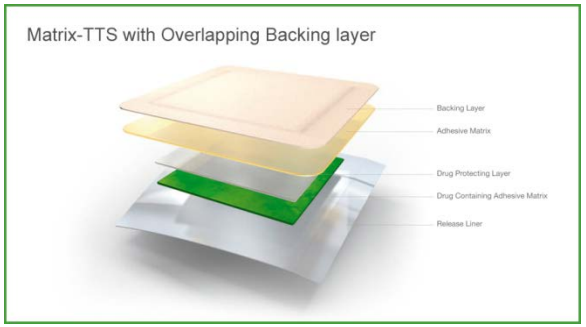
Ulrich M, Themstrup L, de Carvalho N, Manfredi M, Grana C, Ciardo S, Kästle R, Holmes J, Whitehead R, Jemec G, B, E, Pellacani G, Welzel J: **Dynamic Optical Coherence Tomography in Dermatology**. Dermatology 2016;232:298-311

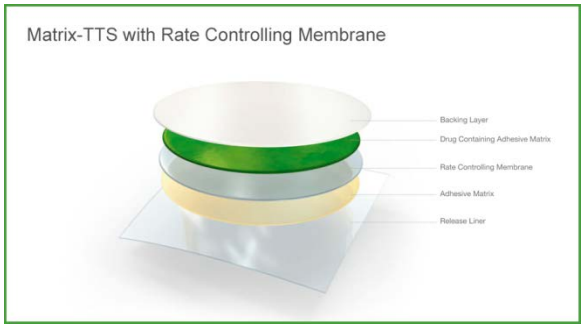
Changes in Skin Morphology

- What other techniques can we use to expand our understanding of the pathophysiology of diseased skin?
  - Can we use imaging or other techniques to better understand the pathophysiology of dermatological diseases?
  - Can we integrate such imaging data into physiology based models to enhance our understanding of drug availability at or near the site of action in diseased skin?

Transdermal Delivery Systems (TDS)

- Design variation even among “Matrix” TDS





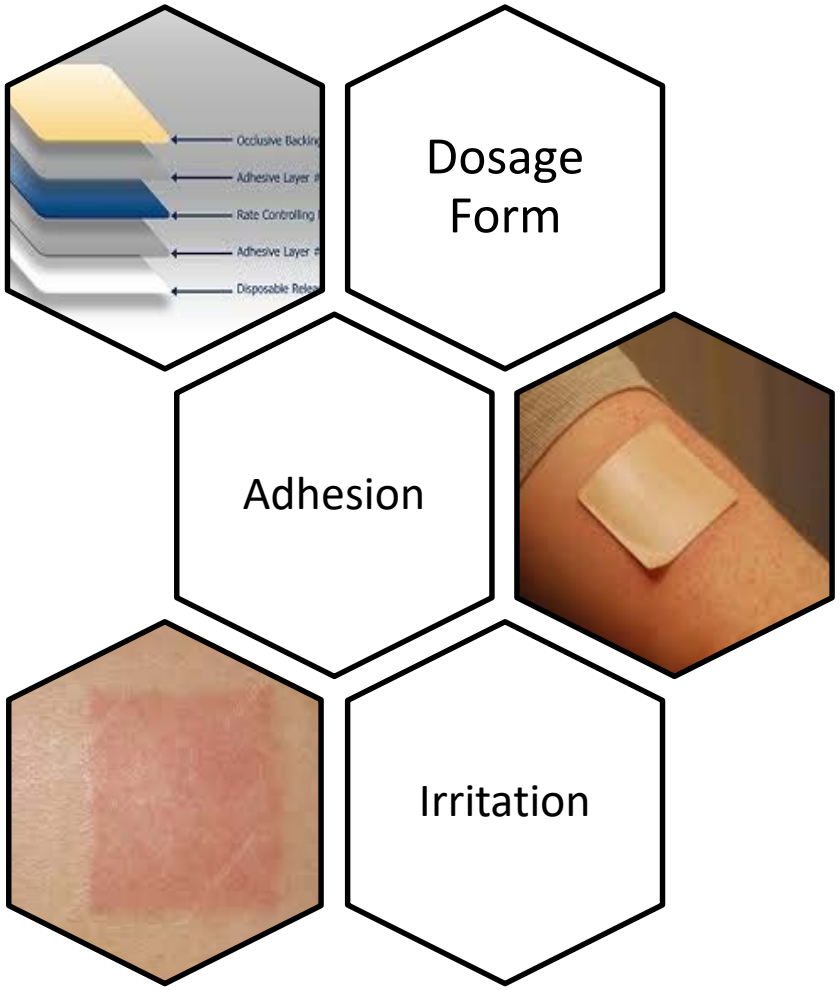
https://ltslohmann.de/en/technology/transdermal-therapeutic-systems/

