Clinical Experience in the NDA Setting with the Maximal Usage Study Paradigm

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Food and Drug Administration

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

WARNING: *This presentation contains pictures of skin conditions which might be scary to some of you.*

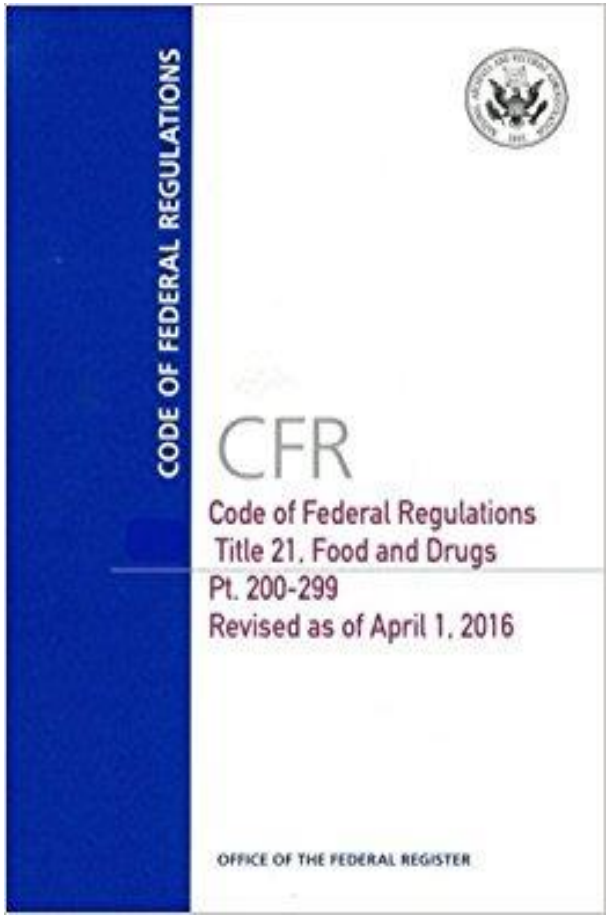
Outline

- Background
  - Regulatory requirement
  - Bioavailability assessment of topical products
- Concepts
  - Maximal usage trial design
  - Timing of maximal usage trial
- How is maximal usage PK data used?
  - Inform labeling
  - Assessment of systemic safety
  - Support clinical bridge for 505(b)(2) submissions
  - Rx to OTC switch: Risk/benefit assessment
- Pediatric maximal usage study
- Waiver of maximal usage study
- Maximal usage beyond NDA
- Relevant literature
- Summary

Background

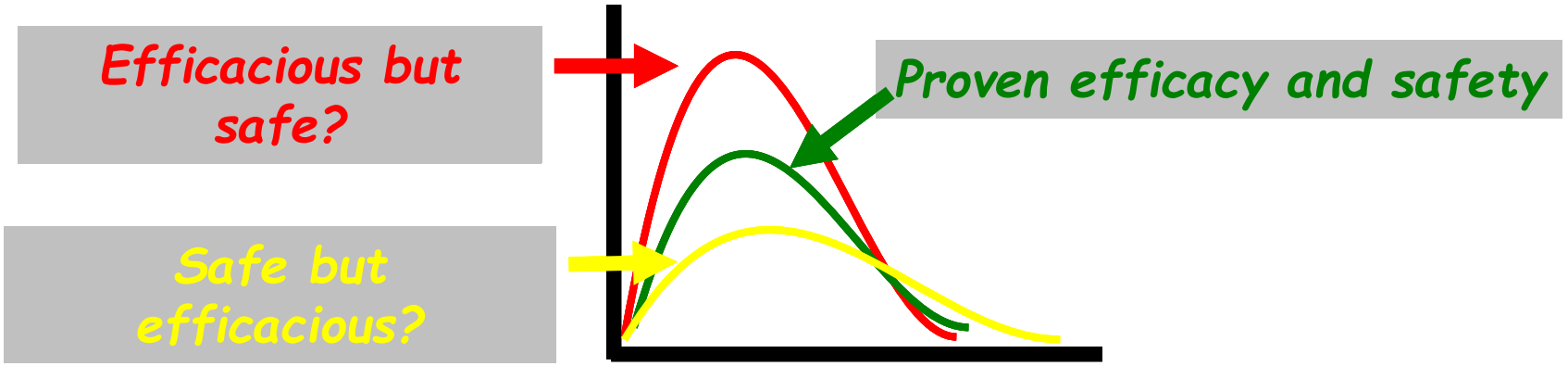
Regulatory requirement

- 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



Topical Bioavailability

- Normally Bioavailability testing is linked to both assessments of safety and efficacy (for systemic treatments) where blood concentrations are a surrogate for effect site concentrations.

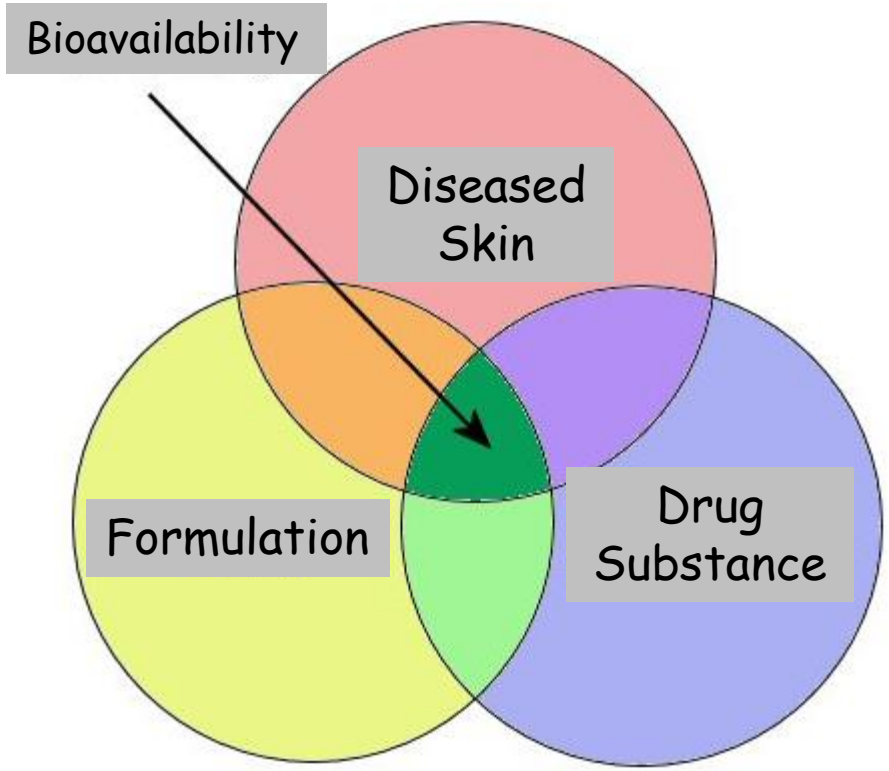


- For topical products where absorption is not normally desired, systemic bioavailability testing is primarily a safety assessment.

Determinants of Topical Bioavailability

- It is the complex interaction of drug substance, formulation-dosage form, and the effect of the disease itself on the barrier function of the skin that determines systemic drug availability.

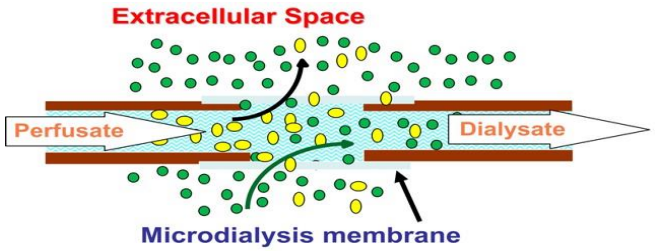
- Dermatologic diseases are unique in that drugs are delivered directly to the target tissues in high concentrations and yet the actual bioavailability is unknown.



