



MUsT: The Must-Have Study in Topical Drug Development

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July 29, 2019



Agenda

- MUsT (**M**aximal **U**sage **T**rial) into a clinical development plan
- Study design considerations
- Practical considerations for study execution

Basic PK considerations for topically applied Rx drugs

- Application directly on the affected skin
- Variability in applied dose
 - Different interpretations of usage instructions (*i.e.* pea size, thin layer, finger tip)
- Treated Skin Surface Area can be Large
 - Acne vulgaris
 - EPIDUO® FORTE Gel (adapalene 0.3% and benzoyl peroxide 2.5%) : Apply a thin layer to affected areas of the face and/or trunk once daily after washing
 - Psoriasis
 - VECTICAL® Ointment 3 mcg/g (Calcitriol) : Apply to affected areas of the body twice daily, the maximum weekly dose should not exceed 200 g
 - Atopic dermatitis
 - EUCRISA® ointment, 2% (Crisaborole)*: Apply a thin layer twice daily to affected areas (in clinical studies, up to 95% treatable BSA)
- Treatment of chronic skin disease

* Marketed by Pfizer

Why do we need a MUsT in topical drug development ?

- **Safety** is the primary objective
- A MUsT intends to capture the systemic exposure under conditions that would maximize the potential for drug absorption in a manner consistent with anticipated clinical use of the product and allowed for in the label
- A MUsT provides key information for
 - Clinical pharmacology program
 - Benefit-risk assessment
 - Drug label

PK relevant questions in topical drug development

- What is the rate and extent of systemic absorption for parent compound and metabolites?
- Is the product safe?
 - What are the safety margins ?
 - Is there a potential to delay cardiac repolarization?
- Prediction and understanding factors of variability in systemic exposure:
 - Does the systemic concentration increase proportionally to the dose?
 - Is systemic accumulation likely to occur?
 - Are there gender, body weight, age, ethnicity effects?
- Are interactions with co-administered drugs likely?
- Is the concentration in the skin enough for pharmacological effect ?
 - Is there any PK/PD relationship ?

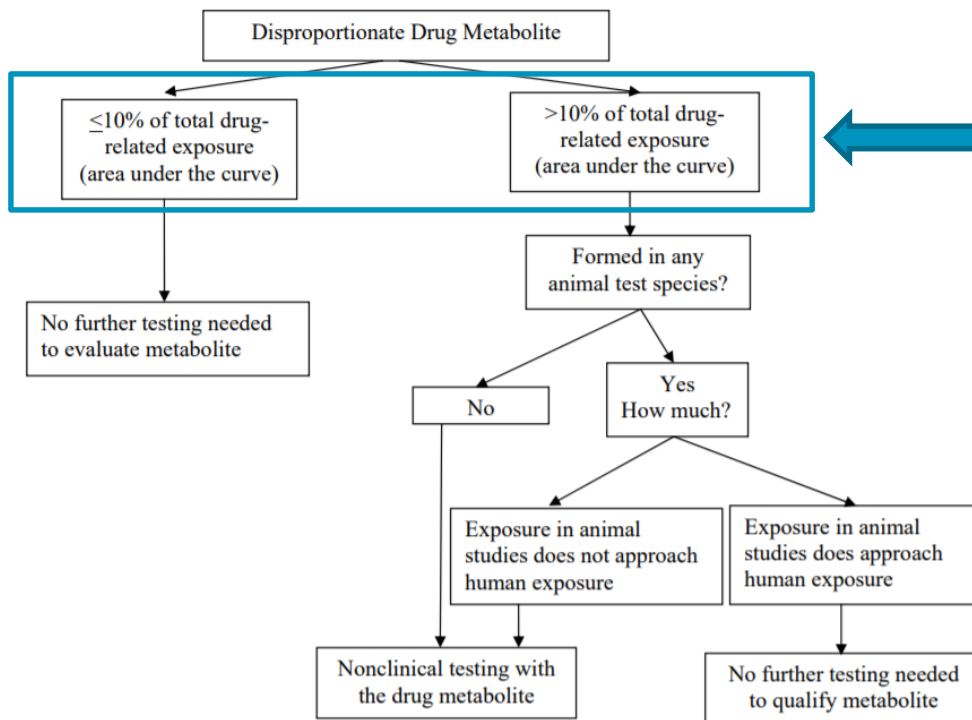
MUsT: Pivotal study for clinical pharmacology program

- Identification of the maximal amount of drug product that could be applied under clinical use conditions
- Quantification of the maximal systemic exposure to the parent compound at metabolites at steady state
 - To calculate the safety margin
 - To support a clinical bridge -505(b)(2) regulatory pathway
 - To identify the major metabolites and/or active circulating metabolites
- MUsT in adults is mandatory for pediatric development
 - To refine the pediatric plan
 - To support waiver

