MUsT and Dermal New Drug Applications

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Disclaimer: *The presentation today are my views on the topic and should not be considered, in whole or in part as being statements of policy or recommendation by the US Food and Drug Administration.*

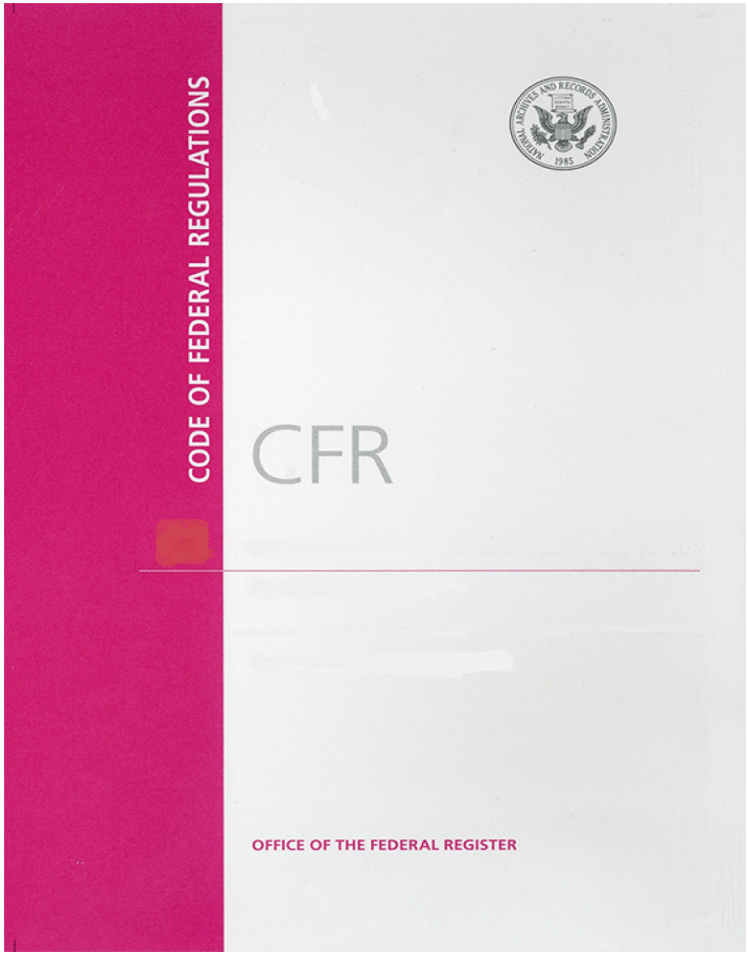
Outline

- Background
  - Regulatory considerations
  - PK studies for topical products – A historical perspective
  - Maximal usage trial design
- Concepts of maximal usage - deconstructed
  - Biological factors
  - Formulation factors
  - Ontogenetic factors
- Relevant literature for further reading
- Summary

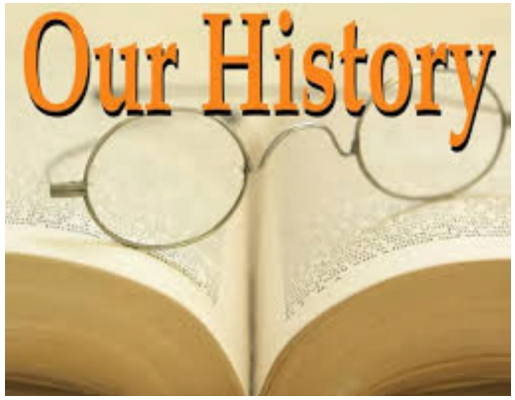
Background

Regulatory considerations

- Code of Federal Regulations (21 CFR 320.21)
  - Evidence measuring the in vivo bioavailability of the drug product that is the subject of the application, or
  - Information to permit FDA to waive the submission of evidence measuring the in vivo bioavailability



Pharmacokinetic studies for topical dermatological products – A historical perspective!



Since mid-1970s – Sponsor's are required to evaluate in-vivo drug BA

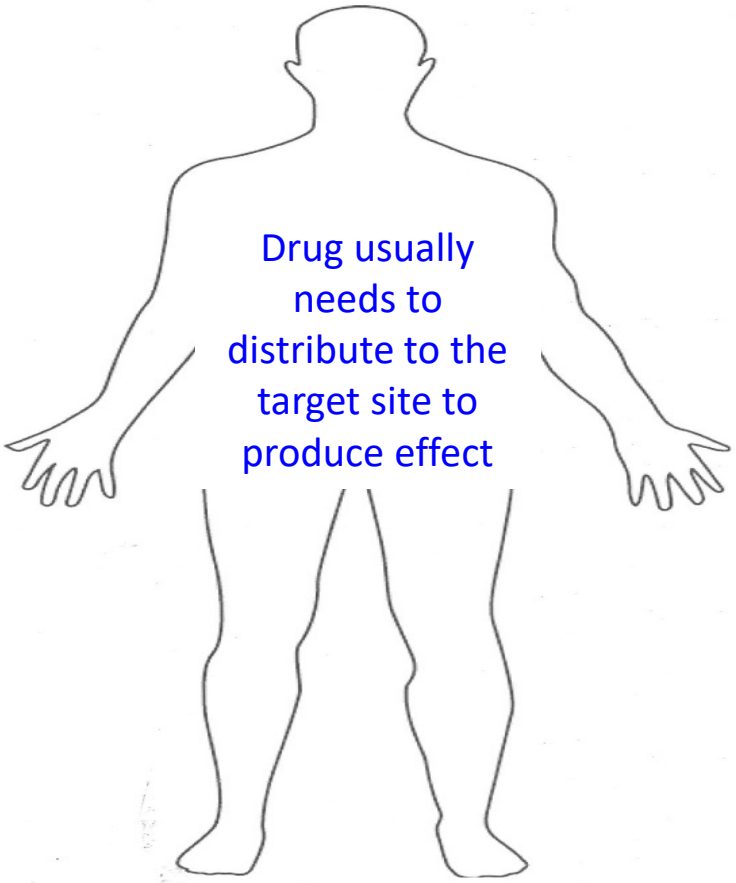
For topical products BA evaluation was not always possible due to bioanalytical limitations

Since late 1990s – Maximal use PK trial is being recommended by the Agency to assess systemic BA for topical products

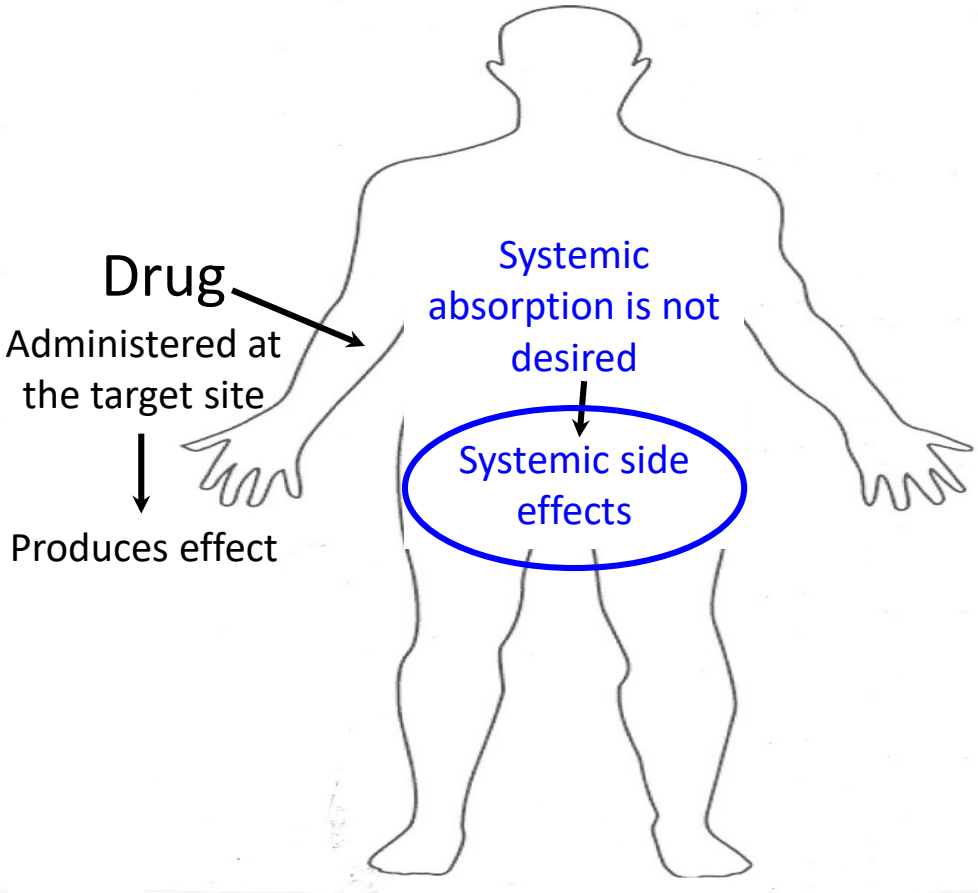
Why are topical dermatological products special?