Bioavailability assessment of topical products

Local bioavailability assessment

- Assess drug concentration at the target site (Skin)
  - Microdialysis
  - Open flow micro-perfusion
  - Tape stripping
  - Tissue biopsy
- Assess exposure-response relationship at the target site



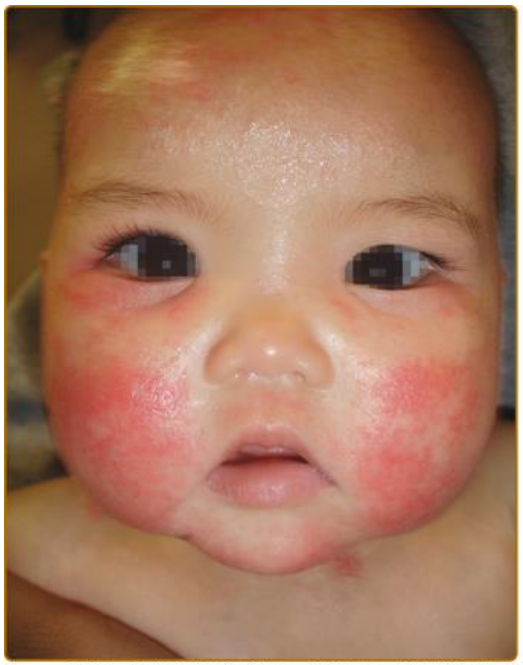
Systemic bioavailability assessment

- Assess systemic drug concentrations under maximal usage conditions
- Assessment of systemic safety

Core concepts

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.
- Do you think pharmacokinetic assessment conducted after applying the topical product on healthy skin would inform systemic safety?
- Hmmm!.....Yes in some cases for example alopecia, pigmental disorders like vitiligo, etc. where the skin is intact.

Maximal Usage Trial
Assessment of systemic safety

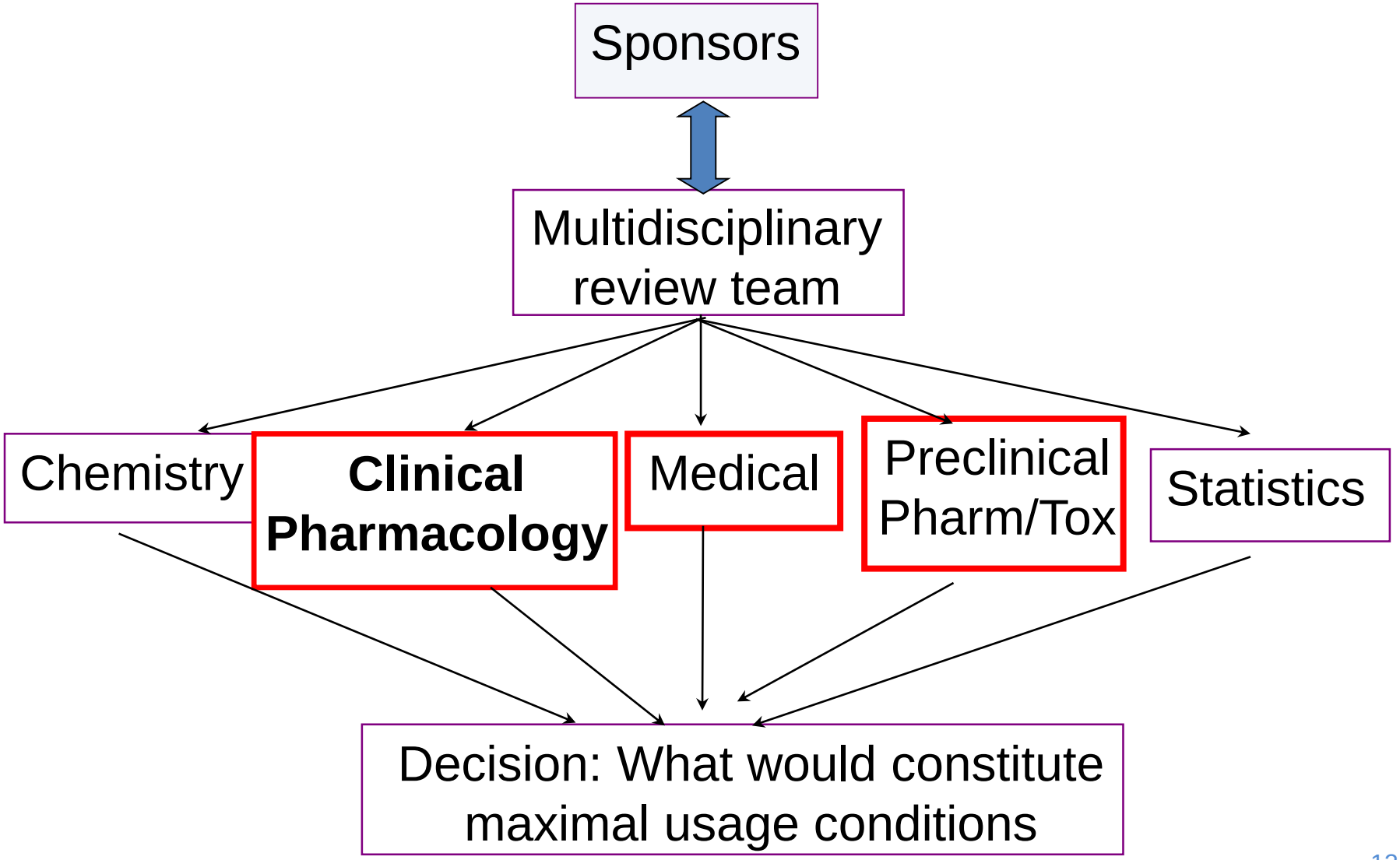
A maximal usage PK trial is conducted by obtaining adequate number of PK samples following administration of the to-be-marketed formulation. This trial should be conducted in a suitable number of subjects with the dermatological disease of interest at the upper range of severity as anticipated in both your clinical trials and proposed labeling. Such a trial 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

The trial itself could be a stand alone trial in phase II or could be a sub-group of subjects in a larger phase III trial. Either approach is acceptable. You should ensure that target patient population is properly represented in this trial.