Decision tree for metabolite assessment

Safety Testing of Drug Metabolites, **FDA guidance Nov 2016**

DECISION TREE FLOW DIAGRAM



MUsT data

MUsT: Pivotal study for clinical pharmacology program

- Identification of the Clinical DDI study(ies) to be conducted
 - Based on *in vitro* drug metabolism studies, drug transporter studies AND maximal systemic exposure at steady state
- Identification of the study(ies) in special populations to be conducted
 - Based on the ADME profile of the drug AND on the maximal systemic exposure at steady state
- Definition of the supratherapeutic exposure for cardiac safety assessment
 - as per ICH E14, the concentration-response relationship for QT/QTc prolongation should be characterized over a large range of concentration, including exploration of concentrations that are higher than those achieved following the anticipated therapeutic doses

MUsT for safety margin calculation

Safety margin is the difference in multiples of exposure between the No Observed (Adverse) Effect Level Dose (NOEL or NOAEL) in the most sensitive animal species and human maximal exposure conditions:

$$\text{Safety Margin} = \frac{\text{Animal Systemic Exposure at NOEL or NOAEL Dose}}{\text{Human Systemic Exposure at Maximum Exposure Conditions}}$$

- The larger the number you have, the safer the drug
- Can be established for several endpoints (systemic toxicity, teratogenicity, fertility, etc)
- The lowest safety margin should be retained for risk evaluation

Safety Margin : example of Differin® Gel, 0.1% (adapalene)

- Adapalene is teratogenic at sufficient systemic exposure
 - As teratogenicity is the most sensitive safety endpoint, the safety margin for clinical use is based on this parameter
- Safety margin calculation :

$$\text{Safety Margin} = \frac{\text{Lowest systemic exposure in rat at the NOAEL Dose (AUC}_{0-24\text{h}}: 204 \text{ ng.h/mL})}{\text{Human Systemic Exposure at Maximum Exposure Conditions (AUC}_{0-24\text{h}}: 2.9 \text{ ng.h/mL})}$$

- Safety margin : **70**

MUsT: Impact on Benefit-Risk Assessment for Rx-to-OTC switch

- The primary consideration for this application is whether the benefits of OTC availability outweigh any potential risk for teratogenic effects on the developing fetus
- Using data from the human PK study performed using maximal topical administration according to the product label gives a safety margin of at least **70-fold for these effects**
 - In order to provide the most conservative safety margin calculation, the highest individual human exposure (2.9 ng.h/mL) was used for the calculation rather than the mean value

Drug Approval Package: Differin Gel, 0.1% (adapalene)

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Company: Galderma Laboratories, L.P.
Application No.:020380Orig1s010
Approval Date: July 8, 2016

Persons with disabilities having problems accessing the PDF files below may call (301) 796-3634 for assistance.

- [Approval Letter\(s\) \(PDF\)](#)
- [Printed Labeling \(PDF\)](#)
- [Summary Review \(PDF\)](#)
- [Officer/Employee List \(PDF\)](#)
- [Office Director Memo \(PDF\)](#)
- [Cross Discipline Team Leader Review \(PDF\)](#)
- [Medical Review\(s\) \(PDF\)](#)
- [Chemistry Review\(s\) \(PDF\)](#)
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- [Clinical Pharmacology Biopharmaceutics Review\(s\) \(PDF\)](#)
- [Proprietary Name Review\(s\) \(PDF\)](#)
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Date created: October 2, 2017

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Differin Gel, NDA 020380 (drug@FDA)
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020380s10_toc.cfm

MUsT: Impact on the drug label information

Soolantra cream : Ivermectin 1 % (w/w)

- Section 7: DRUG INTERACTIONS
 - In vitro* studies have shown that Soolantra cream, at **therapeutic concentrations**, neither inhibits nor induces CYP450 enzymes
- Sections 8, 13: NON CLINICAL
 - The animal multiples of human exposure calculations were based on **AUC comparisons**
 - The maximum topical human dose (MTHD) of Soolantra cream, 1% is **1 g applied once daily**
- Section 12: CLINICAL PHARMACOLOGY
 - At steady state , the highest mean plasma concentrations of ivermectin peaked at 10 ± 8 hours post-dose, the C_{\max} was 2.10 ± 1.04 ng/mL and the AUC_{0-24h} was 36.14 ± 15.56 ng.h/mL (N=15).
 - The apparent terminal **half-life averaged 6.5 days** in patients

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SOOLANTRA safely and effectively. See full prescribing information for SOOLANTRA.