According to 21 CFR 320.1 – Bioavailability (BA) is defined as the rate and extent to which the active moiety is absorbed from the drug product and becomes available at the site of action

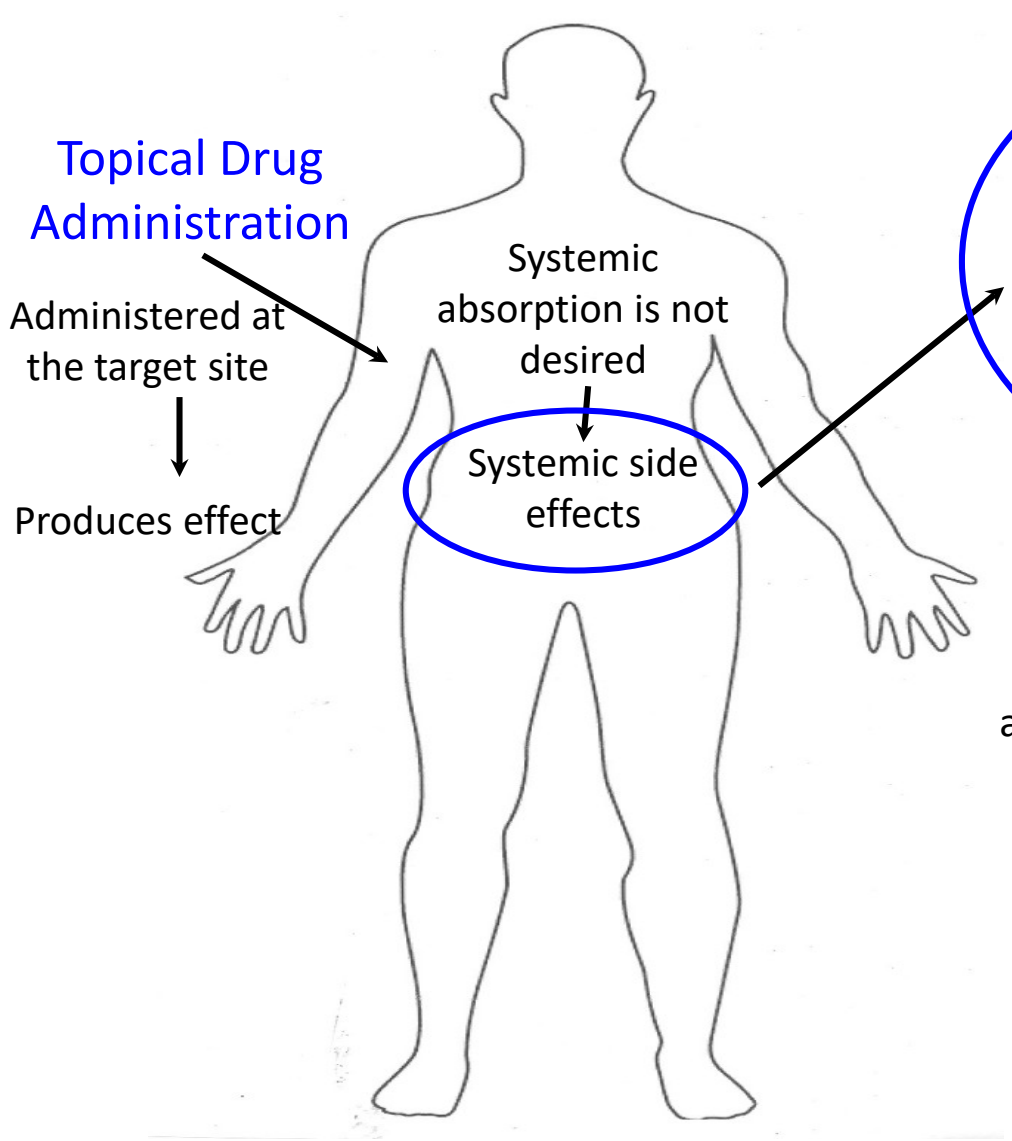
Systemic administration



Topical administration



Systemic bioavailability trial design for topical dermatological products



Clinical trials should be designed in order to maximize topical drug absorption so as to maximize the potential to observe any systemic side effects in order to capture the worst case scenario

Phase 3 safety and efficacy clinical trials focus on the "broad middle" of patient population and recruitment of patients at the upper end of disease severity is not a driver

Maximal Usage Study (MUsT)
Assessment of systemic safety

A maximal usage PK study is conducted by obtaining adequate number of PK samples at steady state following administration of the to-be-marketed formulation. This study should be conducted in a suitable number of subjects with the dermatological disease of interest at the upper range of severity as anticipated in both your clinical trials and proposed labeling. Such a study would attempt to maximize the potential for drug absorption to occur by incorporation of the following design elements:

a) Frequency of dosing
b) Duration of dosing
c) Use of highest proposed strength
d) Total involved surface area to be treated at one time
e) Amount applied per square centimeter
f) Method of application/site preparation

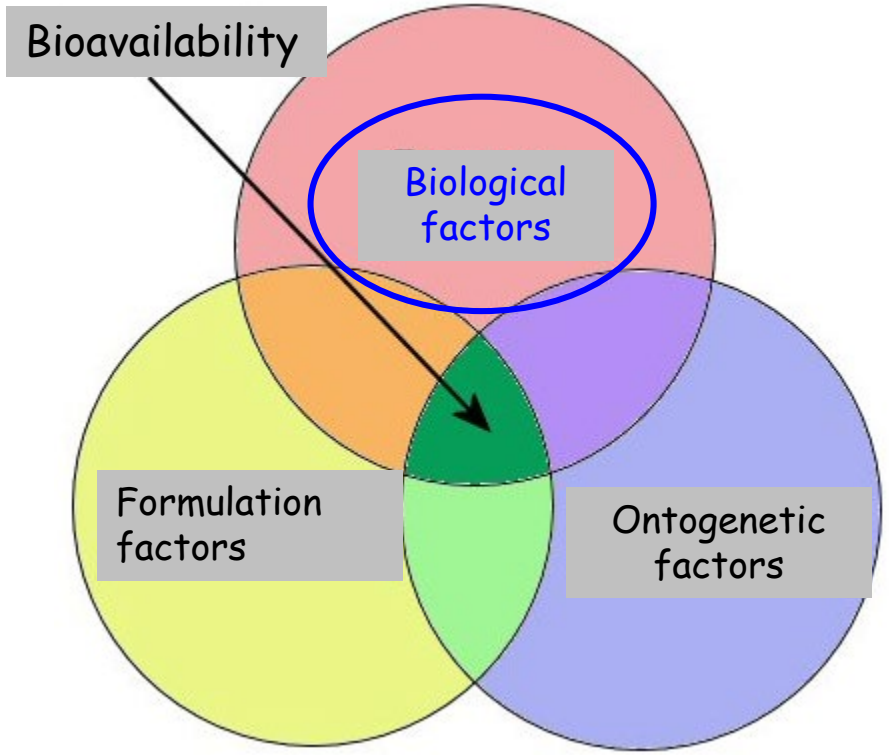
This study could be a stand alone trial in phase II or could be a sub-group of subjects in a larger phase III trial. Amount of formulation used by each subject should be recorded and you should ensure that target patient population is properly represented in this trial.