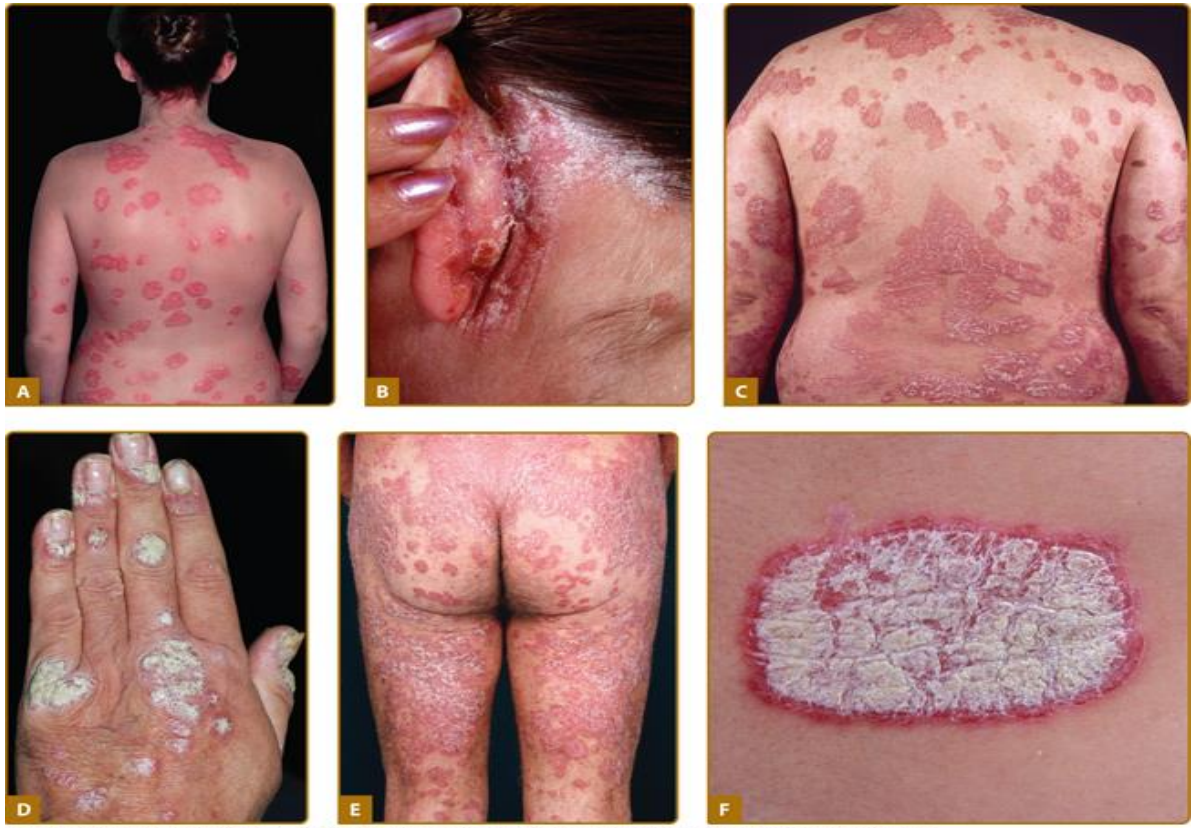
Reference: Bashaw ED et. al, 2015, Maximal Usage Trial: An Overview of the Design of Systemic Bioavailability Trial for Topical Dermatological Products, Ther Innov Regul Sci, 49(1):108-115.

How are maximal usage trials designed?



How are maximal usage trials designed

BSA considerations

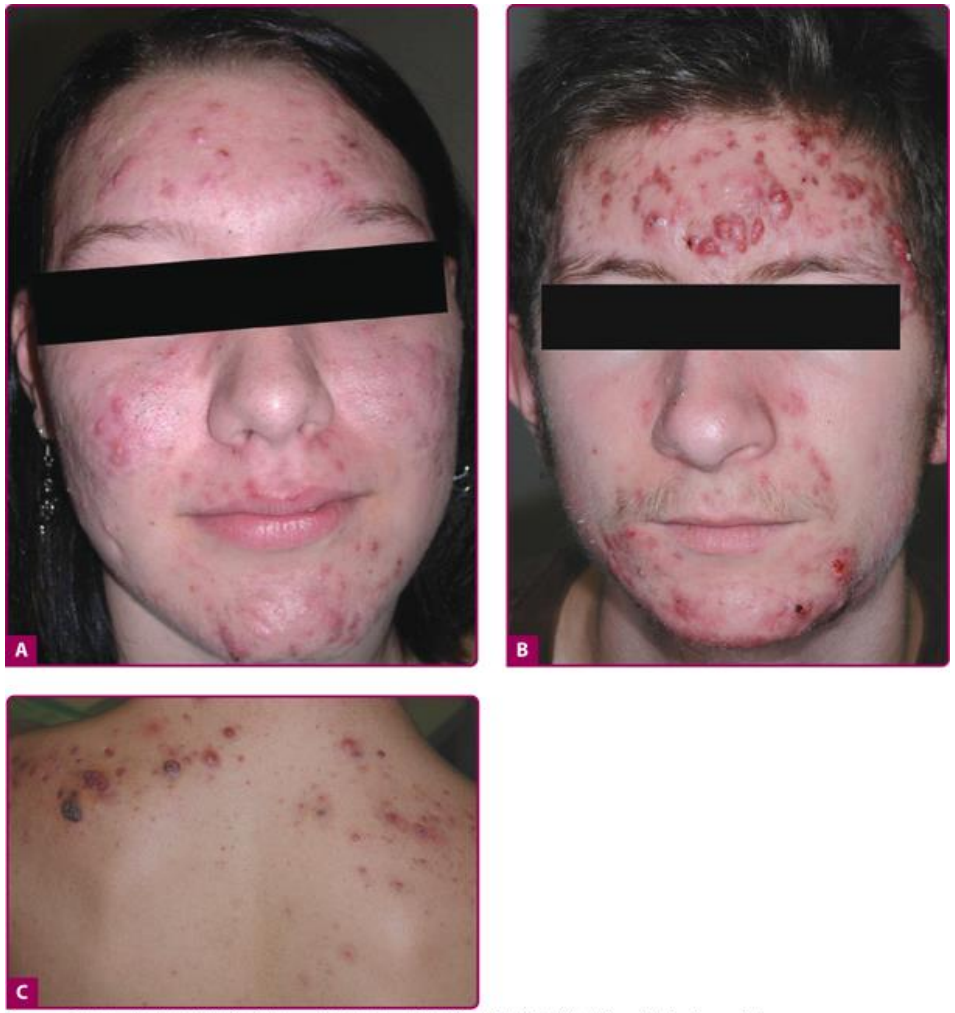


Source: Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, Wolff K: *Fitzpatrick's Dermatology in General Medicine, 8th Edition*: www.accessmedicine.com

Plaque psoriasis – Maximal use conditions include applying the drug to at least 20% BSA involved in adults and at least 10% BSA involved in subjects 12 to 17 years.