SOOLANTRA™ (ivermectin) cream, 1%, for topical use
Initial U.S. Approval: 1996

INDICATIONS AND USAGE

SOOLANTRA cream is indicated for the treatment of inflammatory lesions of rosacea. (1)

DOSAGE AND ADMINISTRATION

- Apply to the affected areas once daily. (2)
- Not for oral, ophthalmic or intravaginal use. (2)

DOSAGE FORMS AND STRENGTHS

Cream, 1%, supplied in tubes of 30 g, 45 g and 60 g (3)

CONTRAINDICATIONS

None. (4)

ADVERSE REACTIONS

In controlled clinical trials with SOOLANTRA the most common adverse reactions (incidence $\leq 1\%$) included skin burning sensation and skin irritation. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Galderma Laboratories, L.P. at 1-866-735-4137 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 04/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

- INDICATIONS AND USAGE
- DOSAGE AND ADMINISTRATION
- DOSAGE FORMS AND STRENGTHS
- CONTRAINDICATIONS
- ADVERSE REACTIONS
- 6.1 Clinical Trials Experience
- 6.2 Post marketing Experience
- DRUG INTERACTIONS**
- USE IN SPECIFIC POPULATION**
- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

10

OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics

12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

Soolantra Cream, NDA 260255, approval date 2014 (drug@FDA)
https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/206255s004lbl.pdf

MUsT : The must-have study

- ✓ What is the rate and extent of systemic absorption for parent and metabolites?
- ✓ Is the product safe?
 - What are the safety margins ?
 - Is there a potential to delay cardiac repolarization?
- ✓ Prediction and understanding factors of variability in systemic exposure:
 - Does the systemic concentration increase proportionally to the dose?
 - Is systemic accumulation likely to occur?
 - Are there gender, body weight, age, ethnicity effects?
- ✓ Are interactions with co-administered drugs likely?
- ✗ Is the concentration in the skin enough for pharmacological effect ?
 - Is there any PK/PD relationship ?

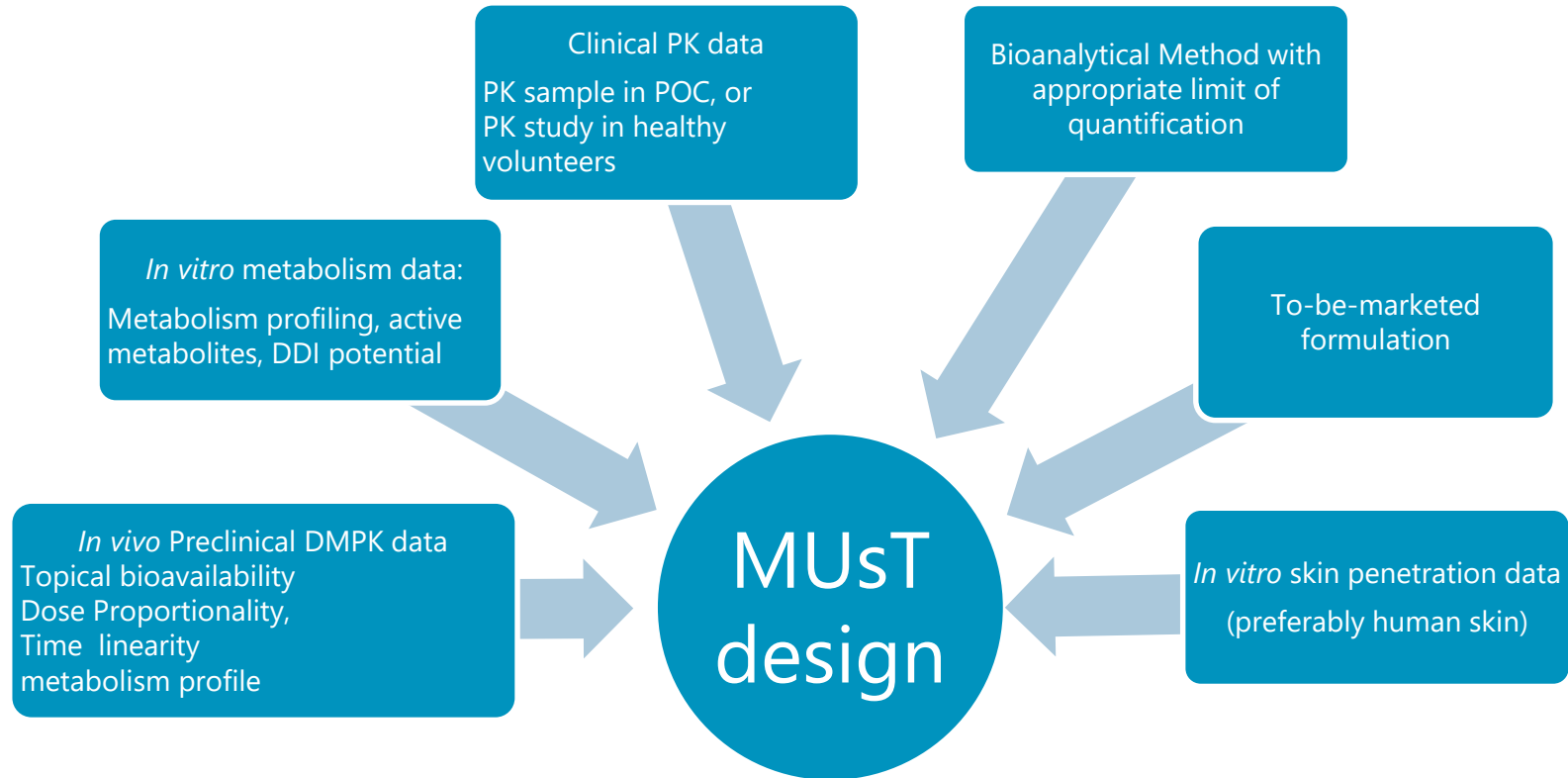
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- Study design considerations
- Practical considerations for study execution