Assessment of Generic TDS Products

- To ensure that generic TDS have the same rate and extent of absorption at the site of action, FDA recommends that applicants demonstrate BE, conducting key comparative product characterizations:
  - An in vivo comparative BE study with pharmacokinetic endpoints[1]
  - An in vivo comparative adhesion study[2]
  - An in vivo comparative irritation/sensitization study[3]
  - An in vitro comparative heat effects study

1. https://www.fda.gov/downloads/drugs/guidances/ucm377465.pdf
2. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM504157.pdf
3. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM622672.pdf

Enhancing Current Methods

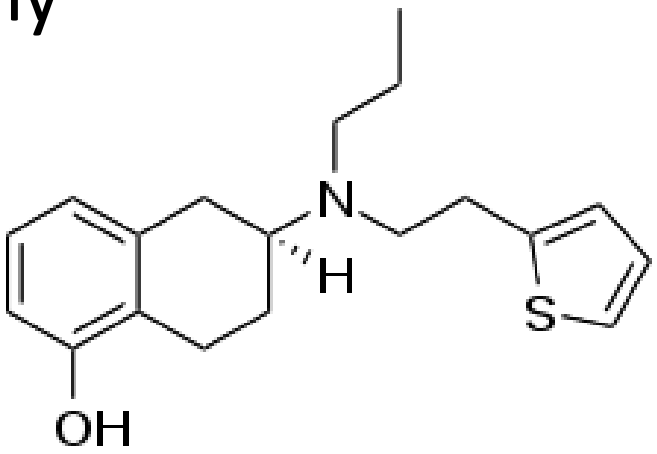


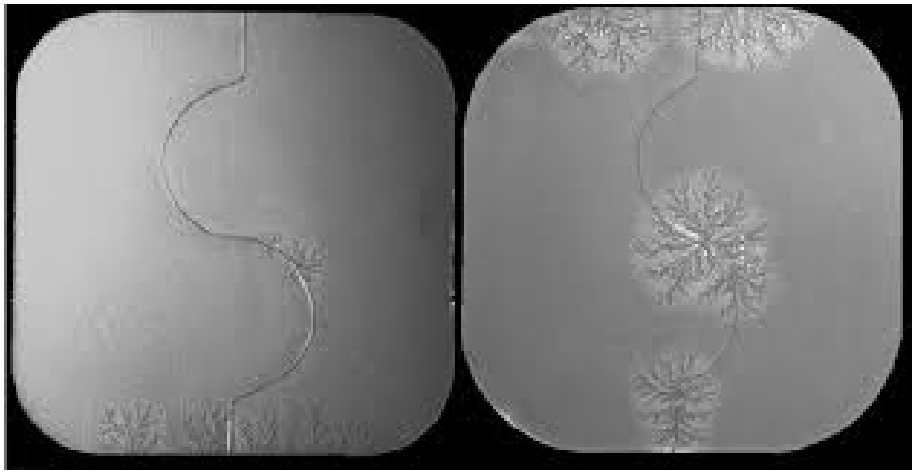
How can we adapt available techniques or methods to better understand these interrelated issues?

Active pharmaceutical ingredient (API)