How are maximal usage trials designed

BSA considerations

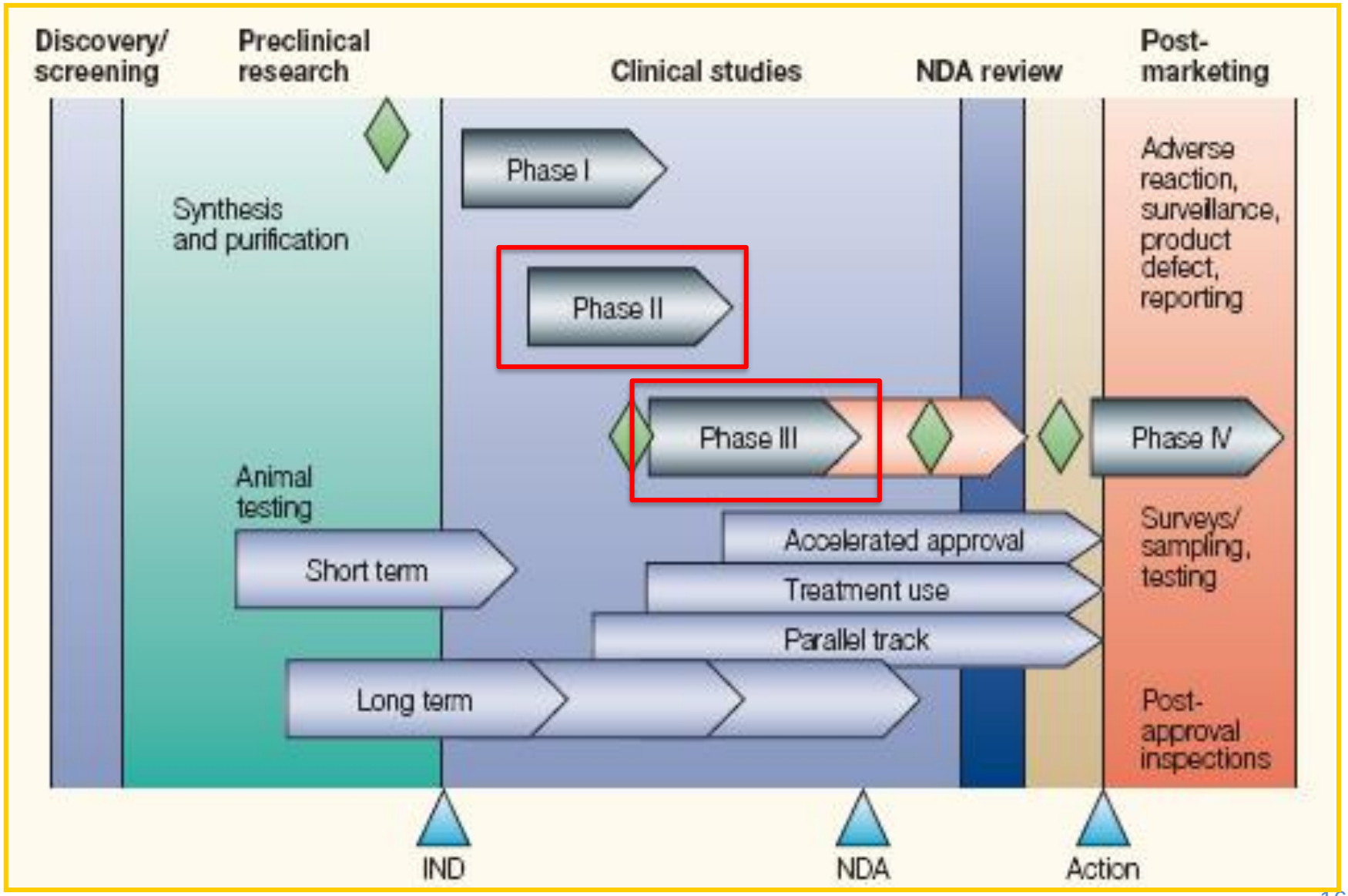


Source: Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, Wolff K: *Fitzpatrick's Dermatology in General Medicine, 8th Edition*: www.accessmedicine.com

Acne vulgaris

Maximal use conditions include applying the drug to the entire face, shoulders, upper chest and upper back

When to conduct maximal use study?



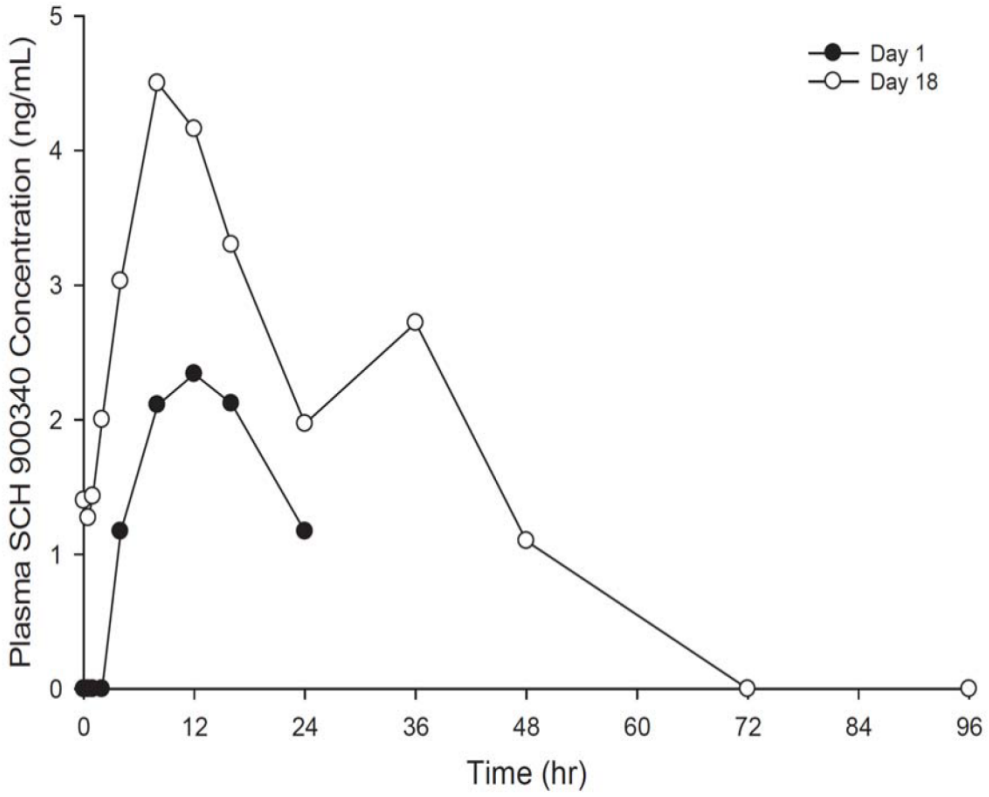
Nature Reviews and Drug Discovery, 2003, Volume 2, Page 71

PK data under maximal usage conditions
How do I use this information?

How are PK data obtained under maximal usage conditions used?

- Assessment of systemic bioavailability to inform labeling
- Assessment of systemic safety
  - Assess the need for a TQT study
  - Assessment of drug interaction potential
- Support clinical bridge for 505(b)(2) regulatory pathway
- Rx to OTC switch – Risk/Benefit assessment

Assessment of systemic bioavailability



Tavaborole topical solution, 5% for onychomycosis

Reference: Clinical Pharmacology and Biopharmaceutics review.
http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/204427Orig1s000ClinPharmR.pdf

Labeling

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

KERYDIN is an oxaborole antifungal [see *Clinical Pharmacology (12.4)*].

12.2 Pharmacodynamics

At therapeutic doses, KERYDIN is not expected to prolong QTc to any clinically relevant extent.

12.3 Pharmacokinetics

Tavaborole undergoes extensive metabolism. Renal excretion is the major route of elimination of the metabolites.

In a clinical pharmacology trial of six healthy adult male volunteers who received a single topical application of 5% ^{14}C-tavaborole solution, tavaborole conjugates and metabolites were shown to be excreted primarily in the urine.

The pharmacokinetics (PK) of tavaborole was investigated in 24 adult subjects with distal subungual onychomycosis involving at least 4 toenails (including at least 1 great toenail) following a single dose and a 2-week daily topical application of 200 µL of a 5% solution of tavaborole to all ten toenails and 2 mm of skin surrounding each toenail. Steady state was achieved after 14 days of dosing. After a single dose, the mean (± standard deviation) peak concentration (C_{max}) of tavaborole was 3.5 ± 2.3 ng/mL (n=21 with measurable concentrations, range 0.618-10.2 ng/mL, LLOQ=0.5 ng/mL), and the mean AUC_{last} ± SD was 44.4 ± 25.5 ng*hr/mL (n=21). After 2 weeks of daily dosing, the mean C_{max} ± SD was 5.2 ± 3.5 ng/mL (n=24, range 1.5-12.8 ng/mL), and the mean AUC_{τ} ± SD was 75.8 ± 44.5 ng*hr/mL.

In another study PK of tavaborole was investigated in 22 subjects aged 12 years to less than 17 years with distal subungual onychomycosis involving at least 4 toenails (including at least 1 great toenail with at least 20% involvement) following once daily application of 5% solution of tavaborole to all ten toenails and 2 mm of skin surrounding each toenail for 29 days. On Day 29, the mean ± SD C_{max} was 5.9 ± 4.9 ng/mL (n=21 with measurable concentrations, range 1.0 -16.4 ng/mL, LLOQ=0.5 ng/mL), and the mean ± SD AUC_{0-24} was 76.0 ± 62.5 ng*hr/mL.

Drug Interaction Studies

In Vitro Studies

In vitro studies have shown that tavaborole, at therapeutic concentrations, neither inhibits nor induces cytochrome P450 (CYP450) enzymes.