Reference: Bashaw ED et. al, 2015, Maximal Usage Trial: An Overview of the Design of Systemic Bioavailability Trial for Topical Dermatological Products, Ther Innov Regul Sci, 49(1):108-115.

Concepts of maximal usage - deconstructed

Determinants of bioavailability following topical administration

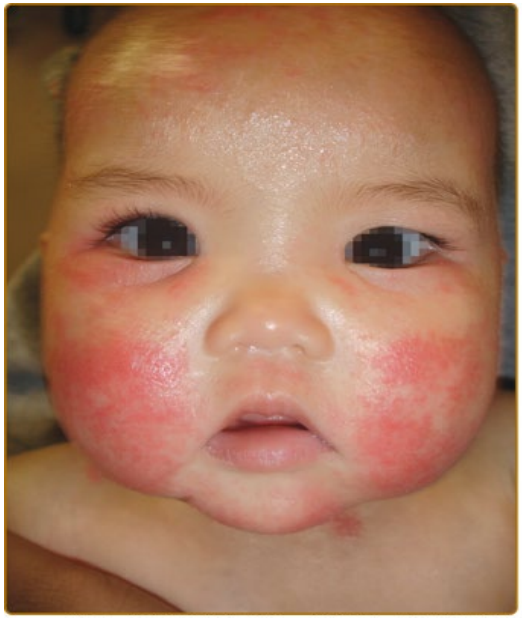
- BA following topical administration is a result of complex interaction of formulation, biological and ontogenetic factors.
- Formulation factors include physicochemical properties of the drug substance, dosage form, composition and characteristics of the formulation, etc.
- Biological factors include, effect of the disease, % BSA involved, etc.
- Ontogenetic factors include impact on bioavailability due to difference in the drug disposition due to development.



Effect of disease on systemic exposure

Healthy Skin
The barrier

Diseased Skin
The barrier?



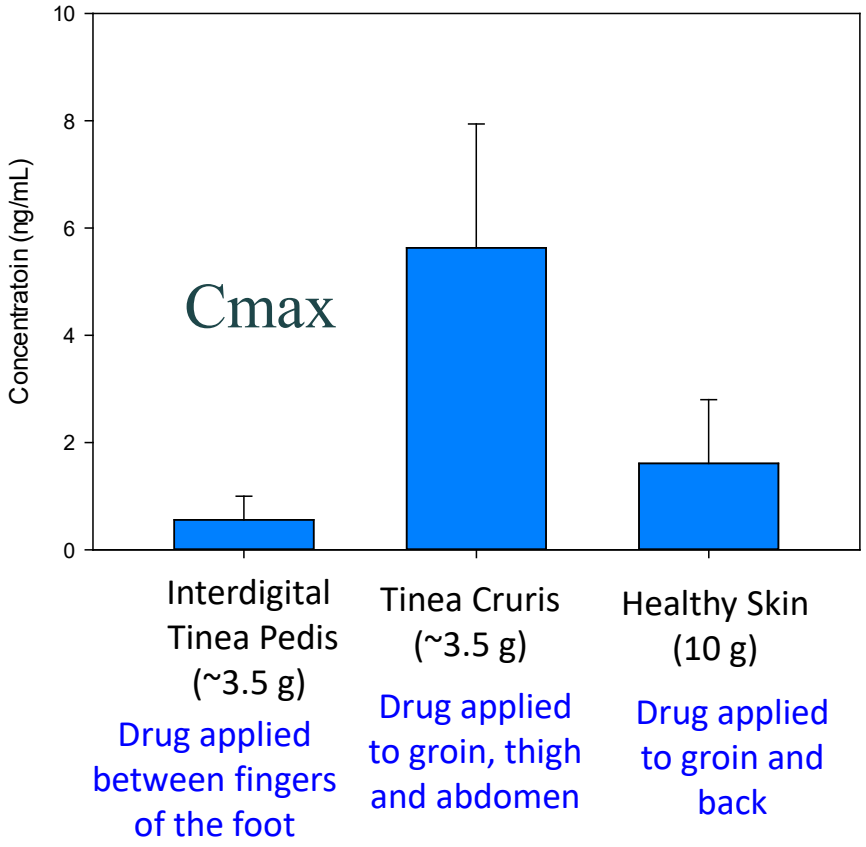
Atopic dermatitis

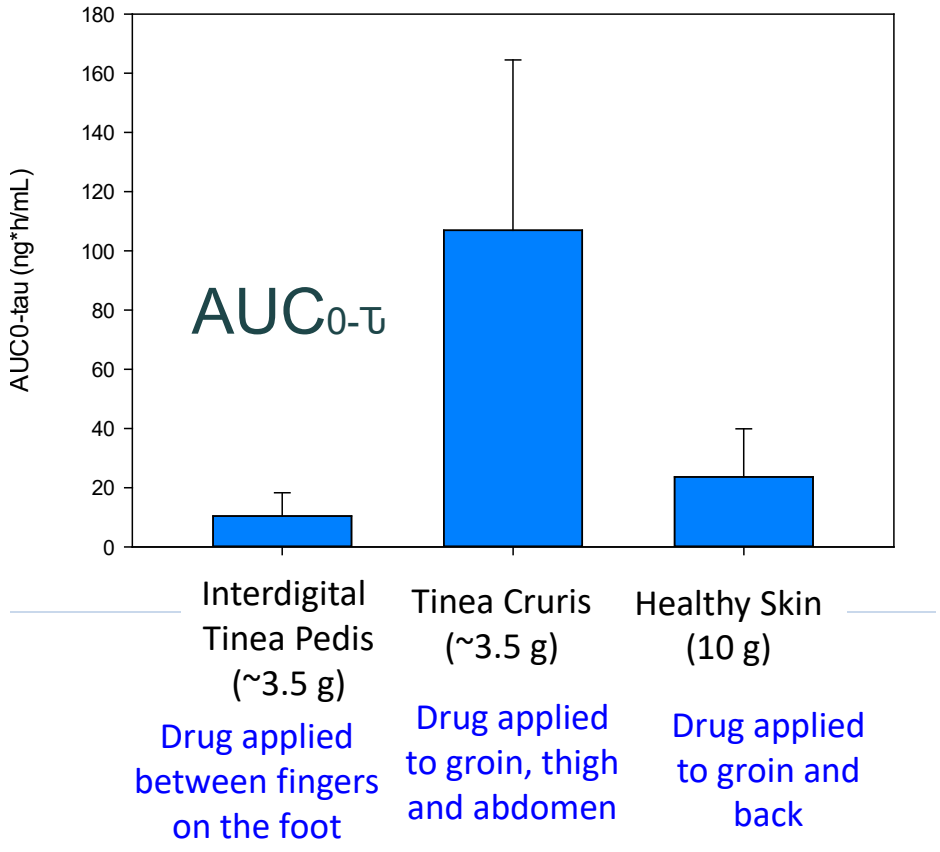
Source: Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, Wolff K: *Fitzpatrick's Dermatology in General Medicine, 8th Edition*: www.accessmedicine.com

- Skin permeation of healthy and diseased skin are different.
- Maximal usage study should be generally done in subjects with the disease of interest.