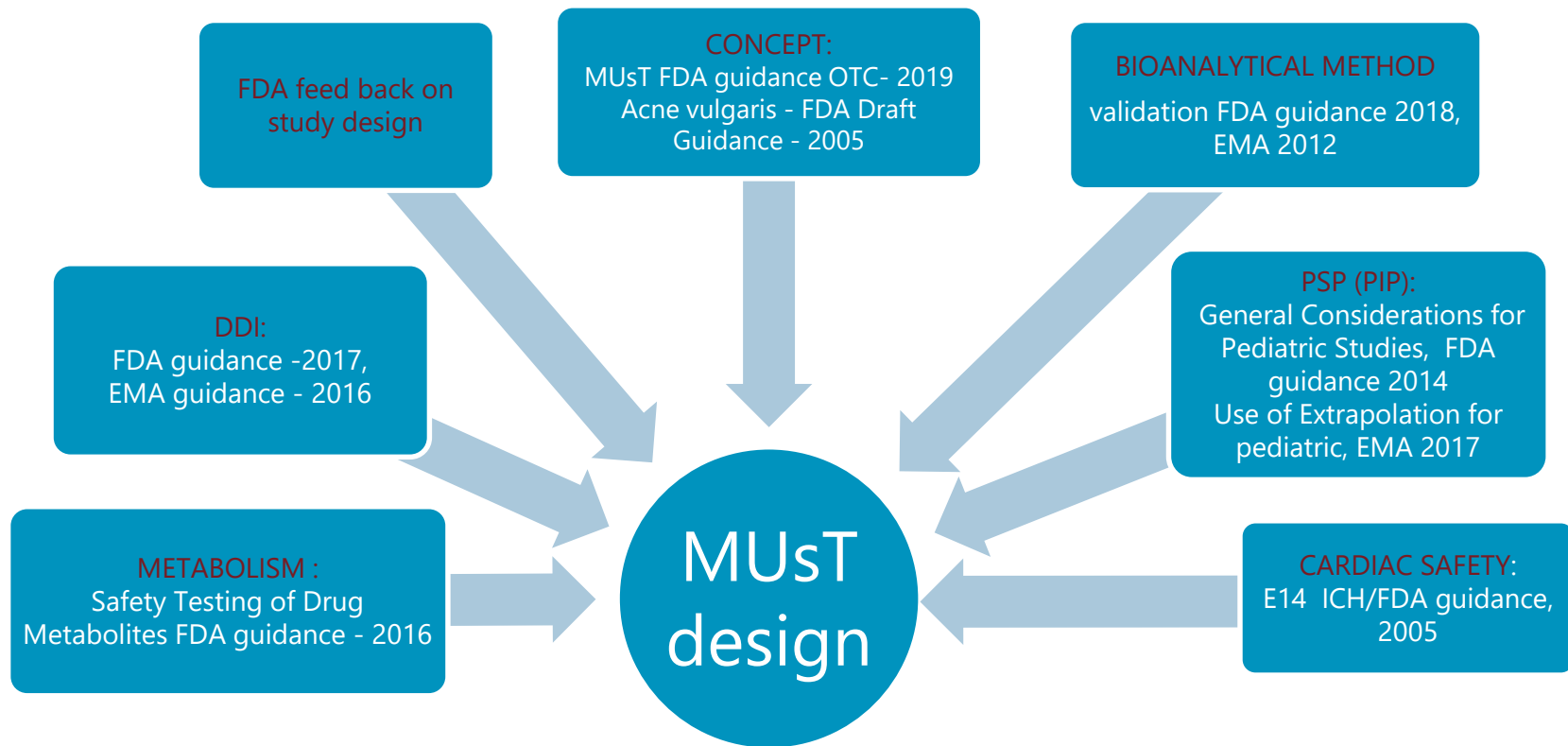
MUsT: key study design considerations

- Clinical pharmacology input is essential to optimize MUsT design and to optimize pharmacokinetic sampling
- MUsT study design should be driven by regulatory guidance
- MUsT should not be considered as a stand alone study in clinical pharmacology development plan
- Agency feed back on study design is a PLUS!