Reference: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/204427s000lbl.pdf

How are PK data obtained under maximal usage conditions used?

- Assessment of systemic bioavailability to inform labeling
- Assessment of systemic safety
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  - Assessment of drug interaction potential
- Support clinical bridge for 505(b)(2) regulatory pathway
- Rx to OTC switch – Risk/Benefit assessment

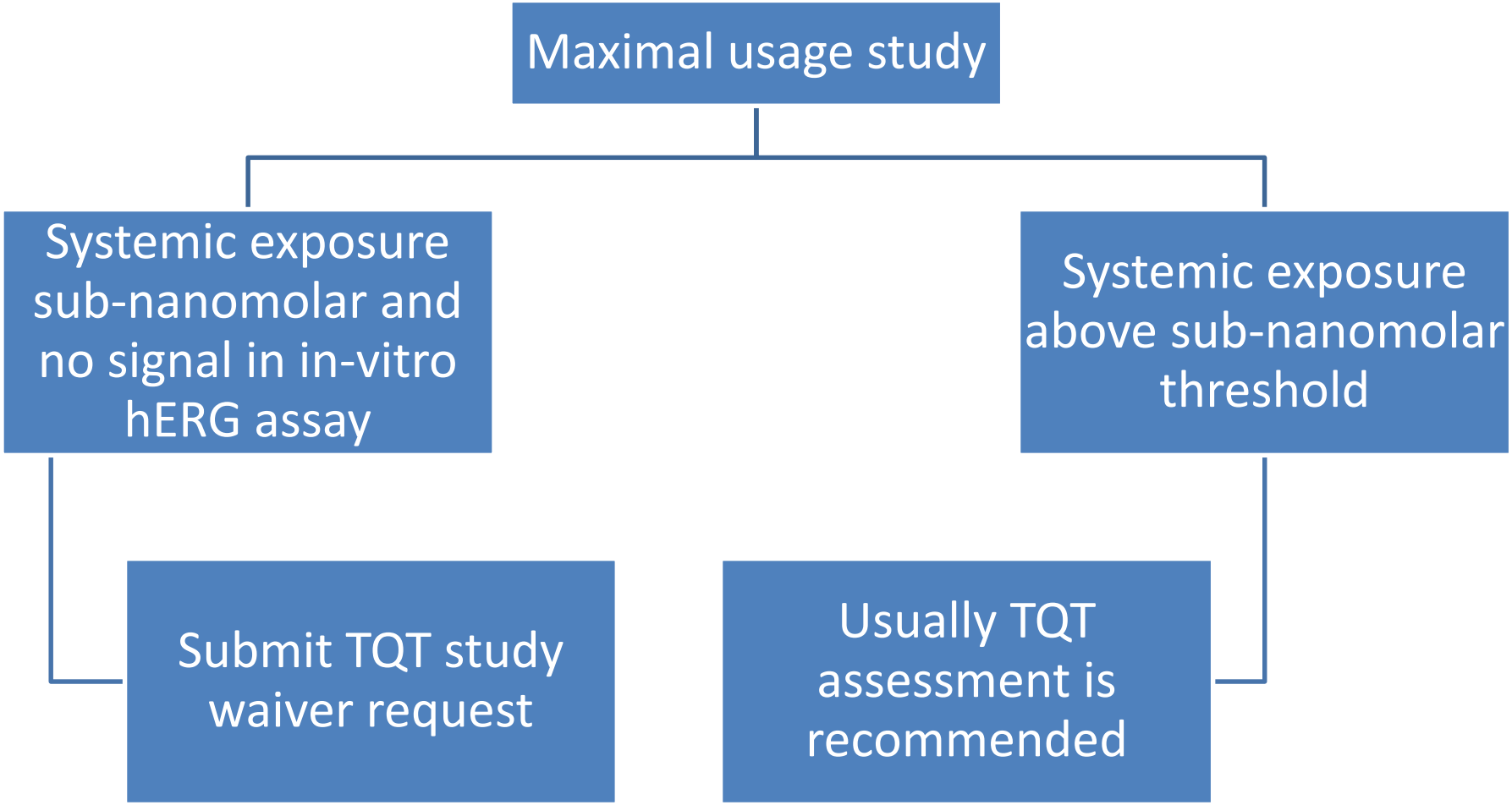
Assessment of systemic safety

- HPA axis suppression is one of the major safety concerns for topical corticosteroids and this is tested under maximal usage conditions
- If the rate of HPA axis suppression is above a certain threshold, then the product may get approved with an age restriction
- There could also be a restriction on the dose and treatment duration

Drug (Trade name)	Indication	HPA axis - % suppressed
Clobetasol propionate Lotion (CLOBEX)	Corticosteroid responsive dermatoses in **adults**	Adults (Psoriasis): 80% Adults (AD): 56% 12 to 17 yr (AD): 64%
Betamethasone dipropionate + clotrimazole Cream (LOTRISONE)	Tinea pedis, cruris and corporis **in 17 yr and older**	Adults: 38% 12 to 16 yr: 40% Tinea pedis 12 to 16 yr: 47% Tinea cruris
Clobetasol propionate Lotion (OLUX-E)	Corticosteroid responsive dermatoses **in 12 yr and older**	12 yr and older: 16% 6 to 11 yr: 47%
Fluticasone propionate cream (CUTIVATE)	Corticosteroid responsive dermatoses **in 3 mo & older**	Adults: Not evaluated 3 mo to 5 yr (AD): 5%

Reference: Approved product labels from drugs@fda

TQT study decision tree for topical dermatological products

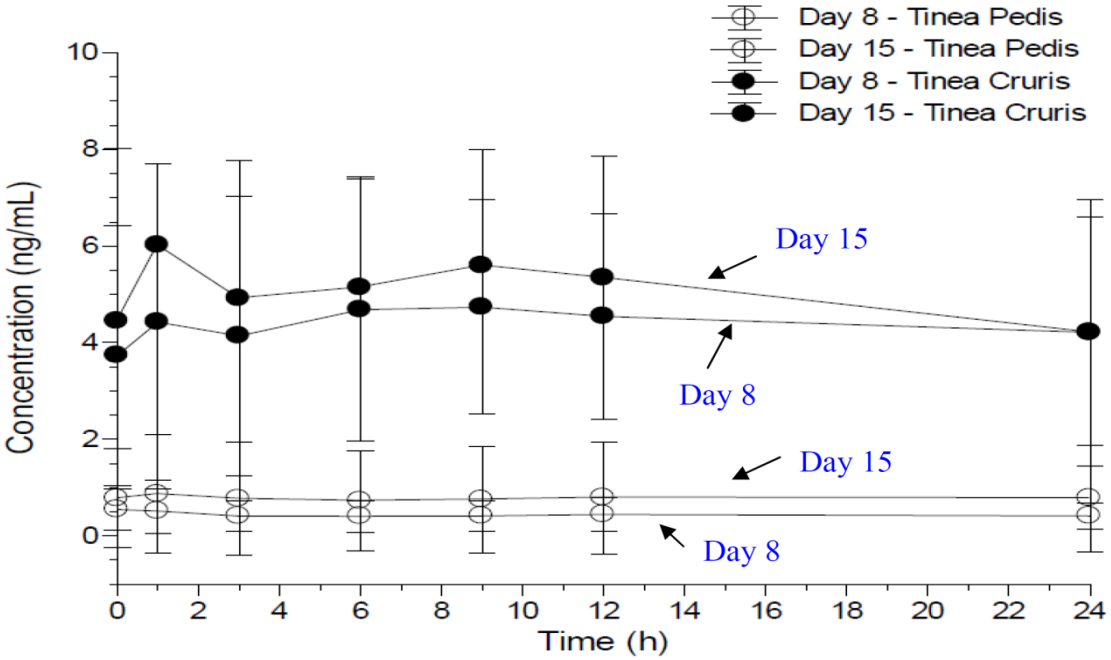


https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/203567Orig1s000ClinPharmR.pdf

Drug interaction assessment

- Drug interaction assessment strategy for topical dermatological products is not different from products administered via other routes
- The systemic exposure under maximal usage conditions is used to assess the need for any clinical DDI study based on in vitro data

Drug interaction assessment



LUZU (luliconazole) cream 1% for tinea pedis and tinea cruris

- In vitro studies indicated that LUZU Cream 1% inhibited the activity of CYP2B6, 2C8, 2C19, and 3A4.
- The most sensitive enzyme, CYP2C19, was further evaluated in an clinical DDI study using omeprazole as a probe substrate in adult subjects with interdigital tinea pedis and tinea cruris under maximal usage conditions .
- The results showed omeprazole systemic exposure increased by approximately 30%.
- LUZU Cream, 1% is considered a weak inhibitor of CYP2C19.