Visualization of the Dosage Form

- Photography





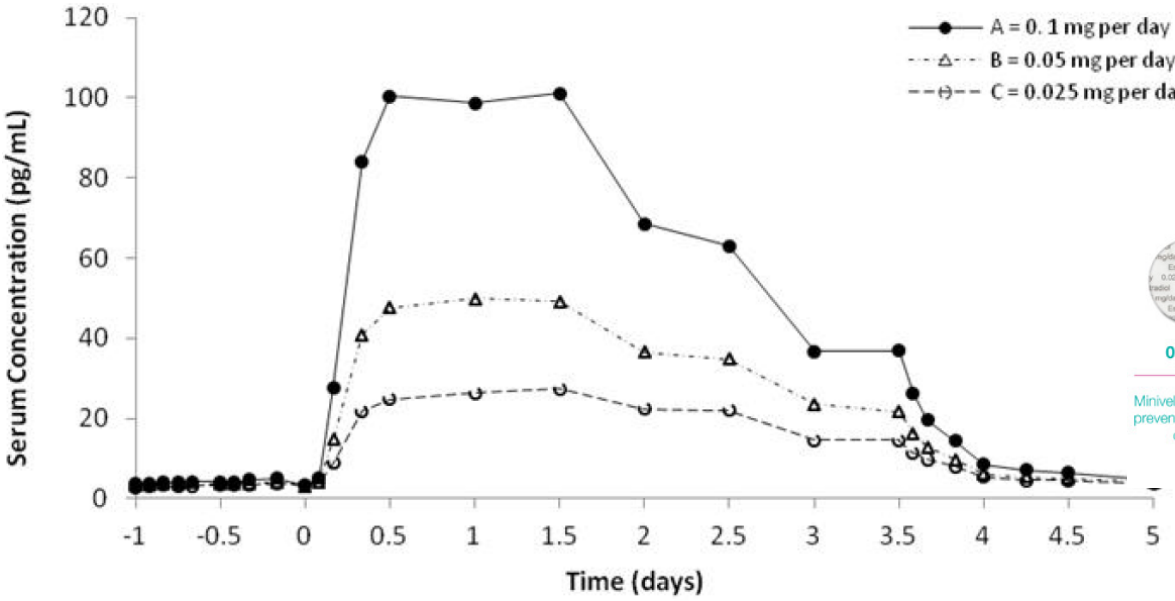
Rietveld Ivo B. and Ćeolin Rene **Rotigotine: Unexpected Polymorphism with Predictable OverallMonotropic Behavior**, Journal of Pharmaceutical Sciences 104:4117–4122, 2015

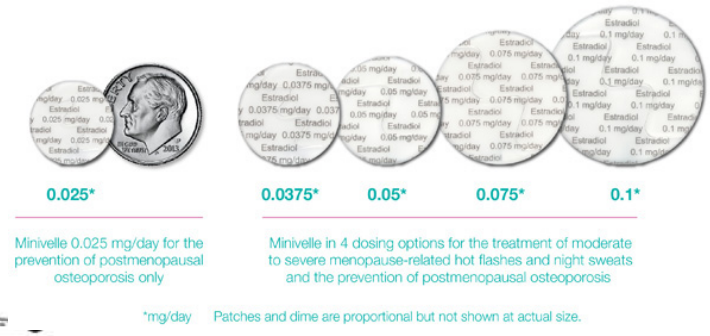
Visualization of the Dosage Form

- What other techniques can we use to expand our understanding of the dosage form?
  - Can we use imaging or other techniques to monitor and/or model crystal growth kinetics and it's potential impact on bioavailability?

TDS Adhesion

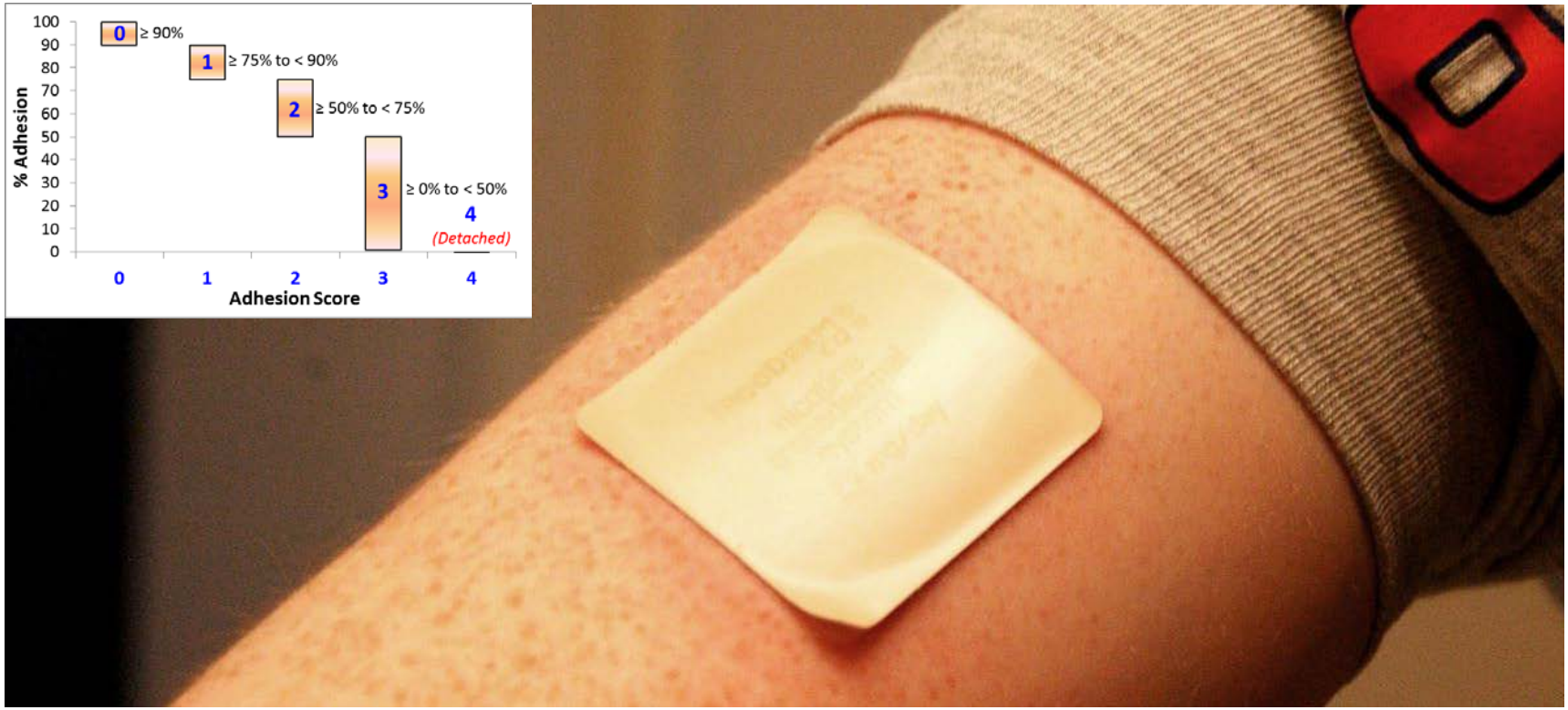
- The surface area of adherence to skin impacts:
  - The rate (strength) and extent of drug delivery





