FDA U.S. FOOD & DRUG ADMINISTRATION

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

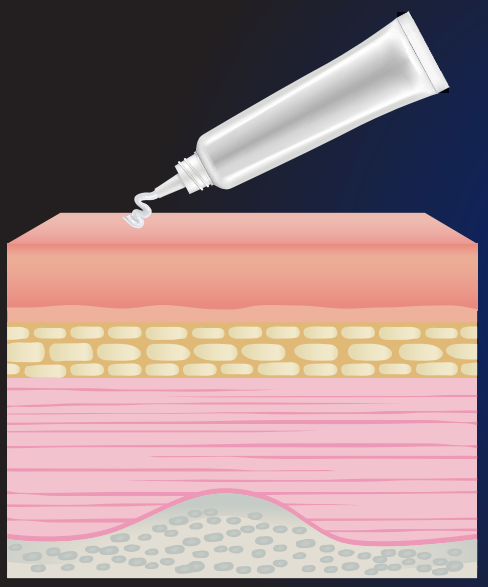
Final Guidance

What is recommended in this guidance?

The final guidance *Maximal Usage Trials for Topical Active Ingredients Being Considered for Inclusion in an Over-The-Counter Monograph: Study Elements and Considerations* provides recommendations on the design and conduct of Maximal Usage Trials (MUsT) to assess the in vivo absorption of topical active ingredients under consideration for inclusion in an over-the-counter (OTC) monograph.

Are you submitting a topical active ingredient being considered for inclusion in an OTC monograph?

FDA recommends MUsT to assess the potential for and extent of systemic exposure by a topical active ingredient that occurs as part of the determination of whether an OTC drug containing that active ingredient is generally recognized as safe and effective (GRASE) for its intended use.



MUsT Can Help Answer the Following Questions:

Does the active ingredient have dermal penetration and systemic exposure and, if so, to what extent?

If there is systemic exposure, does the exposure change in different populations or conditions?

When considered with other available safety and effectiveness data, do the plasma levels support that the ingredient is generally recognized as safe and effective under the intended conditions of use?

Guidance Snapshots are a communication tool and are not a substitute for the guidance document.
To learn more about Maximal Usage Trials for Topical Active Ingredients Being Considered for Inclusion in an Over-The-Counter Monograph, read the guidance:
https://www.fda.gov/media/125080/download

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MUsT Study Elements and Considerations

Study Population and Size

The study population should be representative of the population expected to use the product. The sample size should be large enough to provide an estimate of the maximum exposure considering any potential sources of intersubject and intrasubject variability.

Dosage and Application

Subjects should be dosed at the highest daily dose and frequency sought for inclusion in labeling and if used chronically, until levels of the active ingredient have reached steady state. The amount of test article applied, the surface area treated, and the site preparation (e.g., washing) should be consistent with proposed directions for use in the OTC monograph.

Formulation

In general, at least four market image formulations should be tested and should include the maximum concentration of the active ingredient proposed for inclusion in the applicable OTC monograph. At least one of the formulations tested should include a permeation enhancer to evaluate the potential effects of such agents.

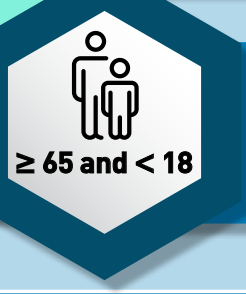
Sample Collection & Analytical Testing

The time points for blood sample collection should adequately capture the the maximum concentration (Cmax), time to maximum concentration (Tmax), and the entire concentration-versus-time profile. The assay used in the MUsT should be validated according to current good laboratory practices (21 CFR part 58).

Safety Testing

MUsT studies should collect safety-related data during the regularly scheduled physical examinations and study visits.

Geriatric & Pediatric Populations



When the drug is expected to be used in the geriatric population, a sufficient number of geriatric subjects should be enrolled in the MUsT study. Generally, data should be collected in adults first before considering whether a MUsT is also necessary in children.

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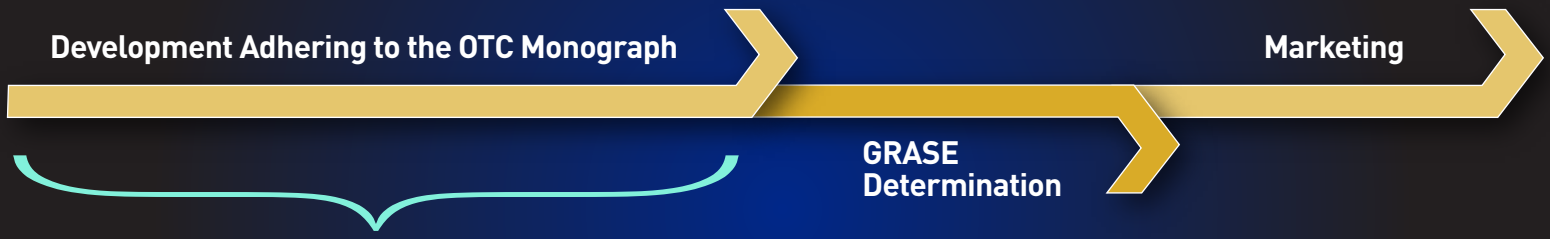
Background About the Guidance

MUsT has been used in the development of topical products in the prescription drug space for over 20 years. The unique application of the MUsT concept for OTC monographs is that a specific active ingredient and not a final drug product/formulation is under consideration. This guidance provides important recommendations to sponsors on critical study elements, data analysis, and considerations for special topic areas (e.g., pediatrics, geriatrics) for MUsT. The FDA will use information from a MUsT to identify the potential for systemic exposure and determine the need for additional safety data to support a finding that an OTC product with that active ingredient is generally recognized as safe and effective (GRASE) for its intended use. As follow up to publication of the sunscreen proposed rule in February 2019, this guidance provides industry with clear direction on how to approach MUsT studies.

Why is this guidance important?

As an example, despite what we know about prevention, skin cancer caused by sun exposure remains one of the most common cancers diagnosed in the United States. We know that the use of sunscreens, when used with other sun protective measures, is one of our most effective weapons against skin cancer. Because sunscreens are designed to work on the surface of the skin, some have proposed that sunscreens would not be absorbed in appreciable quantities, making MUsTs unnecessary. However, an original research article in the Journal of the American Medical Association found that application of 6 sunscreen active ingredients from 4 commercially available sunscreens resulted in plasma concentrations exceeding the FDA-established threshold for potentially waiving some nonclinical toxicology studies for sunscreens.

Drug Development Timeline – When to Apply the Guidance Recommendations?



During OTC Monograph Development:

The conduct of a MUsT should be consistent with maximal use of the product as specified by existing or anticipated labeling. Thus MUsTs for an OTC monograph product should be conducted as early as possible once both dosing frequency, amount to be applied, target populations, and other relevant factors are identified. Such testing should be conducted using multiple formulations, including formulations that are designed to maximize the potential for absorption. The collected samples from the MUsT should then be analyzed, and the systemic exposures to the active ingredients of interest should be evaluated using standard PK measures. The FDA expects to use the resulting in vivo PK data, in conjunction with data from animal toxicity studies, to estimate a safety margin for systemic exposure to the active ingredient in the relevant category of OTC monograph drug products.

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