Change in disease states affect drug absorption

Product: Luliconazole cream 1%

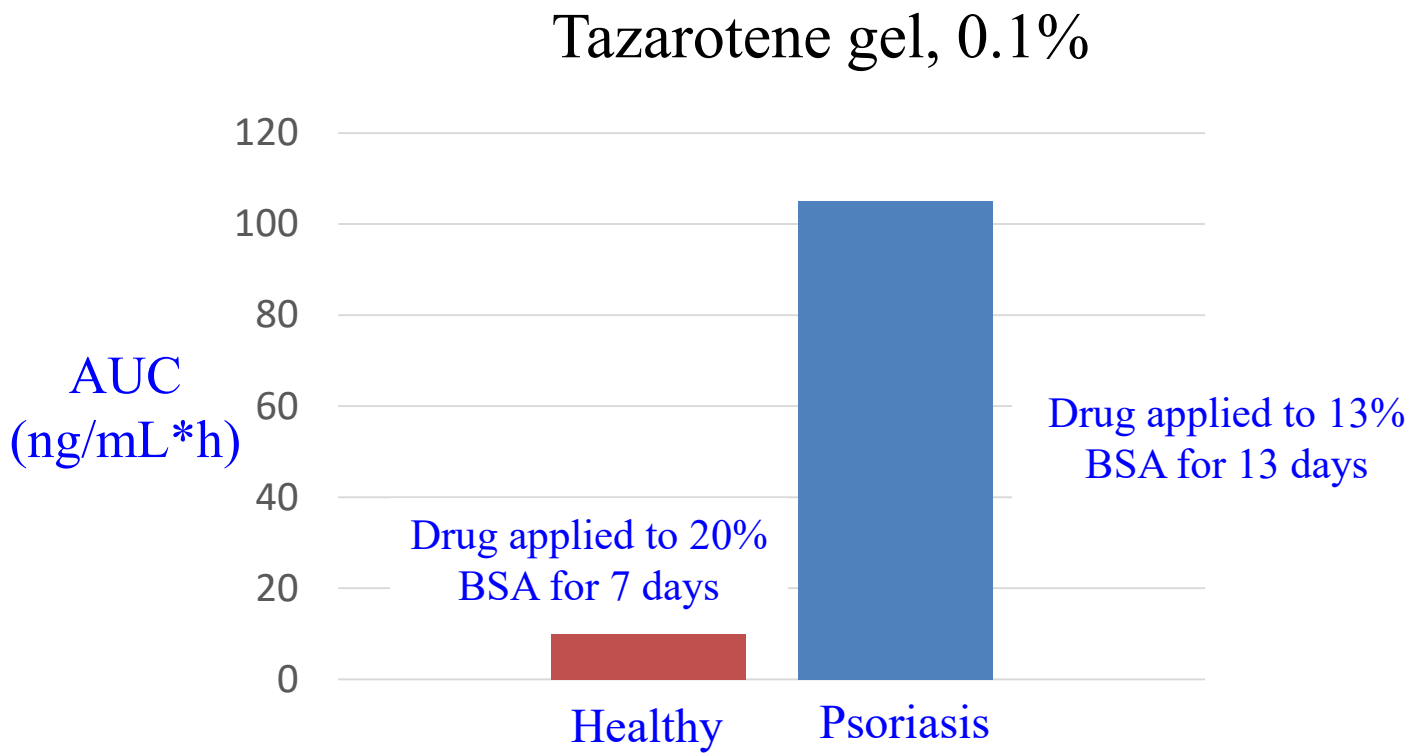




- Even though a lower dose was applied, the bioavailability of luliconazole was ~ 4 fold higher in subjects with tinea cruris compared to healthy skin

Reference: Adapted from raw data in NDA 204153 - Clinical Pharmacology and Biopharmaceutics review.
http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204153Orig1s000ClinPharmR.pdf

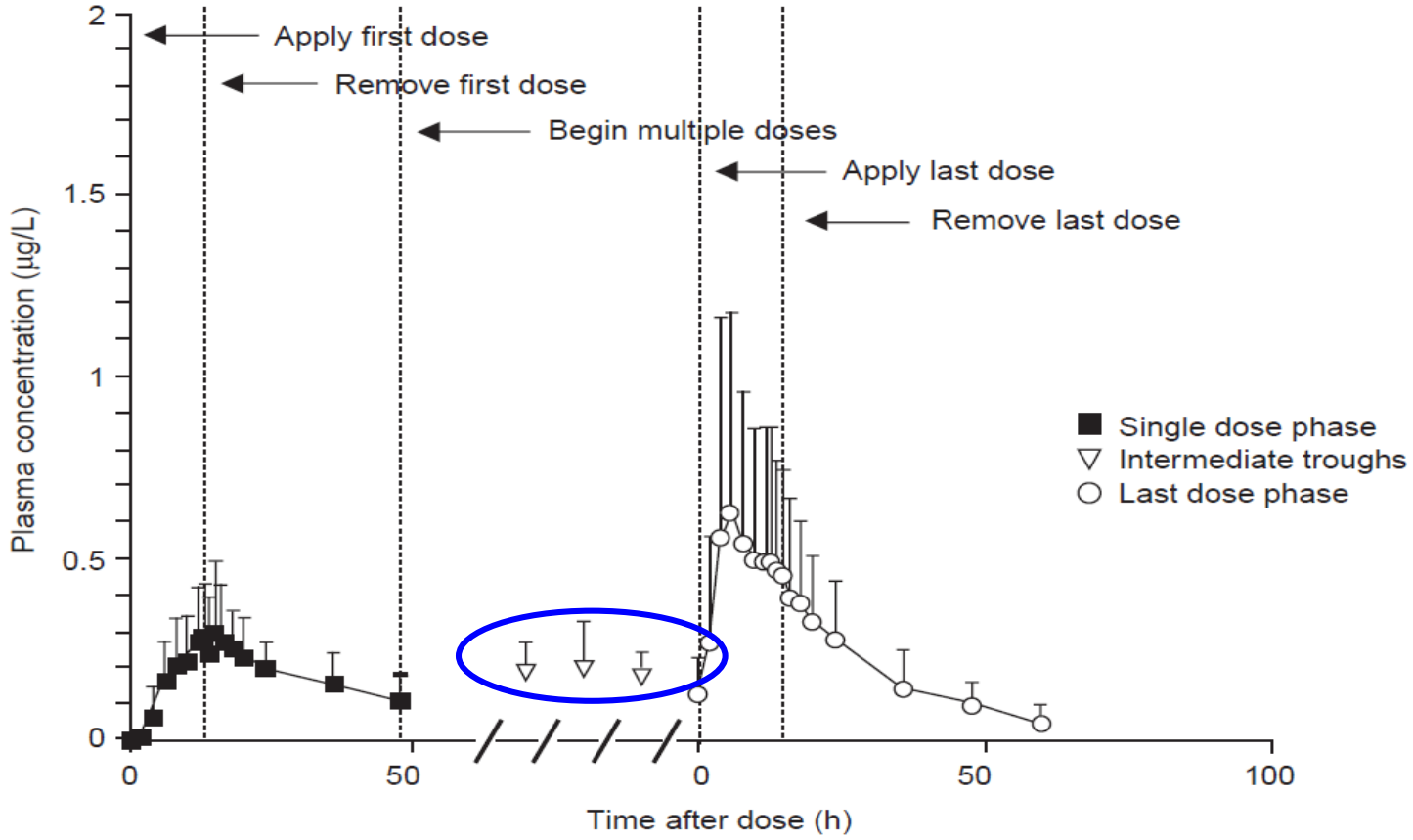
Drug absorption – Healthy versus Disease skin



- Disease has an impact on the bioavailability.
- Tazarotene is a teratogen and assessment of BA under maximal use conditions is needed for systemic safety assessments and labeling

Reference: Tang-Liu DD, Matsumoto RM, Usansky JI (1999) Clinical pharmacokinetics and drug metabolism of tazarotene: a novel topical treatment for acne and psoriasis. Clinical pharmacokinetics 37:273-87