Minivelle® (estradiol) TDS prescribing information

Assessing Generic TDS Adhesion



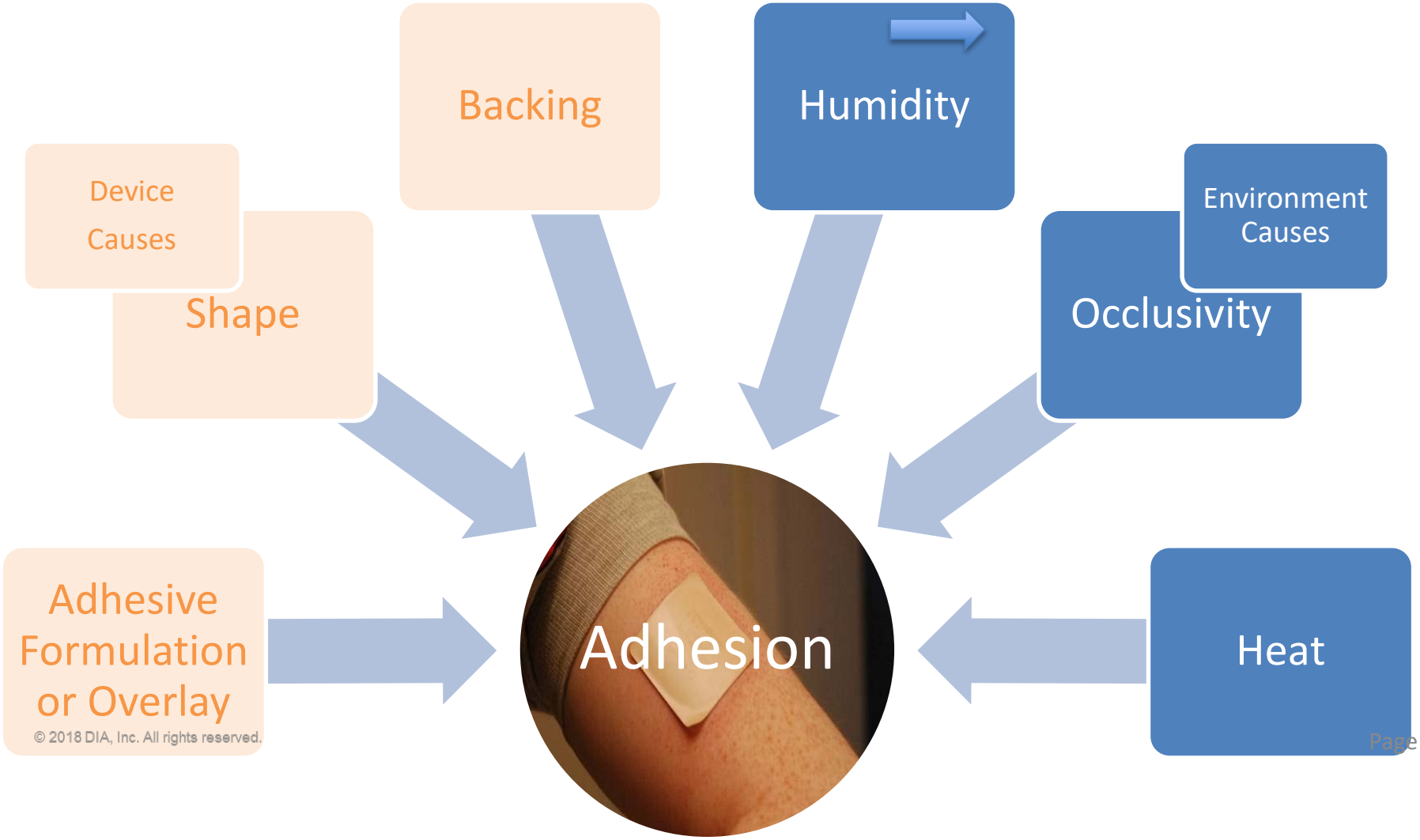
https://en.wikipedia.org/wiki/Transdermal_patch (Free Media)