Reference: Clinical Pharmacology and Biopharmaceutics review.
http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204153Orig1s000ClinPharmR.pdf

How are PK data obtained under maximal usage conditions used?

- Assessment of systemic bioavailability to inform labeling
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- Support clinical bridge for 505(b)(2) regulatory pathway
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What is 505(b)(2)?

What is 505 (b)(2)?

- A 505(b)(2) application is one for which one or more of the investigations relied upon by the applicant for approval were not conducted by or for the applicant and for which the applicant has not obtained a right of reference from the person by or for whom the investigations were conducted.

What type of information can the applicant rely on?

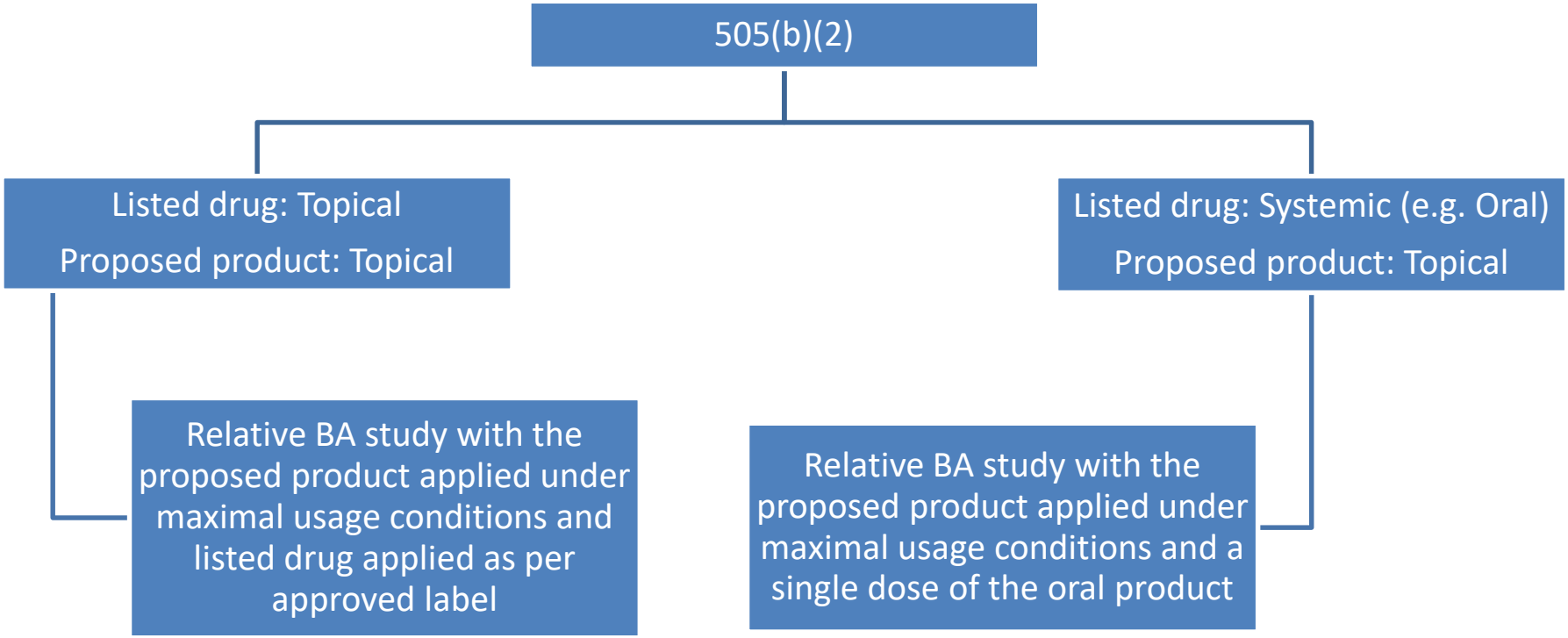
- The Agency's finding of safety and effectiveness form an approved drug
- Published literature

What should be included in 505(b)(2) applications?

- A relative bioavailability study comparing the proposed product to the listed drug (if any)

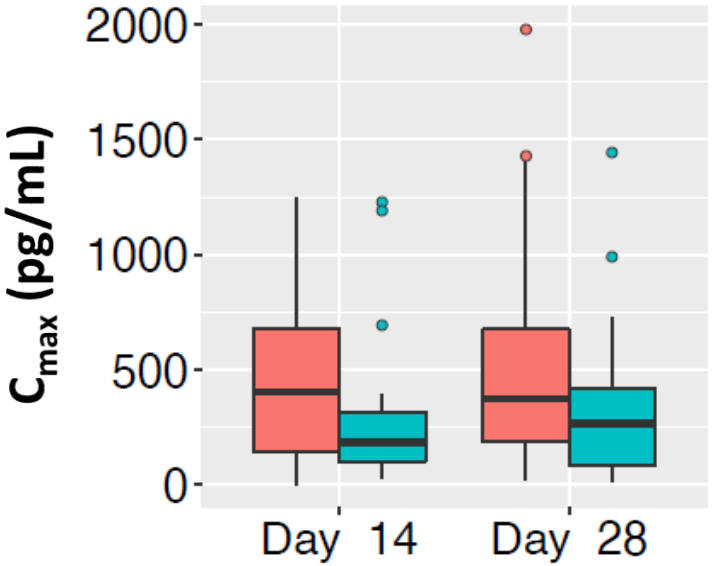
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/applications-covered-section-505b2

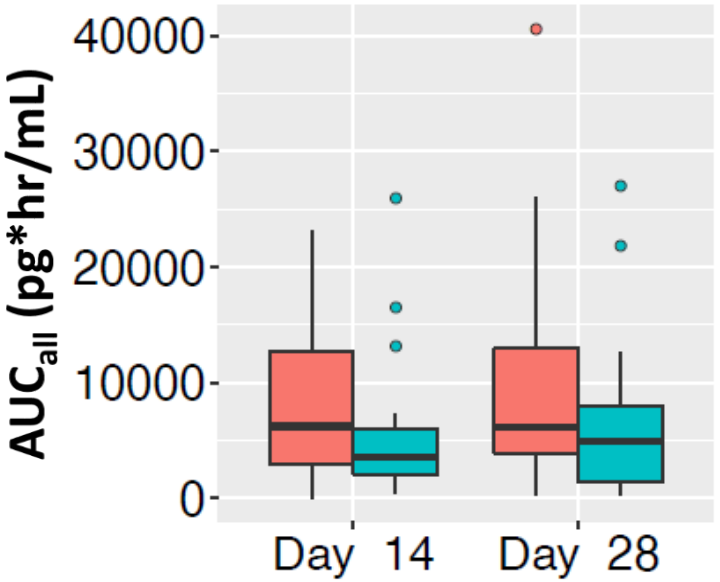
Role of maximal usage study in supporting a clinical bridge for a 505(b)(2) regulatory pathway



