

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

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April 23, 2019

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Office of Generic Drugs | CDER | US FDA

# Disclaimer

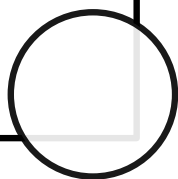


- This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

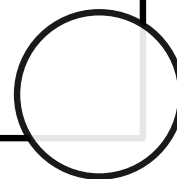
# Topical Dosage Forms



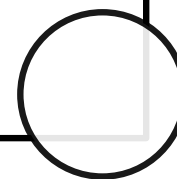
Ointment



Gel



Cream



# Topical Dosage Forms



## **Dermal**

*Aerosol Foam*  
*Cream*  
*Gel*  
*Lotion*  
*Ointment*  
*Patch*  
*Shampoo*  
*Spray*  
Solution  
Suspension

## **Ophthalmic**

*Emulsion*  
*Ointments*  
Solution/Drops  
Suspension/Drops

## **Otic**

Solution/Drops  
Suspension/Drops  
Oil/Drops

## **Rectal**

*Aerosol Foam*  
*Gel*  
*Suppository*  
Enema  
Powder  
Solution

## **Vaginal**

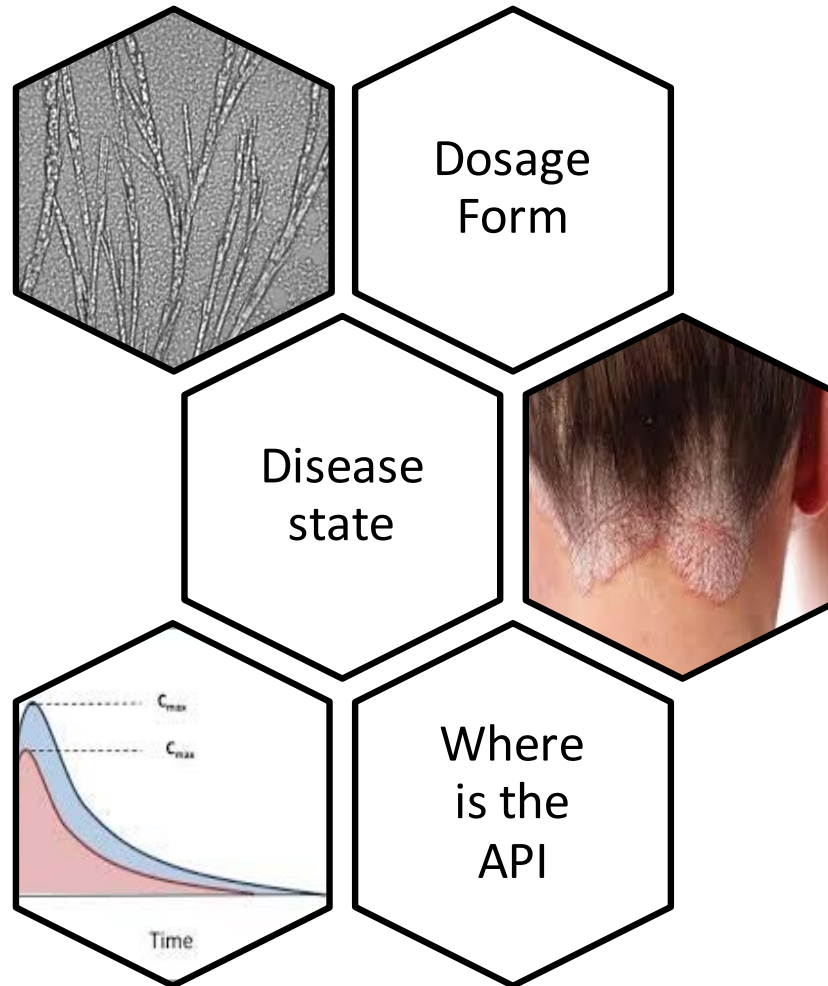
*Cream*  
*Gel*  
*Suppository*  
Insert  
Ring