Assessing Generic TDS Adhesion

- Draft guidance for industry on assessing generic TDS adhesion
  - Published June, 2016 and Revised October, 2018[1]
  - Introduced a new statistical analysis approach
  - Revised criteria for primary and secondary endpoints
  - Discussed numerous critical study controls, for example
    - Discouraged tampering with TDS
    - Discouraged restrictions on normal subject motion
    - Emphasized assessment of to-be-marketed TDS

1. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM504157.pdf

Factors Contributing to Failure



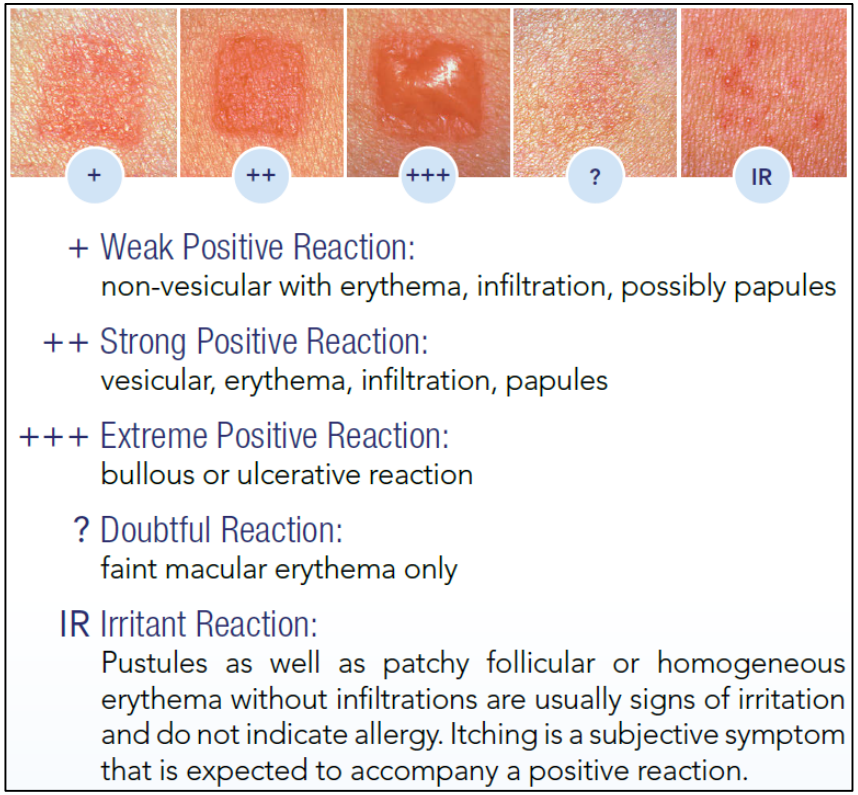
Adapted from Audra Stinchcomb, PhD, Complex Drug-Device Generic Combination Products Meeting, 2018

