

A History of Dermal Absorption Assessment at the FDA: Quo Vadis?



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A SHORT HISTORY OF DERMAL DRUG EVALUATION AT THE FDA

Dermal Drug Review "Paleoregulatory"*



- Prior to the early 1990s, most topical dermatologicals had little or no direct assessment of in vivo bioavailability.
- Clinical efficacy trials or surrogate markers of drug absorption were used.
- Waivers of in vivo bioavailability testing were the norm and not the exception
- "Maximal dosing" was an unknown concept
- Actually, any assessment of dermal absorption was unexplored





Common Features of In Vivo Dermal Bioavailability Studies pre-1990

- Study done in subjects with healthy skin
- Study done on small surface areas
- Study done with inadequate analytical methods
- Study done with too few subjects
- Study done as a single dose study

The information gained from such studies was *inadequate* for any attempts at linking exposure to any safety related issues.

Why Do We Need to Know?



It has been the lack of an ability to assess local drug concentrations and a lack of correlation between systemic levels and local therapeutic effect that has required the use of clinical trials to assess bioavailability and the issue of association of adverse effects with exposure.



Bioavailability



>21 CFR § 320.1 Definitions.

➤ (a) Bioavailability means the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes <u>available at the site of action</u>.



Determinants of Topical Bioavailability



It is the complex interaction of drug substance, formulationdosage form, and those skin factors that affect the barrier function of the skin that determines systemic drug availability, its profile over time, and product design selection.







MAXIMAL USAGE, DRUG DEVELOPMENT, AND YOU

The Maximal Use Trial



- In the mid 1990s the FDA developed and implemented the use of the "maximal use" trial as part of an in vivo bioavailability program.
 - Outgrowth of the dissatisfaction with previous bioavailability assessments
 - >Made possible by the refinement of analytical methodologies
- "Maximal" being defined here as the highest dose in terms of such factors amount, concentration, and surface area that were to be studied in clinical trials and placed into labeling.
 - Thus the dose being evaluated was based on the highest dose (in terms of the factors above) for which approval was sought by the sponsor.
 - ➤The focus of the data being collected here would be on systemic safety, thru the evaluation of in vivo plasma levels following maximal dosing.

The Maximal Use Trial



- Trial design has been presented and discussed at various national meetings and workshops (AAPS, FIP-BioInternational, ASCPT, etc.)
- ➤ As part of the standardization process of the recommendation, a standard comment was developed that was conveyed to Sponsors in regulatory meeting and was captured in some FDA Guidance documents (prior to the publication of the MUsT guidance itself in May 2018)
 - 2005 FDA Draft Guidance for Industry "Acne Vulgaris: Developing Drugs for Treatment"
 - ➢ 2015 FDA Draft Guidance for Industry "Head Lice Infestation: Developing Drugs for Topical Treatment".

Maximum Use Trial "Standard Language"



It has been the Agency's policy to request that a maximal usage trial be undertaken 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 and has been used successfully by other sponsors

Published in the Scientific Literature



Article

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 lead to systemic adverse effects. The classic example of this is hypothalamic-pituitary-adrenal axis suppression due to the use of potent topical corticosteroids.1-3

Since the mid-1970s, as part of the evaluation of any drug product, sponsors have been required to investigate the in vivo bioavailability of their products.4,5 For topically applied products, this has not always been possible due to limitations in analytical methods and an uncertainty in appropriate subject selection and trial design. In response to the regulatory need and the need to address questions from the pharmaceutical industry regarding appropriate trial design, the US Food and Drug Administration in the late 1990s internally developed and implemented a pharmacokinetic (PK) maximal usage trial Email: edward.bashaw@fda.hhs.gov

(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 skin disease.6 Based on the 2004 estimates, for example, the prevalence of acne is reported as 50.2 million people, and the prevalence of contact dermatitis (allergic and irritant) is reported as 72.3 million people in the United States.6

Even though there was a regulatory requirement to do in vivo bioavailability and bioequivalency testing for any new

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a) Frequency of dosing

-Prior to this time, many NDAs for topically applied products were being submitted for chronic application with only single exposure PK.

-While for oral drug products single doses are considered the most sensitive for BA/BE evaluations, for topical products they are of limited utility from a regulatory perspective





b) Duration of dosing

-Like oral controlled release products the duration of the study must be long enough such that the levels detected in the plasma (if any) are the maximal levels possible to inform safety.





c) Use of highest proposed strength

-Often topical products are developed in a range of strengths. Prior to this time sponsors tended to use the lowest concentration, thus minimizing the potential for absorption while maximizing the safety multiple from animal studies.





d) Total involved surface area to be treated at one time

-Historically, for NDAs, topical application was generally limited in adults to <30% of BSA. As an example, for patients with psoriasis who had skin lesions covering >30% BSA, the treatment modality of choice, prior to biologic therapy was, PUVA (Psoralen & UV-A light therapy). Even so NDAs were being submitted for indications such as moderate to severe psoriasis (large surface are involvement) with data from patients with only 5-10% BSA involvement or less.