# 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**”.

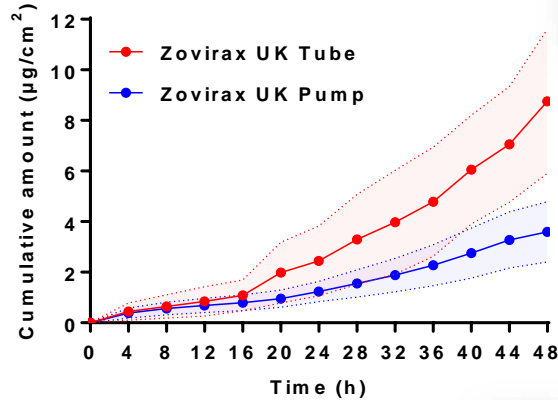
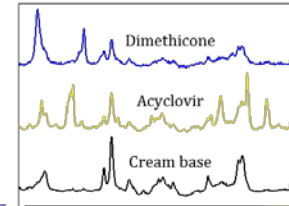
# Developing Efficient BE Methods



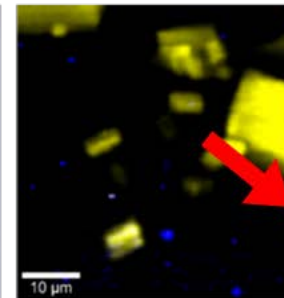
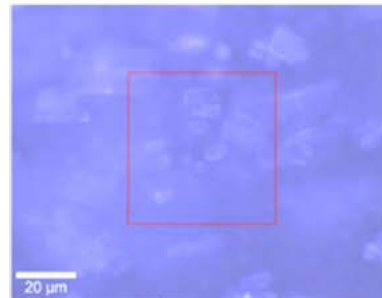
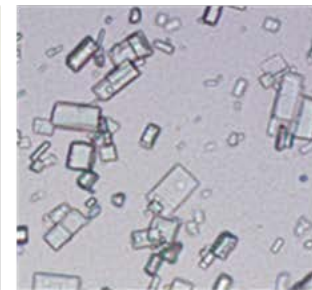
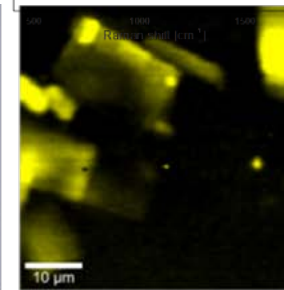
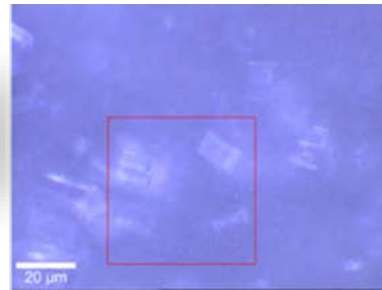
How can we adapt available techniques or methods to better understand these interrelated issues?

# Visualization of the Dosage Form

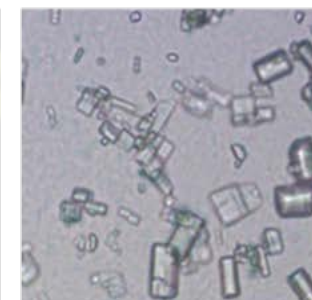
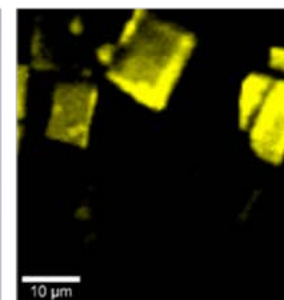
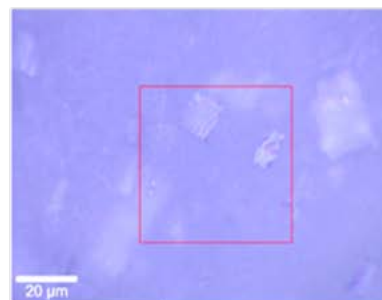
- Raman Spectroscopy



Zovirax<sup>®</sup> UK  
Tube



Zovirax<sup>®</sup> UK  
Pump



Zovirax<sup>®</sup> UK  
Pump  
(from inside container)