Assessing Generic TDS Adhesion

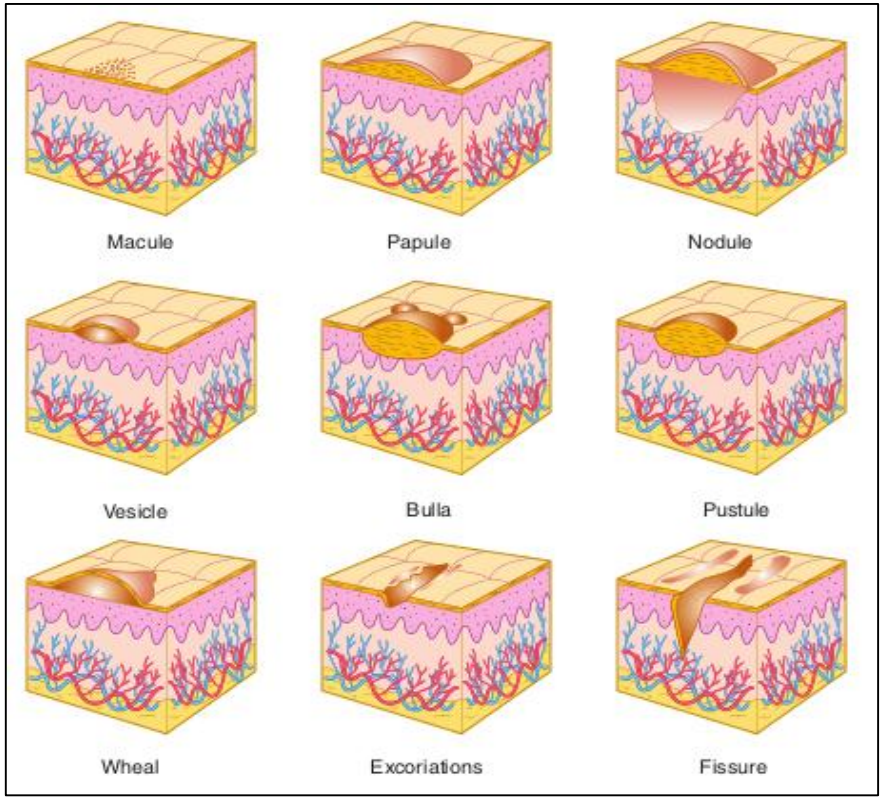
- What other techniques can we use to standardize or refine our current methods for assessment of adhesion?
  - Can we use photographic/imaging techniques for assessing adhesion?
  - Can image analysis or other techniques like machine learning be used to analyze and compare extent of adhesion of products over time?
  - Can data like image data with temporal resolution be used to predict product failure events (100% detachment)?

TDS Irritation/Sensitization (I/S)

- I/S reactions can manifest on the skin in different ways



https://www.smartpractice.com/dermatology (T.R.U.E. TEST®)



http://body-disease.com/wp-content/uploads/2012/03/Skin-lesions.jpeg

TDS Irritation/Sensitization (I/S)

- I/S reactions are scored using two FDA scales:

Scale 1. Dermal Response (Skin Appearance)	Score
No evidence of irritation	0
Minimal erythema that is barely perceptible	1
Definite erythema that is readily visible and minimal edema or minimal papular response	2
Erythema and papules	3
Definite edema	4
Erythema, edema, and papules	5
Vesicular eruption	6
Strong reaction spreading beyond the application site	7

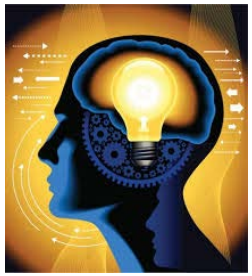
Scale 2. Other Effects (Observation)	Score
Slightly glazed appearance	A (0)
Markedly glazed appearance	B (1)
Glazing with peeling and cracking	C (2)
Glazing with fissures	F (3)
Film of dried serous exudates covering all or part of the TDS site	G (3)
Small petechial erosions and/or scabs	H (3)

TDS Irritation/Sensitization (I/S)

- What other techniques can we use to standardize or refine our current methods for assessment of I/S?
  - Can we use photographic/imaging techniques for assessing irritation?
  - Are there standardized techniques for obtaining images of a specific site over time?
  - Can image analysis techniques be used to analyze and compare the extent of irritation over time compared to the current clinical assessment?

Partnering with the FDA

- Regulatory Science Extramural Research and Development Projects
  - FDA welcomes research proposals for Grants/ Contracts/ Etc.
  - Generic Drug Regulatory Science Initiatives Public Workshop, May 1st, 2019, Silver Spring, Maryland



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https://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/GenericDrugs/ucm585566.htm

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- Michael Roberts, PhD

GDUFA Award U01FD00**4955**

- Audra Stinchcomb, PhD


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