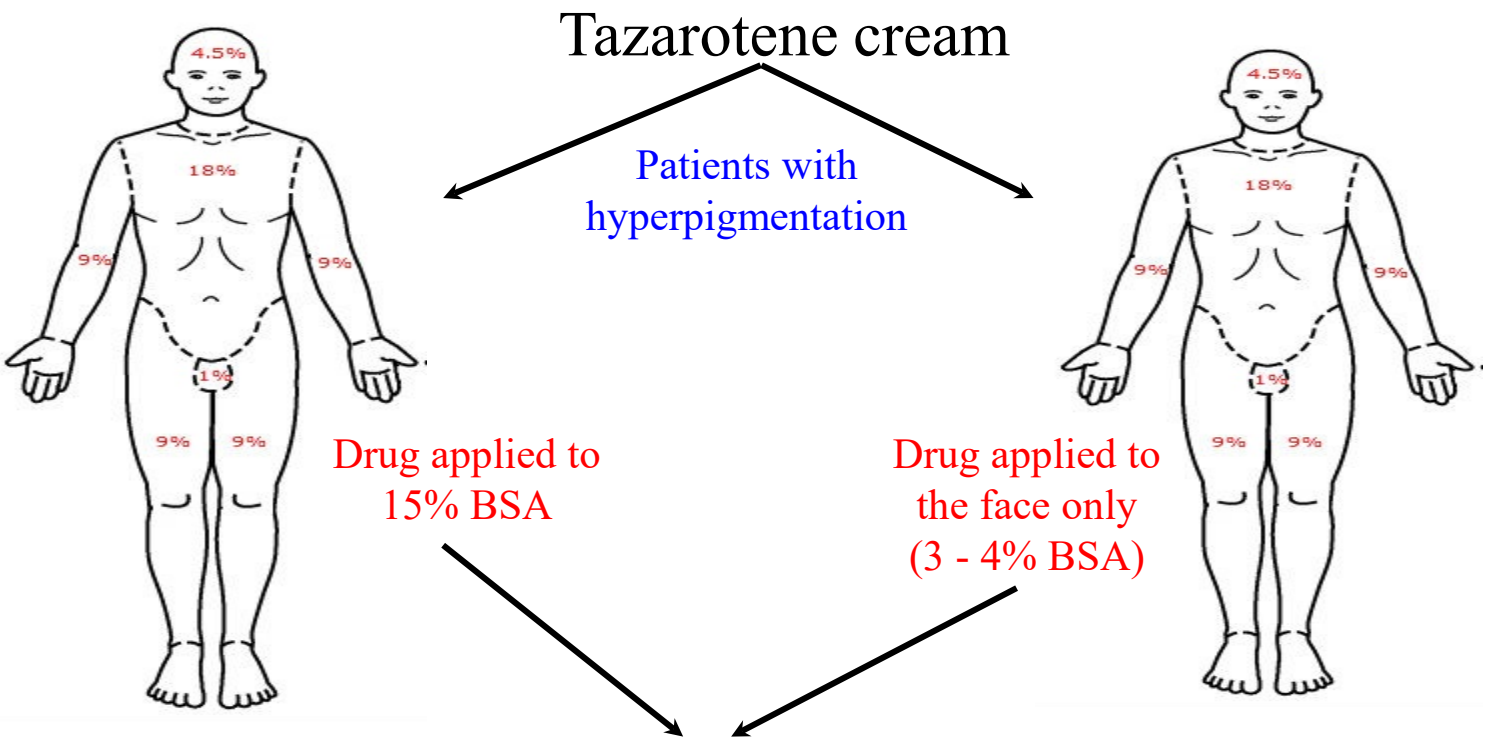
Drug absorption – single dose vs. steady state



- PK assessment under maximal use conditions informs systemic safety and should be done at steady state to account for drug accumulation

Reference: Tang-Liu DD, Matsumoto RM, Usansky JI (1999) Clinical pharmacokinetics and drug metabolism of tazarotene: a novel topical treatment for acne and psoriasis. Clinical pharmacokinetics 37:273-87

Impact of body surface area on drug bioavailability

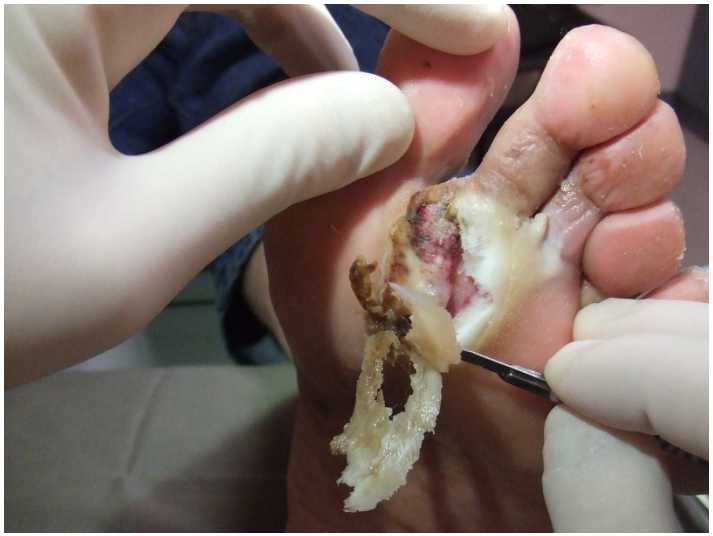


Systemic exposure was 10 times higher in the 15% BSA group compared to the face only group (3 - 4% BSA).

Reference: Avage Cream Label (Label approved on 30 September 2002)
http://www.accessdata.fda.gov/drugsatfda_docs/label/2002/21184s2lbl.pdf

Method of application and site preparation

Debridement for diabetic foot ulcer



- Debridement procedure removes dead tissue from the surface and thus alters drug absorption

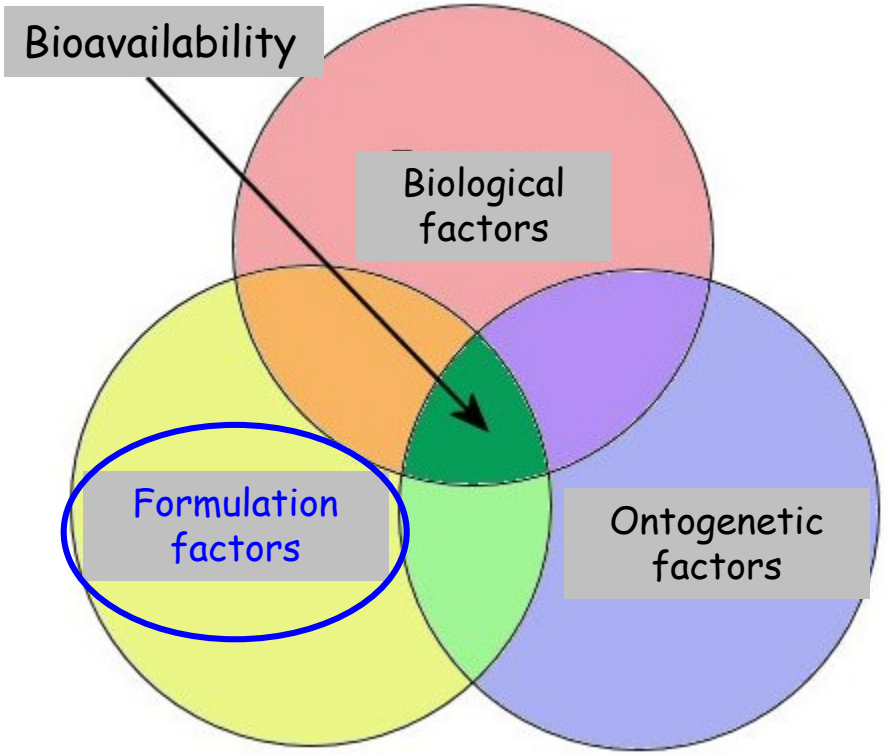
Occlusive dressing

- Occluded conditions might alter drug absorption compared to non-occluded conditions