# 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

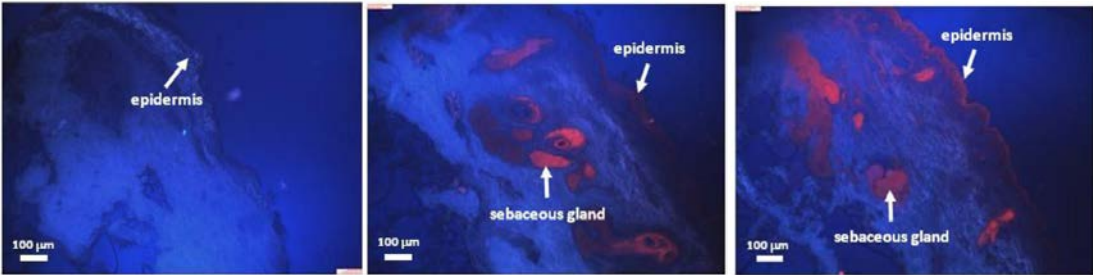
- Fluorescence Microscopy

**Fluorescence microscopy images**

*Ex vivo human facial skin*

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

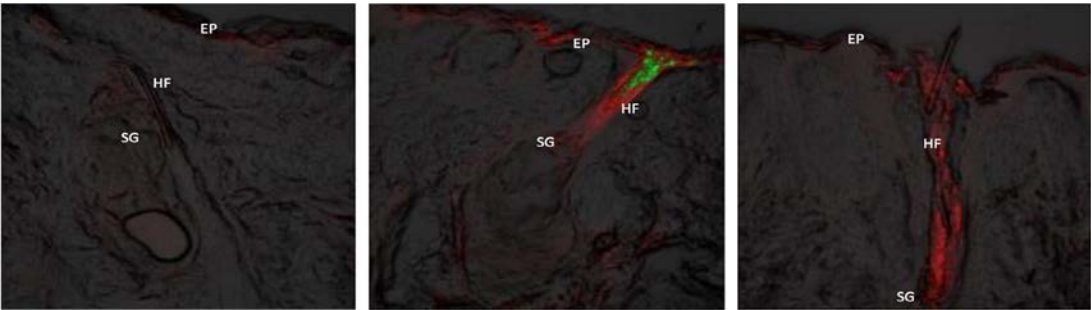
*Minocycline fluorescence in red*



**Two-photon fluorescence microscopy**

*Ex vivo human facial skin*

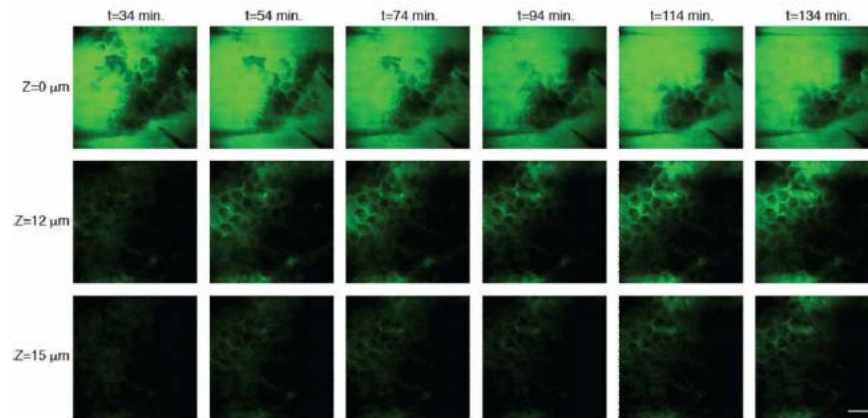
- Control (endogenous fluorescence in the absence of minocycline in epidermis (EP), hair follicle (HF), and sebaceous gland (SG))
- 1% BPX-01
- 4% BPX-01 at 4 hours