Key experimental data to optimize MUSt study design



Regulatory guidances to consider for MUSt study design



Agenda

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Study population

- The study population should be representative of the population expected to use the product
- The study population should present the upper range of disease severity in order to cover the safety of subjects that will be enrolled in the upcoming Phase 3 studies
- A step wise approach should be adopted for pediatric subjects with a new chemical entity
 - Three examples are given (Galderma data)

Example #1: Differin® Gel, 0.1% (adapalene) – acne indication

- To support OTC use of Differin® Gel, 0.1% Galderma conducted a MUsT in adolescent and adult population
 - Adolescent may apply the gel to a large surface area without monitoring from a healthcare provider
- In the original application (1996), PK for Differin® Gel, 0.1% were collected on adults only
- Based on the available safety data, **one single MUsT** study was conducted adolescents AND adults
 - High proportion of subjects with the upper level of disease severity (IGA 4)
 - High proportion of adolescents compared to adults

Material from the Nonprescription Drugs Advisory Committee Meeting, adapalene gel 0.1%, April 15, 2016

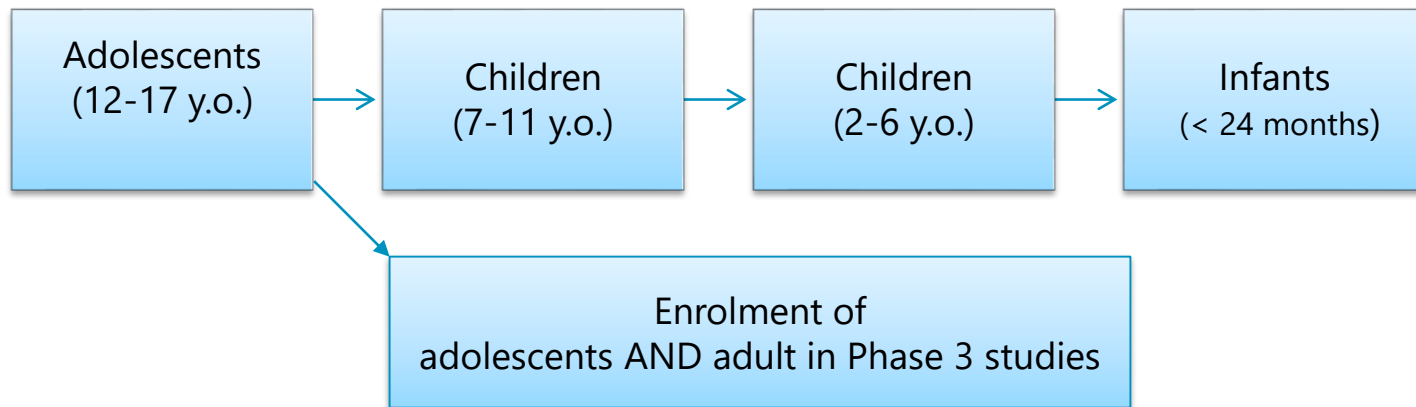
Example #2: New Chemical Entity (NCE)

Topical cream - acne indication

- **2 sequential MUsT** conducted with the to-be-marketed formulation
 - One in adult subjects
 - One in 9 -17 years of age pediatric subjects
- Disease severity – Operational constraints
 - All adult and 12 to 17 year old adolescent subjects had severe acne at baseline with an IGA severity score of 4
 - Because severe acne is not widely present in the lower age group (9-11 yo) an IGA score of at least 3 (moderate) was considered acceptable at baseline in order to enable a sufficient enrollment

Example #3: Step wise approach for an NCE

- The pediatric age range is to be assessed in a step-wise age de-escalation, approach, with adolescent (12 to 17 years) studied prior to younger pediatric subpopulations
- Example : An Accelerated Development process is proposed for this NCE (Integrated Adult & Pediatric Development Process)



Factor affecting skin permeability

Example : Treatment of actinic keratosis for the face and the scalp by photodynamic therapy

Galderma has developed a new treatment regimen in which day light is used in place of red-light illumination

- FDA recommended to combine day light exposure with physical exercise in order to assess the potential of increase of systemic exposure
 - Technical constraints were carefully discussed with clinical site in order to ensure the safety of the patients enrolled in the trial

Drug application

- The drug product should be applied to the entire area potentially affected by the disease
 - Acne : Application of the face, shoulders, back and chest
 - Atopic dermatitis : Up to the total body surface area
 - For a NCE, the safety margins should be considered before applying the drug product to large surface areas
 - PK data collected in previous clinical trial might be helpful to secure the study design
- OR
- Step-wise approach with a gradual increase of treated surface areas