- Results of the relative BA are within the no effect boundary of 80% to 125% or the systemic exposure of the proposed product is lower than the listed drug, a clinical bridge for systemic safety is established
- If the systemic exposure of the proposed product is higher than the listed drug, a clinical bridge may not be considered as established and the applicant might be asked to provide additional evidence to support safety

Topical test product (shown in red) had higher exposure than the topical listed drug (shown in green)





	Parameters	Geometric mean ratio (90% CI)
Day 14	Cmax (ng/mL)	1.8 (109 % - 306 %)
	AUC (h*ng/mL)	1.8 (109 % - 300 %)
Day 28	Cmax (ng/mL)	1.7 (93 % - 294 %)
	AUC (h*ng/mL)	1.7 (91 % - 301 %)

- Clinical bridge for systemic safety was not considered to be established and the applicant had to provide additional evidence to support safety of their product

How are PK data obtained under maximal usage conditions used?

- Assessment of systemic bioavailability to inform labeling
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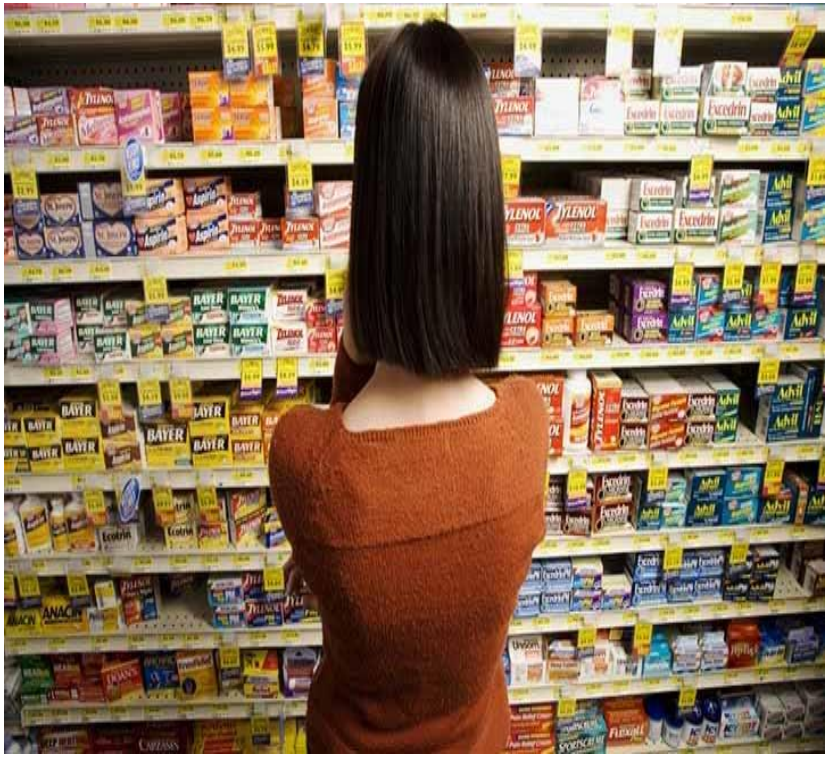
Prescription drug dispensing

Over the counter drug dispensing



The journey of Differin Gel, 0.1% from Rx to OTC and the role of maximal usage trial

Why assess systemic exposure of adapalene following topical application of Differin Gel, 0.1%?

- Adapalene is a retinoid-like drug and there is a concern for teratogenicity based on animal toxicity data

How to evaluate the systemic exposure of Differin Gel, 0.1%?

- Maximal usage trial is currently recommended by the Agency to assess systemic exposure for informing systemic safety

Reference: *Bashaw E.D. et al.; Maximal Usage Trial: An Overview of the Design of Systemic Bioavailability Trial for Topical Dermatological Products; Therapeutic Innovation & Regulatory Science; 2015; 49(1); 108-115.*

Summary of PK parameters of Differin Gel, 0.1%

	C_{max} (ng/mL)	AUC_{0-24} (ng*h/mL)
Day 15 (N =22 and N quantifiable = 21)		
Mean ± SD	0.05 ± 0.03	0.87 ± 0.43
Min, Max	< 0.02, 0.14	0.48, 1.99
Median	0.04	0.7
Day 29 (N = 24 and N quantifiable = 24)		
Mean ± SD	0.05 ± 0.03	0.83 ± 0.49
Min, Max	0.0, 0.171	0.50, 2.90
Median	0.04	0.68

https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/NonprescriptionDrugsAdvisoryCommittee/UCM495796.pdf

Application of maximal usage PK data in RX to OTC switch of Differin Gel, 0.1%

Toxicology data clearly demonstrate a teratogenic signal with oral adapalene, with findings consistent with other drugs in the retinoid class. Congenital anomalies seen in animal studies include cleft palate, microphthalmia, encephalocele, umbilical hernia, exophthalmos, kidney abnormalities, and skeletal abnormalities. However, using data from the human pharmacokinetic study performed using maximal topical administration according to the product label gives a safety margin of at least 70-fold for these effects. Although the margin could potentially be somewhat lower if consumers were to use the product over more than 10% of the body surface area or apply it multiple times per day, data from the actual use study suggest that consumers are likely to apply the product appropriately.

One additional caveat to the calculation of safety margins, particularly for teratogenic effects such as these, is that the actual threshold for an effect in humans is unknown and may be different than in the species tested. One way to evaluate this caveat is to look at available human data on pregnancy outcomes. Post-marketing safety data from 20 years of prescription use demonstrate few cases of abnormal pregnancy outcomes with no clear-cut cases of teratogenic effects due to adapalene. Given the high likelihood of significant underreporting, the absence of reports does not necessarily translate to an absence of events, but nonetheless does provide some information regarding the level of potential risk.

https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/NonprescriptionDrugsAdvisoryCommittee/UCM495796.pdf

Pediatric maximal usage

Adult vs. Pediatric maximal usage conditions

FDA

Adult maximal usage conditions

- Psoriasis – At least 20% BSA involved
- Atopic dermatitis – At least 25% BSA involved in subjects 12 years and older
- Acne vulgaris – Apply to the entire face, shoulders, upper chest and upper back

Pediatric maximal usage conditions

- Psoriasis – At least 10% BSA involved in subjects 12 to 17 years and in subjects below the age of 12 years, at least 3% BSA involved
- Atopic dermatitis – At least 35% BSA involved in subjects below 12 years old.
- Acne vulgaris - Apply to the entire face, shoulders, upper chest and upper back