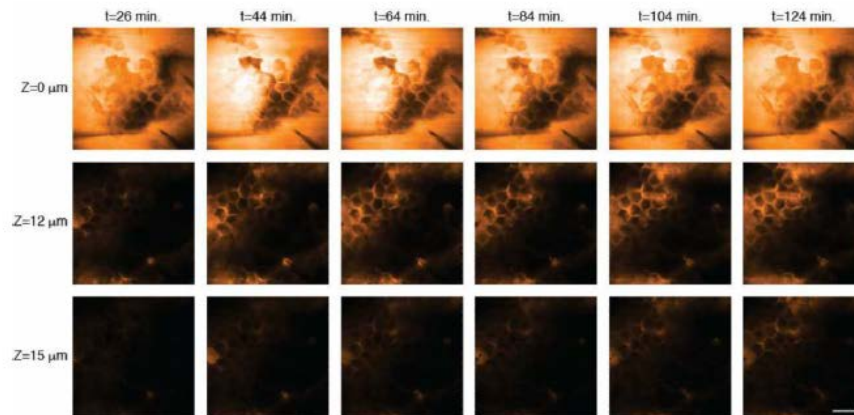
# Distribution of API/Excipients

- Raman Spectroscopy

Ketoprofen



Propylene Glycol (deuterated)



# Distribution of API

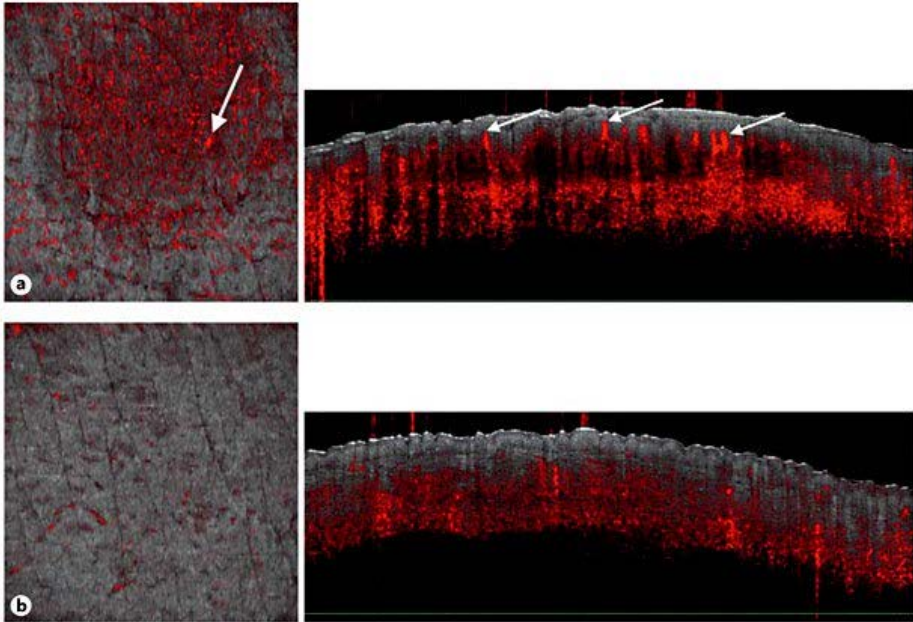


- What other techniques can we use to expand our understanding of rate and extent of availability of API?
  - Can we use alternate techniques for (semi) quantitative assessment of drug at or near the site of action?
  - For imaging, most techniques appear to require modifications to the API (e.g., deuteration 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)

# Changes in Skin Morphology

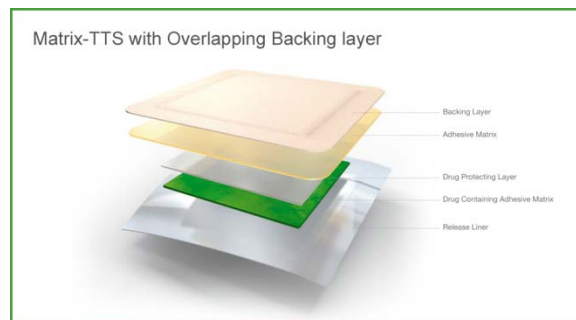


- What other techniques can we use to expand our understanding of the pathophysiology of diseased skin?
  - Can we use imaging or other techniques to better understand the pathophysiology of dermatological diseases?
  - Can we integrate such imaging data into physiology based models to enhance our understanding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