Determinants of bioavailability following topical administration

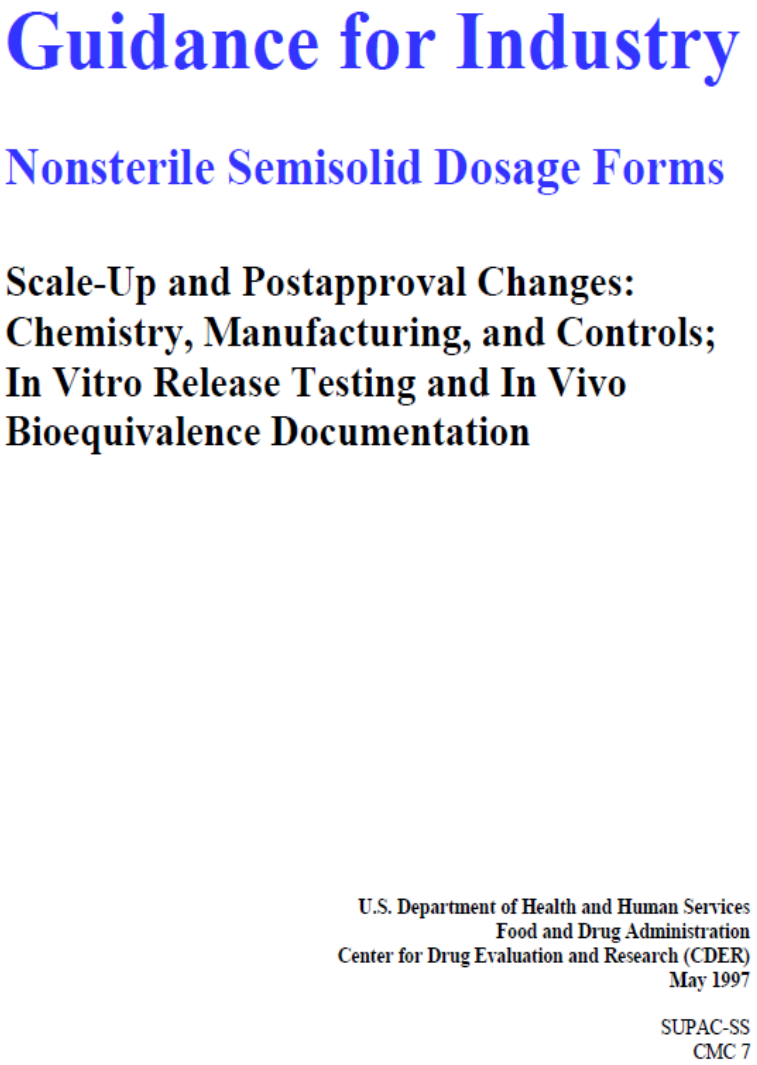
Summary of biological factors

- Healthy vs. disease skin
- Effect of BSA
- Steady state – effect of drug accumulation
- Method of drug application and site preparation



Change in formulation

- To-be-marketed formulation should be used
- If there are changes in the formulation, refer to SUPAC guidance for nonsterile semi solid dosage forms for data needs to support the change.
- If multiple strengths are being developed, then the maximal use PK trial should be conducted with the highest proposed strength



Guidance for Industry

Nonsterile Semisolid Dosage Forms

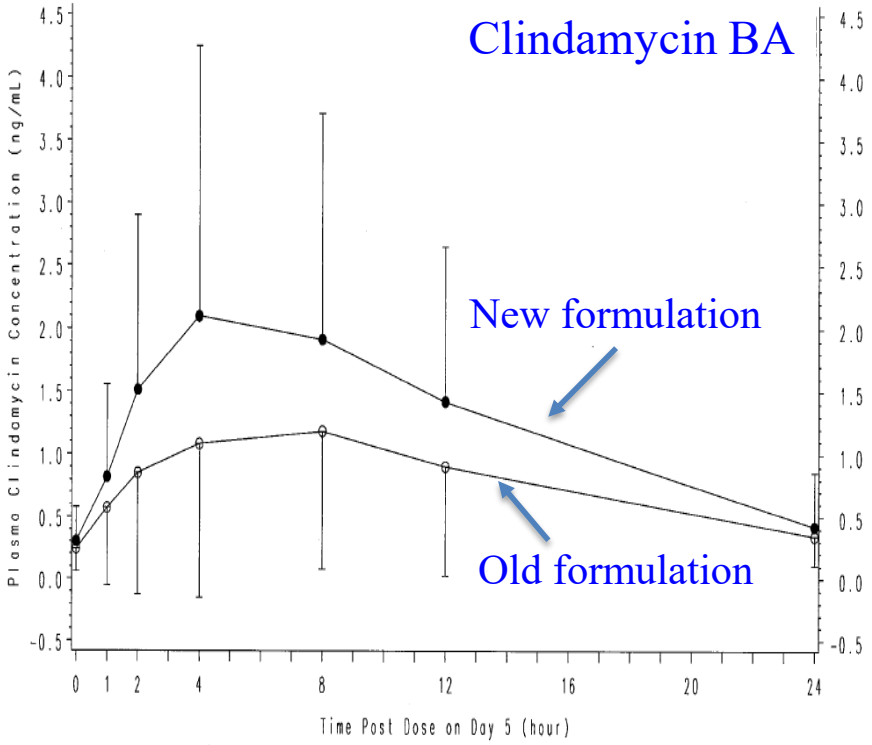
Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
May 1997

SUPAC-SS
CMC 7

Impact of excipient change on drug bioavailability

Clindamycin and tretinoin gel



- Surfactant system was changed in the formulation.
- This change was considered as a Level 3 change as per SUPAC- SS guidance.
- A new maximal usage study was conducted.
- The BA of clindamycin increased by ~ 1.6 fold while that of tretinoin remained unchanged.
- Impact of this increase in drug BA on systemic safety needs to be addressed.

Reference: NDA 50803- Clinical Pharmacology and Biopharmaceutics review.
http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/050803Orig1s000ClinPharmR.pdf

Cross-study comparison of systemic exposure from different dosage forms of Adapalene

Trade name	PK data (N/C = Not Calculated)		
	$N_{quantifiable}/N_{total}$	Mean C_{max} (ng/mL)	Mean AUC_{0-24} (ng*h/mL)
Differin Gel, 0.1%	24/24 (18 adolescents + 6 adults)	0.05 ± 0.03 (Range 0.025 – 0.17)	0.83 ± 0.49 (Range 0.50 – 2.90)
Differin Cream, 0.1%	N/C (adults)	N/C	N/C
Differin Lotion, 0.1%	2/14 (adults)	(Range 0.10 – 0.13)	N/C
	5/14 (adolescents)	0.13 ± 0.05 (Range 0.10 – 0.24)	3.07 ± 1.21 (Range 1.86 – 4.93)

Reference: April 15, 2016 Meeting of the Nonprescription Drugs Advisory Committee Meeting for Differin Gel Rx to OTC Switch
https://www.fda.gov/media/97529/download

Approval of lower strengths

Original approval in 1997 – 0.1% strength

Currently approved strengths

Retin-A Micro (tretinoin) Gel microsphere 0.1%, 0.08% and 0.04% for topical use
Initial U.S. Approval: 1997

INDICATIONS AND USAGE

Retin-A Micro (tretinoin) Gel microsphere, 0.1%, 0.08% and 0.04%, is a retinoid, indicated for topical treatment of acne vulgaris. (1)

12.3 Pharmacokinetics

Tretinoin is a metabolite of Vitamin A metabolism in man. Percutaneous absorption, as determined by the cumulative excretion of radiolabeled drug into urine and feces, was assessed in 44 healthy men and women after single and repeated daily applications of 500 mg of a 0.1% tretinoin gel formulation. Estimates of *in vivo* bioavailability, mean (SD)%, following both single and multiple daily applications, for a period of 28 days with the 0.1% gel, were 0.82 (0.11)% and 1.41 (0.54)%, respectively. The plasma concentrations of tretinoin and its metabolites, 13-*cis*-retinoic acid, all-*trans*-4-oxo-retinoic acid, and 13-*cis*-4-oxo-retinoic acid, generally ranged from 1 to 3 ng/mL and were essentially unaltered after either single or multiple daily applications of Retin-A Micro (tretinoin) Gel microsphere, 0.1%, relative to baseline levels. Clinical pharmacokinetic trials have not been performed with Retin-A Micro (tretinoin) Gel microsphere, 0.04% and 0.08%.