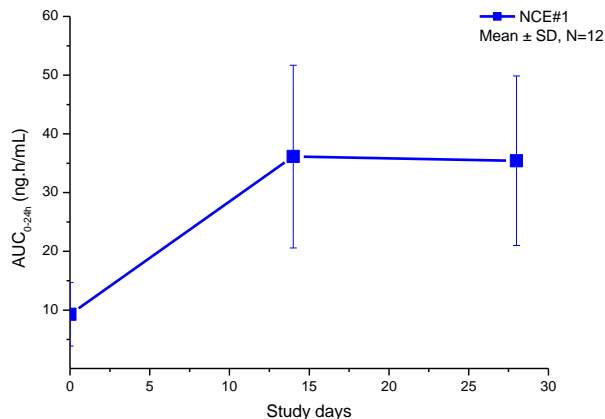
Drug application

- A thin layer of drug product should be applied to the entire area potentially affected by the disease with no limitation of the maximal applied dose
 - The applied dose per cm^2 should be calculated retrospectively
 - The applied dose should be carefully controlled
- Technical constraints to be discussed with the clinical sites before the start of the study, specifically for pediatric subjects during school days

Concept of maximal achievable dose: Differin[®] Gel, 0.1 %

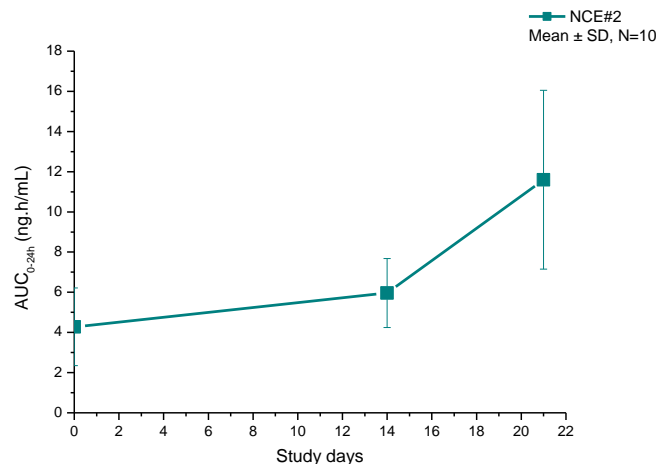
- Under maximal use conditions (MUsT)
 - The applied dose varied among subjects from 1.2 to 2.9 g
 - A mean of **2.0 ± 0.4 g** of Differin[®] Gel, 0.1 % was sufficient to leave a thin film of drug product to all the skin areas potentially affected by acne (Face, shoulders and trunk)
- Under clinical use conditions, 86% of the 947 subjects of the actual use study used less than 1 g of Differin[®] Gel, 0.1% per day
 - Mean use was **0.6 g** per day

Study duration should cover the steady state conditions



NCE #1 : Steady state reached by week 2

- Predictable and linear PK profile (Soolantra® Cream, 1%)



NCE #2 : Steady state NOT reached

- Gradual increase of plasma concentration with the number of applications
- Further increase in systemic exposure in a longer treatment period cannot be excluded (Galderma internal data)

Study duration should be sufficient to cover the chronic treatment

C_{trough} obtained with Soolantra[®] Cream, 1%

C_{trough} (ng/mL)	MUsT (N=15)	Phase 2 (N=50)	Phase 3 /LTS (N=109)	Phase 3/LTS (N=105)
Week 2	1.3 ± 0.5	-	-	-
Week 4	1.4 ± 0.6	0.7 ± 0.8	-	-
Week 12	-	0.8 ± 1.1	0.5 ± 0.7	0.4 ± 0.5
Week 32	-	-	0.4 ± 0.4	0.4 ± 0.5
Week 52	-	-	0.3 ± 0.4	0.4 ± 0.6