# Transdermal Delivery Systems (TDS)



- Design variation even among “Matrix” TDS



# Assessment of Generic TDS Products



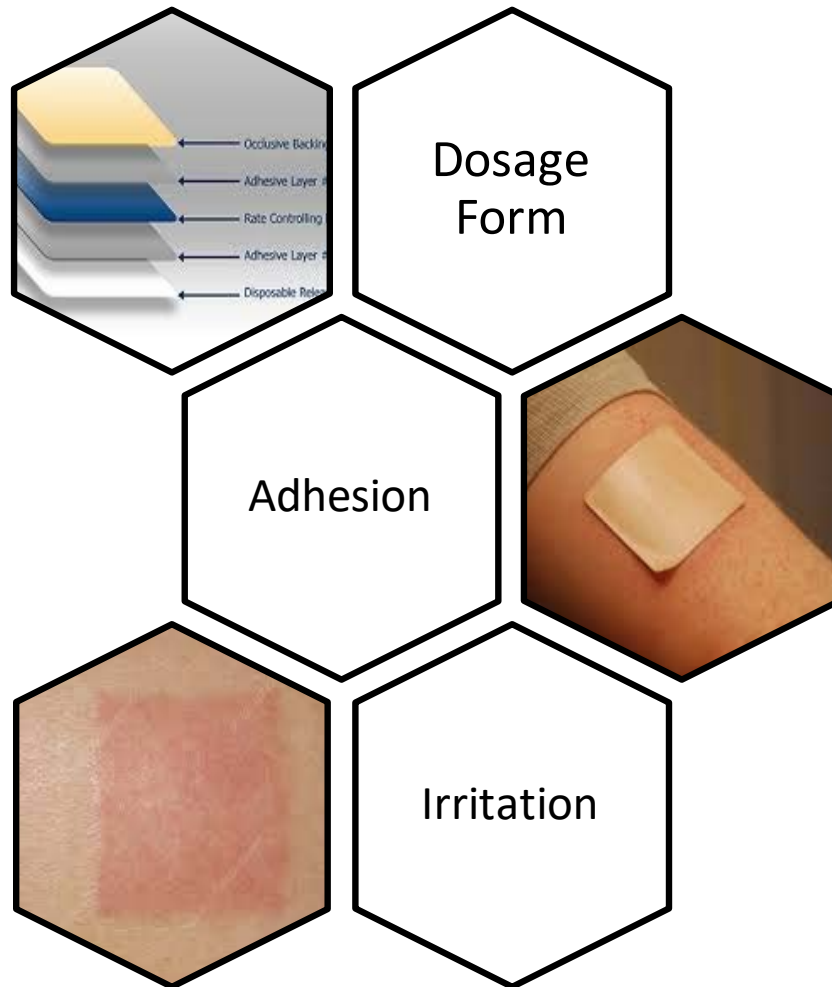
- To ensure that generic TDS have the same rate and extent of absorption at the site of action, FDA recommends that applicants demonstrate BE, conducting key comparative product characterizations:
  - An in vivo comparative **BE study** with pharmacokinetic endpoints<sup>1</sup>
  - An in vivo comparative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

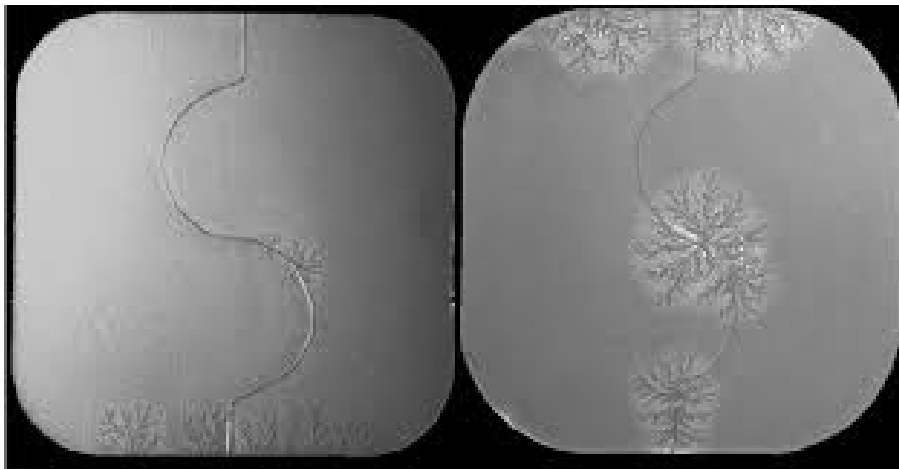
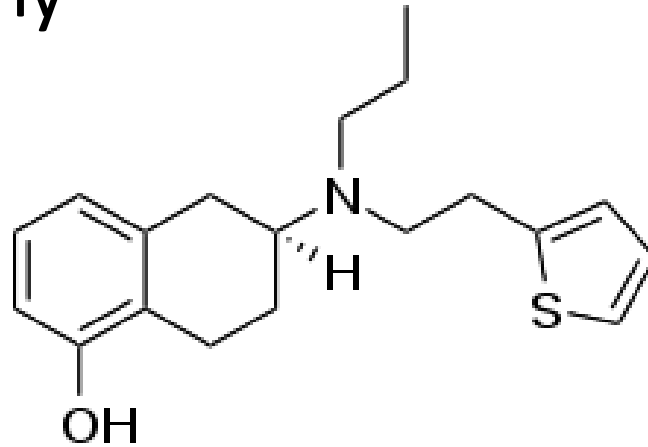