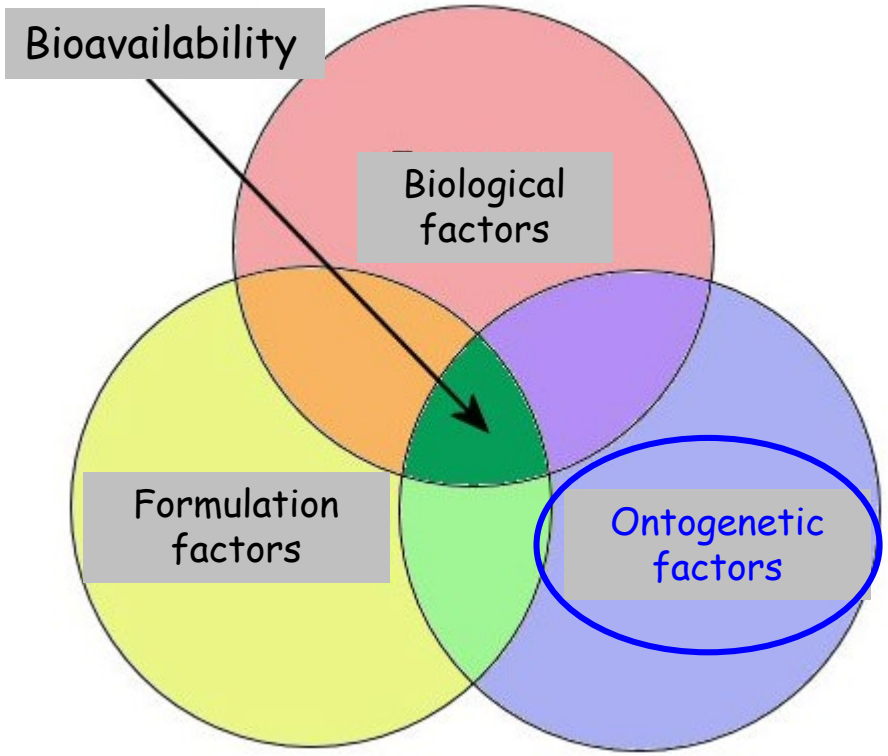
Amount applied per square centimeter

- Dosing of topical products is highly variable
- Amount applied in the maximal use PK trial should be recorded and compared with that used in the Phase 3 safety and efficacy trials

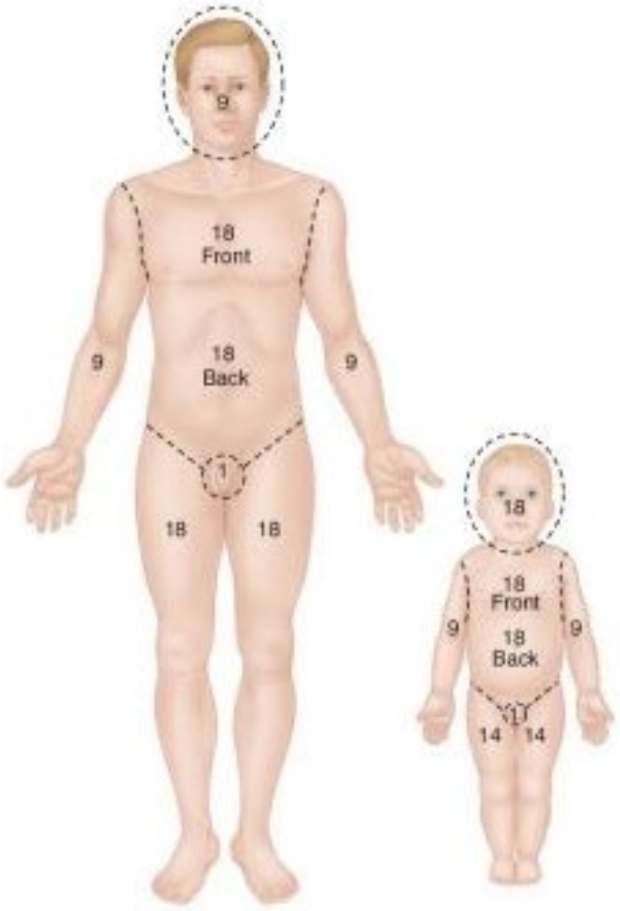
Determinants of bioavailability following topical administration

Summary of formulation factors

- Change in formulation could impact drug bioavailability
- Different dosage forms could produce different systemic exposure
- The dose in the MUsT and pivotal Phase 3 trials should be recorded



Ontogenetic differences



- Pediatric subjects cannot be assumed to be miniature adults.
- The body surface area to volume ratio is larger in pediatric subjects and this could result in higher drug exposure.
- Drug metabolism and excretion pathway might not be fully mature especially in neonates and infants affecting drug disposition.
- In pre-mature infants skin is not fully mature and hence skin permeability could be different.

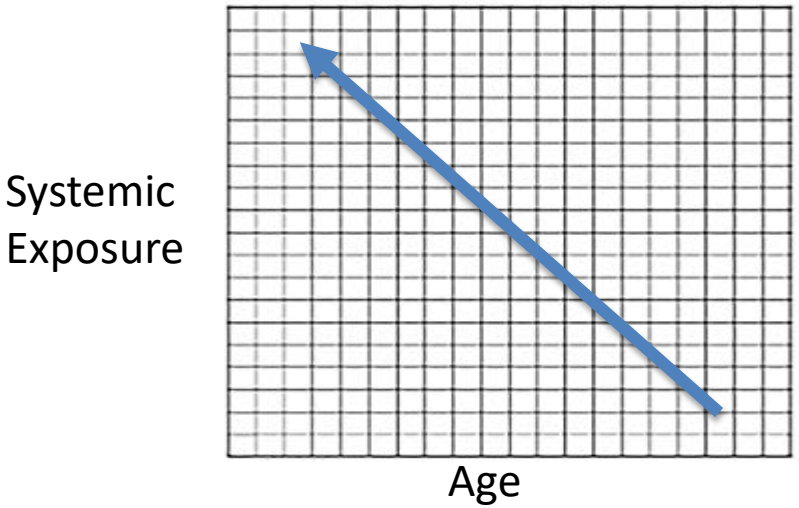
Pediatric maximal use – Head lice

Drug X Head lice	Age Group	C_{max} (ng/mL)	AUC (ng*h/mL)
	<12 months	230	670
	1 to <2 years	150	410
	2 to <3 years	160	600
	3 to 17 years	50	190

- Drug was applied as a single dose the entire scalp and hair and rinsed off after 10 minutes.
- Increase in systemic drug concentrations with decrease in age could be due to larger surface area to body mass ratio and/or ontogenetic differences in physiological processes affecting ADME

Pediatric maximal use
Minocycline Foam - Acne vulgaris

Age	Cmax (ng/mL)	AUC (h*ng/mL)
Adult	1.3	23.0
15 to less than 17 years old	2.0	40.8
12 to 14 years old	2.8	54.1
9 to 11 years old	4.5	90.9



Reference: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212379s000lbl.pdf

Pediatric maximal use
Tazarotene Lotion - Acne vulgaris

12.3 Pharmacokinetics

Following topical application, tazarotene undergoes esterase hydrolysis to form its active metabolite, tazarotenic acid. Tazarotenic acid is highly bound to plasma proteins (greater than 99%).

Systemic exposure following topical application of ARAZLO was evaluated in 28 subjects in an open-label, randomized, pharmacokinetic study. Subjects aged 9 years and older with moderate to severe acne applied approximately 4 grams of ARAZLO to the entire face (excluding eyes and lips), neck, upper chest, upper back and shoulders once daily for 14 Days.