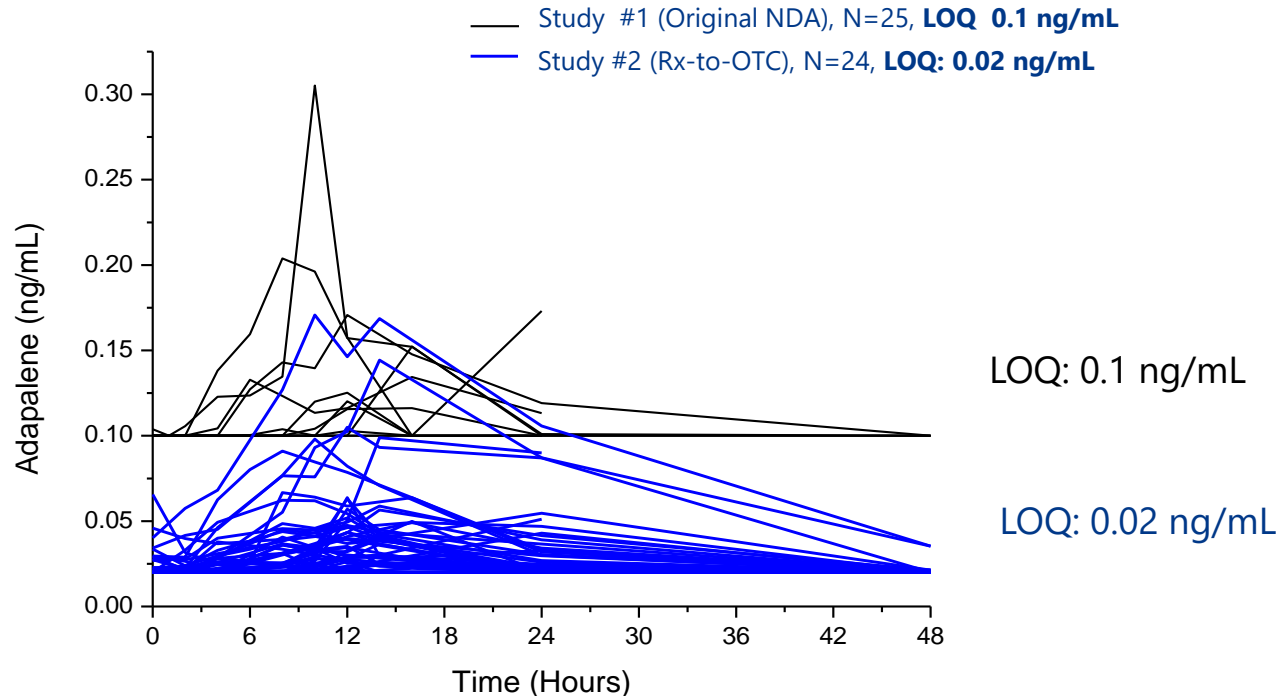
- The 4-week MUsT study captured the effect of maximal use on systemic absorption
- Lower systemic exposure under clinical use conditions

Soolantra cream: Clinical pharmacology and biopharmaceutics review of NDA: 206255, Approval date 2014 (Drugs@FDA)

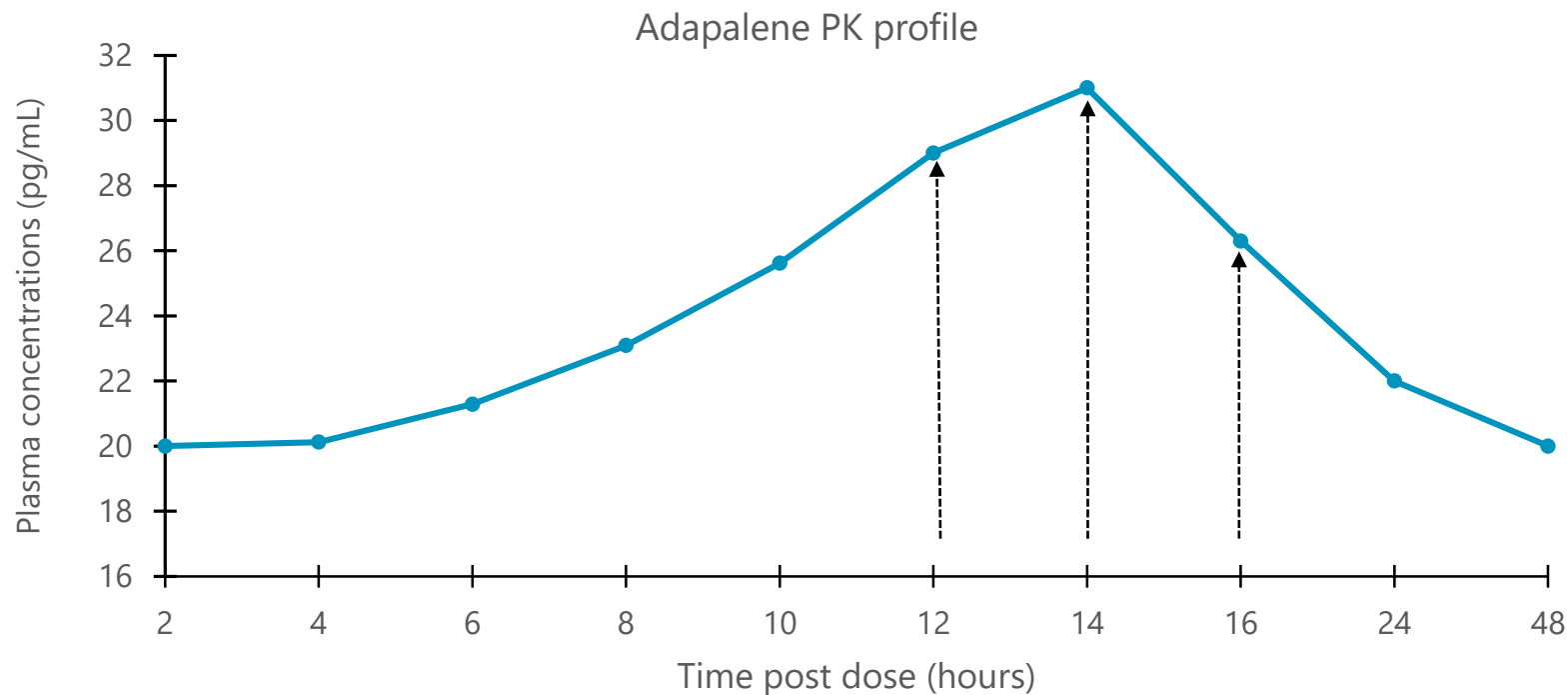
Sensitive analytical methods are scientifically critical