How can we adapt available techniques or methods to better understand these interrelated issues?



# Visualization of the Dosage Form

- Photography



# Visualization of the Dosage Form

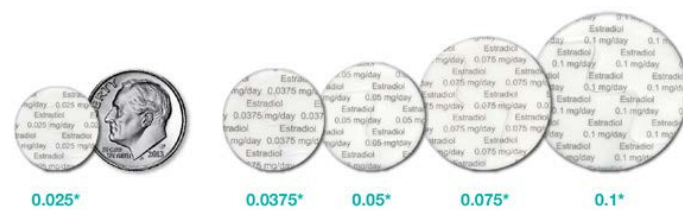
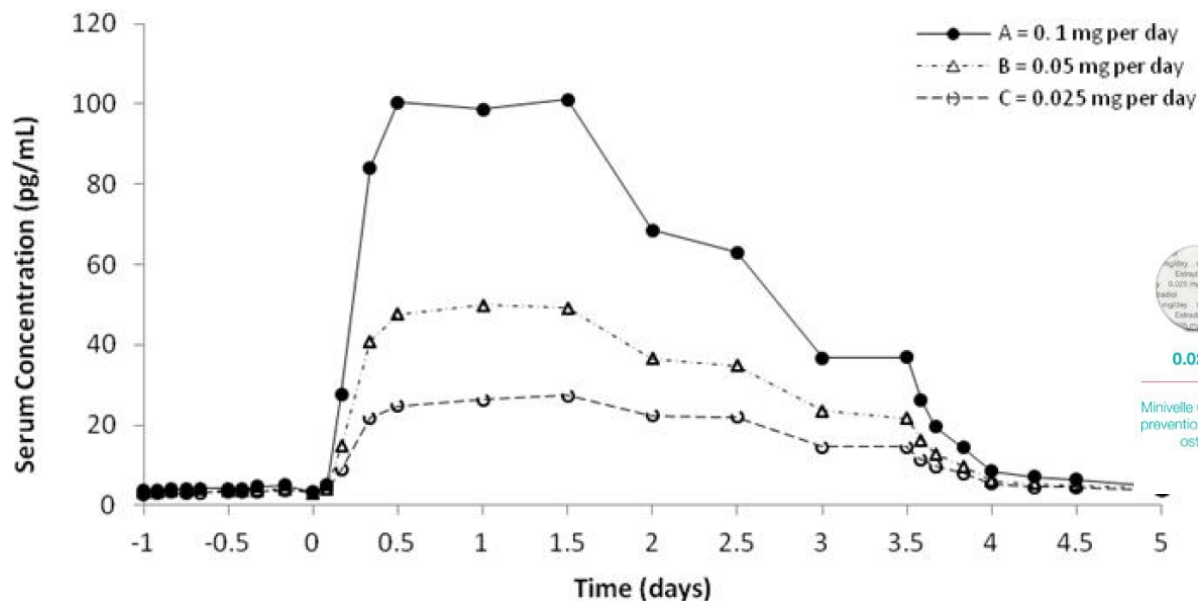


- What other techniques can we use to expand our understanding of the dosage form?
  - Can we use imaging or other techniques to monitor and/or model crystal growth kinetics and its potential impact on bioavailability?