The majority of collected samples had concentrations below the limit of quantification (LOQ) for tazarotene (0.005 ng/mL). The mean C_{max} and mean $AUC_{(0-t)}$ values for tazarotene from quantifiable samples were 0.007 ng/mL and 0.164 ng*hr/mL on Day 14 to 15, respectively. The mean C_{max} and $AUC_{(0-t)}$ of tazarotene in subjects aged 9 to less than 12 years was approximately 3.7 and 3.6 fold higher, respectively, compared to that observed in subjects 12 years and older.

Tazarotenic acid concentrations were measurable in the majority of samples following single and repeated topical administration of ARAZLO (LOQ = 0.005 ng/mL). The mean C_{max} and $AUC_{(0-t)}$ values for tazarotenic acid from quantifiable samples were 0.365 ng/mL and 5.72 ng*hr/mL on Days 14 to 15, respectively. The mean C_{max} and $AUC_{(0-t)}$ of tazarotenic acid in subjects aged 9 to less than 12 years was approximately 2.4 and 2.3 fold higher, respectively, compared to that observed in subjects 12 years and older.

Reference: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211882s000lbl.pdf

Pediatric safety assessment under maximal usage conditions

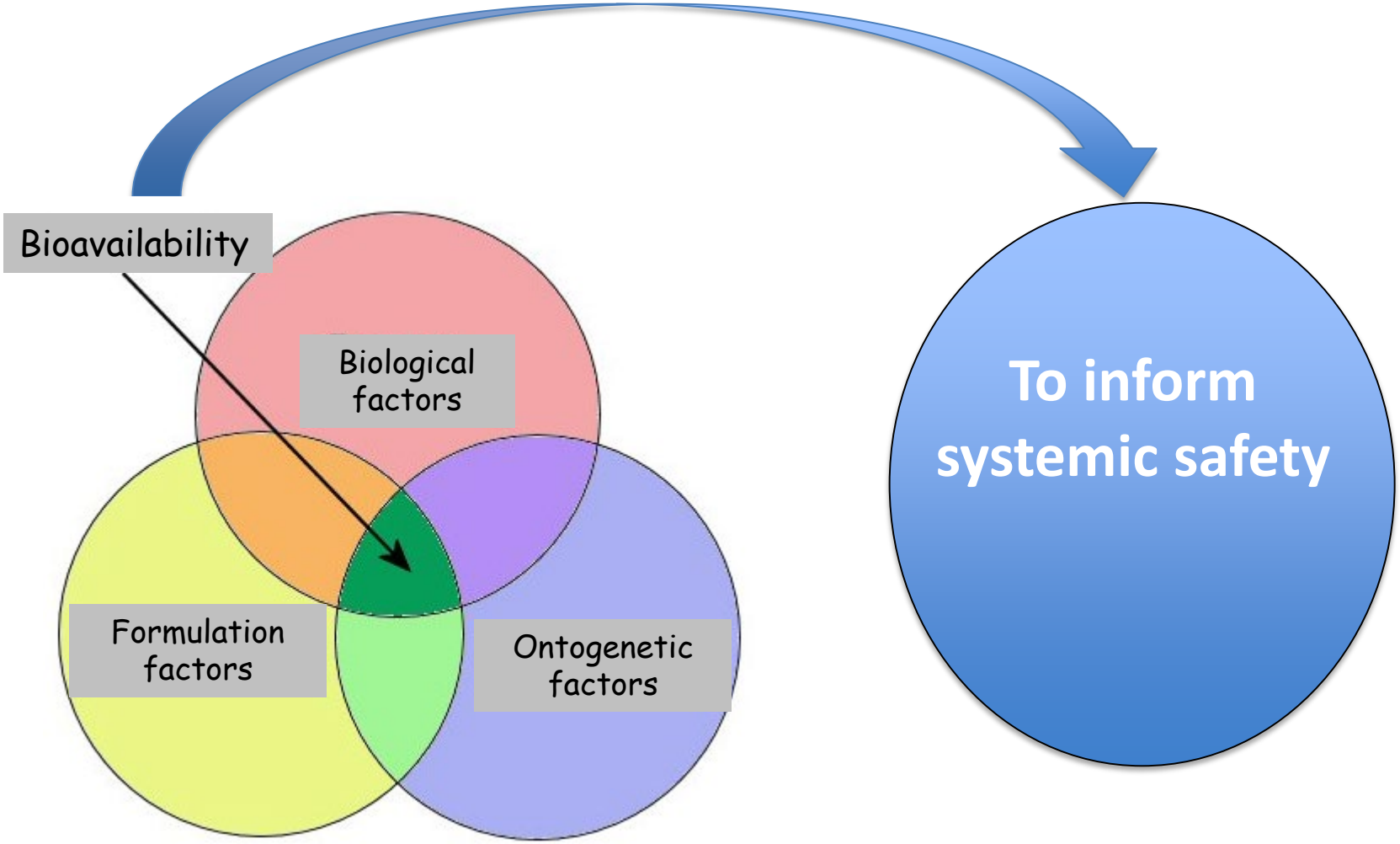
- HPA axis suppression rate for Diprolene AF Cream, 0.05% in subjects with atopic dermatitis

Age Group	3mo-1yr	2yr-5yr	6yr-8yr	9yr-12yr
%	**50**	**38**	**32**	**17**

- HPA axis suppression rates increased with decrease in age range

Reference: Adapted from presentation by Denise Cook, MD at the Joint Meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee and the Nonprescription Drugs Advisory Committee (2005)

Purpose of maximal usage study



Summary

- This presentation looked into the components of maximal usage study which have been revised and refined following years of experience.
- Although individual concepts impacting drug absorption were presented, the interplay between these components impact the systemic drug bioavailability of a topically administered drug.
- Pediatric subjects should not be considered as miniature adults and assessment of systemic absorption under maximal usage conditions is critical to inform systemic safety in this population.
- FDA encourages discussion of the design of the maximal usage study prior to initiation.

Relevant literature for further reading

Therapeutic Innovation
& Regulatory Science
2015, Vol. 49(1) 108-115

DOI: 10.1177/2168479014539157
tirs.sagepub.com

Maximal Usage Trial: An Overview of the Design of Systemic Bioavailability Trial for Topical Dermatological Products

Edward Dennis Bashaw, PharmD[1], Doanh C. Tran, PhD[1], Chinmay G. Shukla, PhD[1], and Xiaomei Liu, PharmD[1]

Abstract

Dermatologic diseases can present in varying forms and severity, ranging from the individual lesion and up to almost total skin involvement. Pharmacokinetic assessment of topical drug products has previously been plagued by bioanalytical assay limitations and the lack of a standardized study design. Since the mid-1990's the US Food and Drug Administration has developed and implemented a pharmacokinetic maximal usage trial (MUsT) design to help address these issues. The MUsT design takes into account the following elements: the enrollment of patients rather than normal volunteers, the frequency of dosing, duration of dosing, use of highest proposed strength, total involved surface area to be treated at one time, amount applied per square centimeter, application method and site preparation, product formulation, and use of a sensitive bioanalytical method that has been properly validated. This paper provides a perspective of pre-MUsT study designs and a discussion of the individual elements that make up a MUsT.

Keywords

Dermatology, Topical Drug Delivery, Absorption, Clinical Pharmacology, Maximal Use

Introduction

Dermatologic diseases are complex and present in varying forms and severity. Since these diseases are present in and manifested on the skin, they are usually treated by applying the drug topically to the target site. With the topical treatment, the general assumption, historically, was that the systemic absorption was generally low when compared to systemic administration. However, due to the compromised barrier properties of diseased skin, the topically applied drug can reach the systemic circulation and (MUsT) design to address these issues. This trial design is also referred to as a maximal use PK trial. This paper provides a perspective of pre-MUsT study designs and presents a discussion of the individual elements that make up a MUsT.

Background

Dermatologic diseases are very common, with current estimates being that, at any time, 1 of 3 Americans has an active

Maximal Usage Trials for Topically Applied Active Ingredients Being Considered for Inclusion in an Over-The - Counter Monograph: Study Elements and Considerations

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Thank you for your attention!


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