Example of Differin[®] Gel, 0.1 %

Adapalene quantified by 2 different methods with different Limit Of Quantification (LOQ)

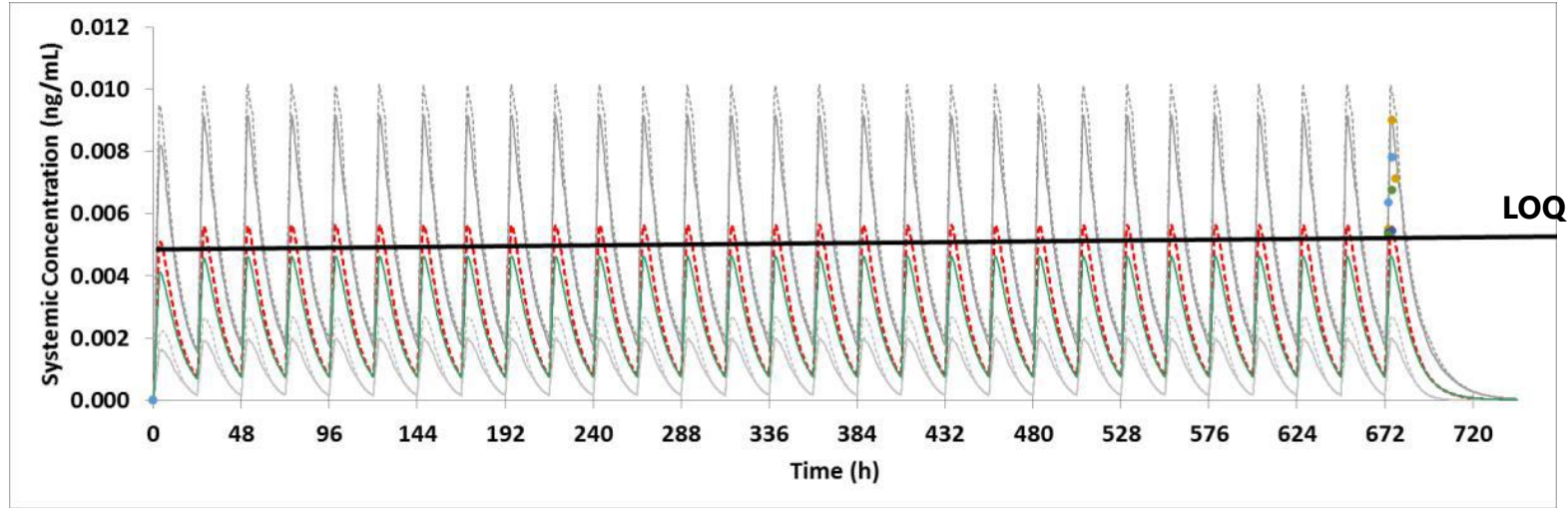


PK sampling scheme should capture the complete PK profile



- 12 to 16 hours post dose time points are essentials for an accurate determination of C_{max} and T_{max}

Physiologically based pharmacokinetic modelling (PBPK) to bridge clinical gaps in pediatric population



Red line dotted line : Simulated systemic exposure levels in 9-11 years old + P5-P95 percentile light grey

Green line : Simulated systemic exposure levels in 12-17 years + P5-P95 percentile light grey

Markers : Clinically observed profiles from 12-17 years-old

➤ PBPK model has no limitation in reporting non-quantifiable concentrations

Key messages

- Clinical pharmacology program
 - MUsT should not be considered as a stand alone study done only to fulfill one regulatory requirement
 - MUsT provides critical information for the clinical pharmacology program
- Exchanges
 - Study design should be discussed with the agency BEFORE conducting the study
 - Operational feed back from clinical experienced sites is instrumental
- Concept of Developability
 - The assessment of human systemic exposure to parent compound and metabolites under the clinical use conditions is essential for safety
- Prior knowledge
 - An extensive preclinical PK and metabolism package is essential to minimize risk of failure when conducting a MUsT
 - MUsT should not be the FIRST clinical PK study for an NCE

MUsT Key messages

- Flexibility
 - MUsT study design should be adapted according to the critical points raised within the project

“Strategy was not planning in a sense of working through an established list, but rather that it requires quick and appropriate responses to changing conditions”

Sun Tzu (Chinese general and philosopher who lived over 2,000 years ago -importance of strategy)

I ❤️ PK

Questions ?