# TDS Adhesion



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

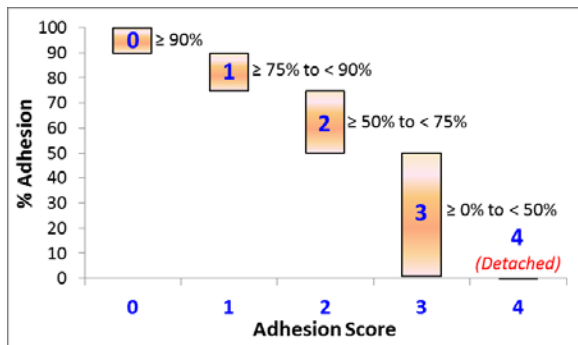


Minivelle 0.025 mg/day for the prevention of postmenopausal osteoporosis only

Minivelle in 4 dosing options for the treatment of moderate to severe menopause-related hot flashes and night sweats and the prevention of postmenopausal osteoporosis.

\*mg/day      Patches and dime are proportional but not shown at actual size.

# Assessing Generic TDS Adhesion

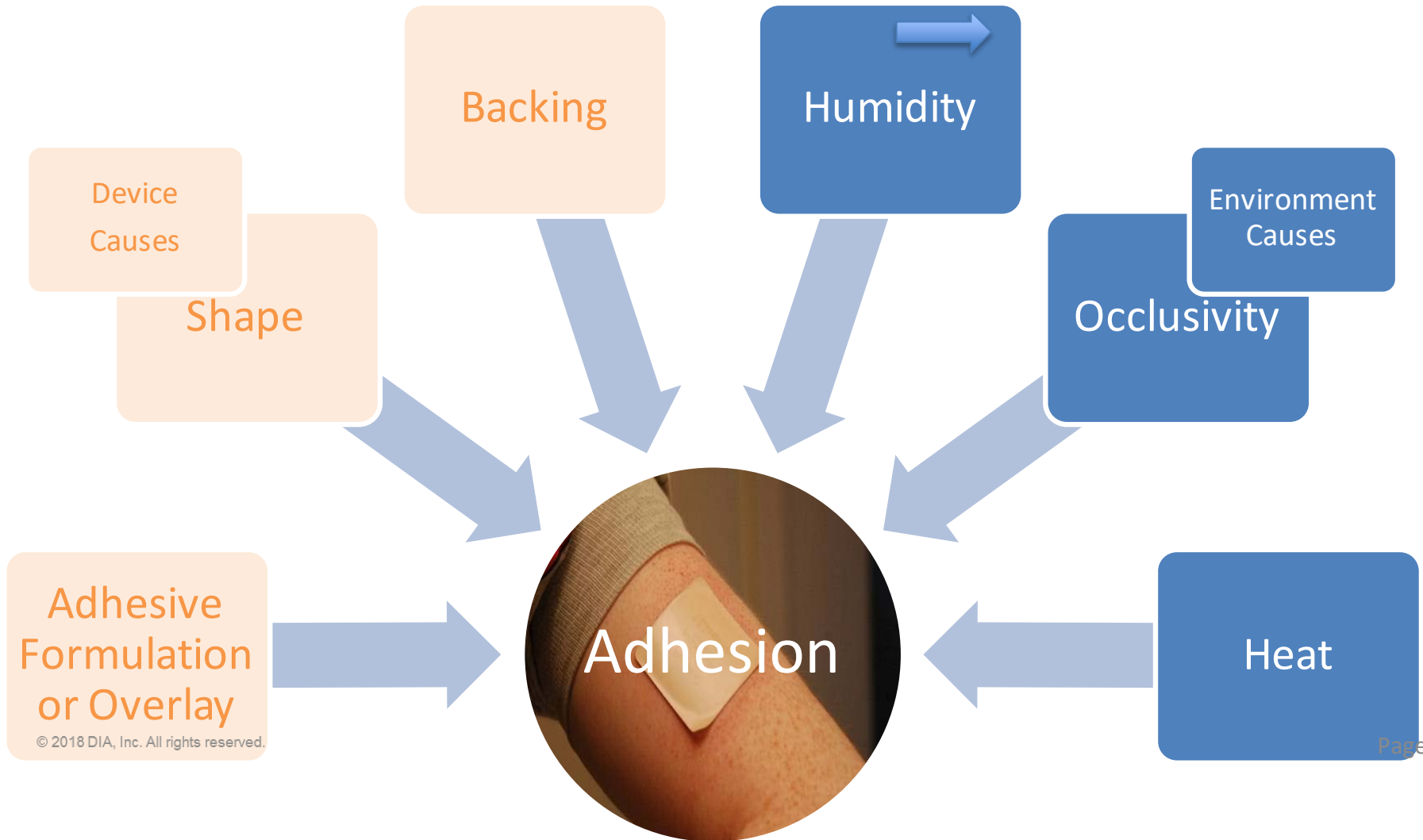


# Assessing Generic TDS Adhesion



- Draft guidance for industry on assessing generic TDS adhesion
  - Published June, 2016 and Revised October, 2018<sup>1</sup>
  - 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

# Factors Contributing to Failure



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# 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



+

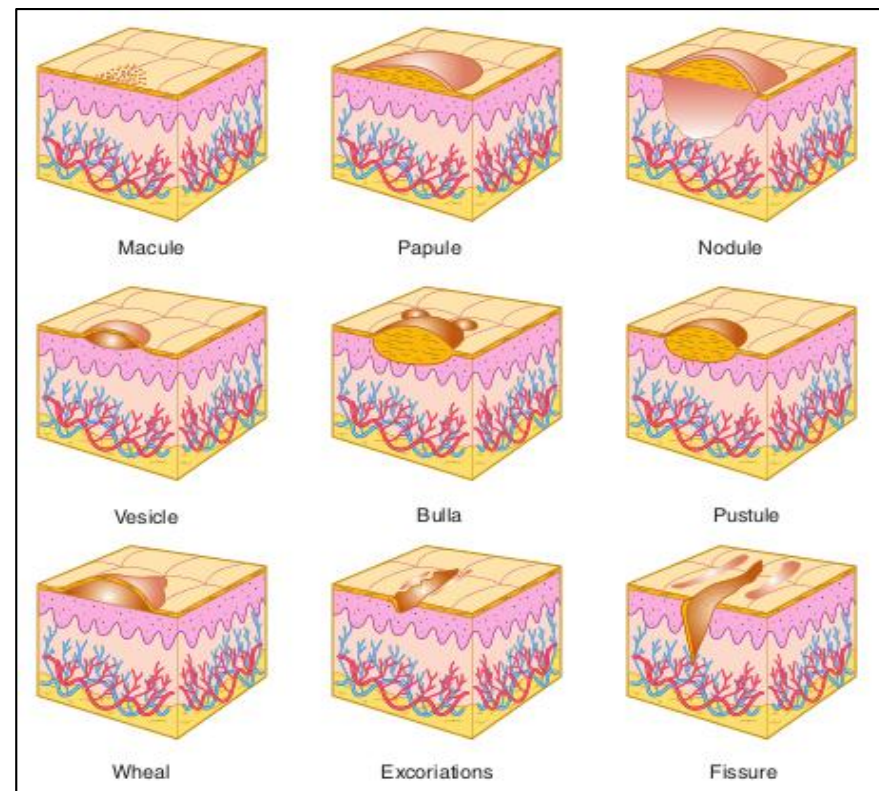
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?

IR

- + Weak Positive Reaction:**  
non-vesicular with erythema, infiltration, possibly papules
- ++ Strong Positive Reaction:**  
vesicular, erythema, infiltration, papules
- +++ Extreme Positive Reaction:**  
bullous or ulcerative reaction
- ? Doubtful Reaction:**  
faint macular erythema only
- IR Irritant Reaction:**  
Pustules as well as patchy follicular or homogeneous erythema without infiltrations are usually signs of irritation and do not indicate allergy. Itching is a subjective symptom that is expected to accompany a positive reaction.



<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:

<b>Scale 1. Dermal Response (Skin Appearance)</b>	<b>Score</b>
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

<b>Scale 2. Other Effects (Observation)</b>	<b>Score</b>
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 1<sup>st</sup>, 2019, Silver Spring, Maryland



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GDUFA Award U01FD00**4955**

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