BSA
$$(m^2) = \sqrt{\frac{\text{height } (\text{cm}) \times \text{weight } (\text{kg})}{3600 } (\text{cm } \text{kg/m}^4)}}$$



e) Amount applied per square centimeter

-To maximize the amount that can be absorbed one must test the maximum amount labeled for use by the patient. One cannot expect that all subjects will interpret usage instructions in a similar manner (i.e. "a golf ball sized amount".) By testing at the maximum amount recommended to be applied, this has the double advantage of both evaluating the efficacy of the product/ingredient at the highest level of skin loading and by maximizing the potential for absorption we can have a better evaluation of safety at this upper limit of use.





f) Method of application/site preparation

 Related to both the use of soaps and washes but also to debridement in some instances as in wound care or diabetic foot ulcer



The Maximal Usage Trial



- Designed to evaluate the potential for systemic drug absorption at the upper limit of use covered by the clinical trials and allowed for in the label in the patient population of interest.
 - While it has been successful in developing better assessments of systemic exposure and safety issues, it is still limited in its ability to assess bioavailability, per se.
- In the last few years it has had extension from NDAs into the OTC Monograph space in order to assist in the safety assessments of these agents.
- The 2018 MUsT Guidance was specifically written to address the need for guidance with these agents as the trial designs need to accommodate the conditions of use of OTC Monograph drugs which differ from a prescription drug.

The PRIMARY Value of a MUsT-NDA or OTC Monograph?



- It allows for the linkage of human exposure data under "full-dose" conditions back to pre-clinical safety studies.
 - Allows for estimation of safety margins relative to pre-clinical markers

It represents a standardized trial design that can be used for formulation optimization studies (NDA or OTC Monograph) or to evaluate special populations.

Key Difference Between NDA and OTC (Monograph) Products



NDA *Product* Monograph *INGREDIENT*





How Many Have Been Done?



2nd Annual Student Intern Science Poster



 FDA. (Accessed January 9, 2014).Draft guidance for industry: acne vulgaris—developing drugs for treatment. http://www.fda.gov/downleads/Drugs/__Caudances/UCM071292.pdf .Published 2005.

MUST Survey 1996-2016 Original NDAs Only



- A total of 66 MUsT trials have been conducted over 20yrs
 - An additional 20-30 trials have also been submitted as part of supplements
- Of the 66 trials they enrolled 1,545 patients
 - 887(58.6%) Male and 658(43.4%) Female







MAXIMAL USE VS. REAL-WORLD USE

Real World Use vs Maximal Use



- The FDA is certainly aware and supportive of the use of real world evidence in drug development, as evidenced by the recent public workshop sponsored by the FDA.
- Coupled with this interest is the obvious question as why such an approach is not being used for topical therapies.



Real World Use



- What actually is "real world use"?
 - Rx products in the setting of "real world use"
 - OTC monograph products in the setting of "real world use"
- For prescription drugs the MUsT paradigm is implemented at the upper limit or maximal dosing conditions reflected in the Phase 3 Trials and for which approval is sought.
- For OTC monograph drugs, considering the potential wide variation in use, if tested at an intermediate level, what about subjects that are "ideal" users?



Hypothetical Usage & Coverage Plot "Unitless by Design"

SPF and Application Amount



- Product A : SPF 30 lotion
- Product B: SPF 100 lotion
- Product C: SPF 100 spray
- Product D: SPF 50 lotion
- Product E : SPF 50 spray
- Product F : SPF 70 lotion

"Real World Use" and Maximal Use

- Defining what "real world use" means is always going to involve compromises and be subjective
 - Physician expectations regarding patient behavior after prescribing
 - Expectation of "ideal use", that is that the patient will use it as labeled and instructed
 - Patient behaviors
 - Does the dosage form/drug stain clothes?
 - Is it cosmetically elegant?
 - Do patients use the product consistently as directed even after clearing is seen?





CONCLUSIONS

Conclusions-General



- Since the mid-1990s, all topically applied products, for topical dermatologic indications, approved under an NDA have had an assessment of in vivo bioavailability testing under "maximal use" conditions
- ✓ The design elements were chosen to MAXIMIZE the ability of the study to detect in vivo blood levels independent of it being for an NDA product or an OTC Monograph active ingredient.
- ✓ For NDA, OTC NDA, and OTC Monograph topical products/ingredients the MUsT paradigm provides important data linking human exposure to pre-clinical safety studies.

Conclusions-Real World Use in a Dermal Setting



- "Real World Use", while seemingly appealing in principle, is subject to a number of limitations for topically applied products, especially in an OTC (NDA or Monograph) setting where usage occurs without a "learned intermediary"
 - the vagaries of definition
 - Where do you set the bounds of "Real World Use" in the regulatory pre-approval sense for NDA products?
 - For OTC Monograph products, how do we account for cross product and formulation differences which can impact consumer application?

Conclusions-Sunscreen Specific



- The use of the MUsT in the evaluation of sunscreen safety has been a topic of discussion with both the medical community, industry, and academia for many years including public outreach at AAD Annual Meetings, the Photomedicine Society Annual Meeting, AAPS, DIA and other national meetings.
- The FDA sponsored sunscreen study was done as a public pilot study to both demonstrate how such a study could be done with sunscreens and to get an estimate as to the degree of absorption
- The FDA has *NOT* said that Sunscreens are unsafe

Conclusions

In this preliminary study involving healthy volunteers, application of 4 commercially available sunscreens under maximal use conditions resulted in plasma concentrations that exceeded the threshold established by the FDA for potentially waiving some nonclinical toxicology studies for sunscreens. The systemic absorption of sunscreen ingredients supports the need for further studies to determine the clinical significance of these findings. These results do not indicate that individuals should refrain from the use of sunscreen.

The Maximal Usage Trial



- Designed to address earlier shortcomings of dermatologic research
- Does NOT represent the end of FDA thought on dermal drug development.
 - Technology evolves
 - New Methods and New Sciences
 - In vitro Permeation Testing (IVPT) as a developing regulatory method
 - ≻Q3 Testing
 - >In silico methods (modeling and simulation)
 - >As science evolves FDA's methods will have to evolve as well
 - Todays meeting is designed to facilitate the discussion of these methods, their application currently, and future extensions



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