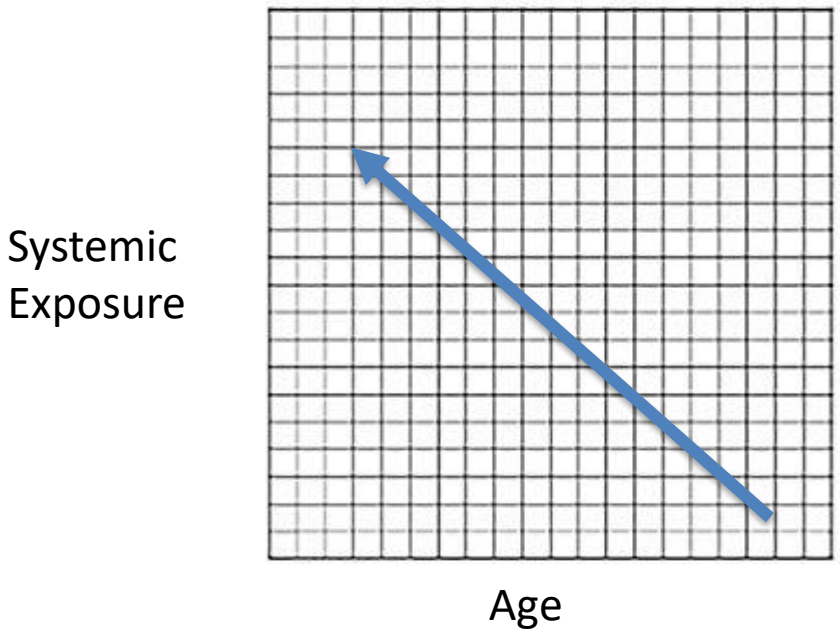
Pediatric maximal use – Head lice

	Age Group	C_{max} (ng/mL)	AUC (ng*h/mL)
Drug X Head lice	<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 to 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 ontogenic differences in physiological processes affecting ADME

Pediatric maximal use – Drug Y - 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



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**

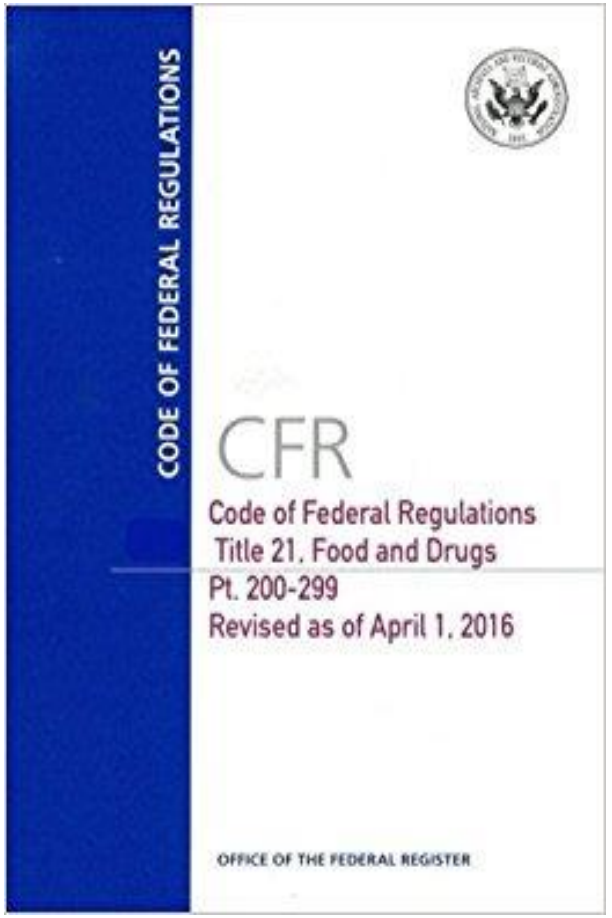
- HPA axis suppression rates appear to be higher with decrease in age
  - Drug approved for the treatment of corticosteroid responsive dermatoses in subjects 13 years of age and older
  - Use in subjects below the age of 13 years is not recommended due to potential for HPA axis suppression

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)

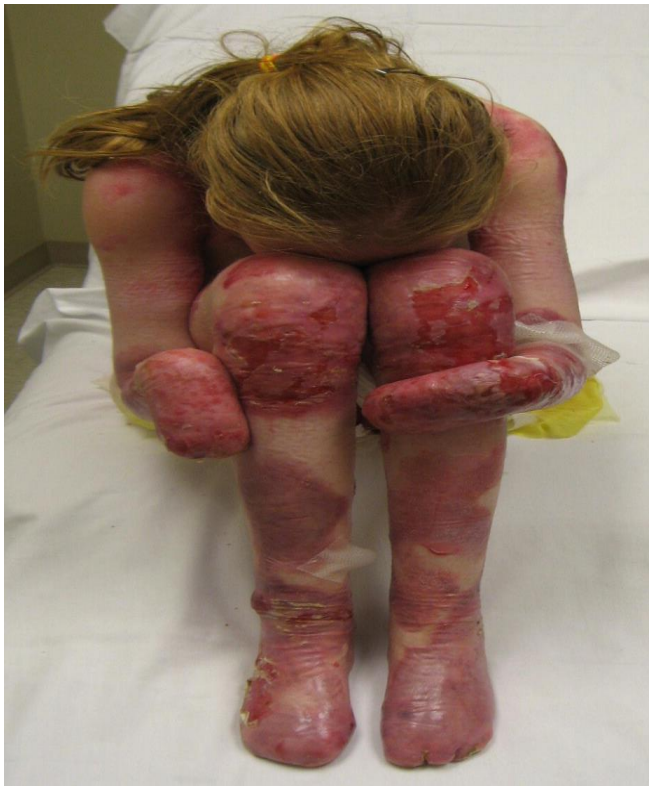
Waiver of Maximal Usage Study

Regulatory requirement

- 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



Difficulty in obtaining PK



Reference: Book - Longitudinal Observation of Pediatric Dermatology in Patients; Ch – Dystrophic Epidermolysis Bullosa; Pg 207 - 215; Feb 2019, ISBN: 978-3-319-98100-0; Publisher: Springer Nature Switzerland

- Epidermolysis bullosa (EB) is a group of genetic conditions that cause the skin to be very fragile and to blister easily.
- Dystrophic EB is the most severe type where the skin is so fragile (like butterfly wings) that blisters and skin erosions form in response to minor injury or friction, such as rubbing or scratching.
- Assessment of complete PK profile is nearly impossible in such patients as needle pick to obtain blood samples elicits an immune response that worsens the disease.
- Maximal usage study was waived based on information such as projected safety margins based on animal toxicity, clinical safety monitoring plan, etc.

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%.

High daily dietary intake value

- Arginine for example, is a semi-essential amino acid which is synthesized in the human body as well as obtained from dietary sources like milk, meat, nuts, chickpeas, soybeans, etc.
- If the topical dose contains arginine which is below the daily intake value from dietary sources, maximal usage study could be waived.

Minor changes in the formulation

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

Relevant literature for further reading

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

DOI: 10.1177/2168479014539157
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Maximal Usage Trial: An Overview of the Design of Systemic Bioavailability Trial for Topical Dermatological Products

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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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Maximal usage beyond NDA

- The concept of maximal usage is not just restricted to small molecules.
- Biologics delivered locally for treatment of local conditions might need to conduct maximal usage trial and assess systemic safety.

Summary

- Background
  - Bioavailability assessment or information to support waiver of BA assessment is a regulatory requirement
  - Factors affecting the bioavailability of topical products
- Concepts
  - Maximal usage trial design
  - Timing of maximal usage trial
- How is maximal usage PK data used?
  - Inform product labeling
  - Assessment of systemic safety
    - HPA axis suppression assessment
    - TQT decision tree
    - Drug interaction assessment
  - Support clinical bridge for 505(b)(2) submissions
  - Rx to OTC switch: Risk/benefit assessment
- Pediatric maximal usage study
  - Importance of pediatric maximal usage assessment to inform systemic safety
- Waiver of maximal usage study

WARNING: *This presentation contains pictures of skin conditions which might be scary to some of you.*

If these pictures have motivated you and evoked a desire to do something for patients with skin diseases, then there could be a potential opportunity for you with the dermatology review team in the Office of Clinical Pharmacology

How can I be part of OCP?

- Reviewers have a variety of different backgrounds (Pharm.D., Ph.D., MD) and skill sets
- Submit a CV approximately 3-4 months before completion of degree program (ocp@fda.hhs.gov)
- Phone and/or on-site interview
- Assistance with visa processing

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Thank you for your attention!


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