Master MUst elements

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Disclaimer

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Agenda

• Background
• MUsT key elements
• MUsT program for Sunscreen
• Master protocol
• Regulatory action & advice
• Summary
Background

• What is MUst?
  – Maximal Use Trial program enables the assessment of systemic concentrations of a topically applied drug product under maximal use conditions.

• Why is MUst important?
  – For topical OTC products such as sunscreens and antiseptics, safety concerns are critical as OTC drug products are used by a large population with a wide age range.
  – Once an active ingredient is included in the monograph category I (GRASE), many different formulations can be developed and marketed without additional studies.

• Why do we need Master protocol?
  – Consistency and clarity in data interpretation.
  – Time and resource effective for drug development
“Standard Design Elements” of MUsT under OTC monograph*

✓ 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 (area)
✓ Method of application/site preparation

* Final Guidance for Industry: Maximal usage trials for topically applied active ingredients being considered for inclusion in an Over-The-Counter monograph: Study elements and consideration (May 2019)
Common Key Elements

• Demographics of subjects
  – Number of subjects representing general US demographics across sex, ages, and races.

• Body surface area
  – Maximal body surface area per topical application that is consistent with proposed use.

• Frequency of application
  – Maximal number of uses per day (over an 8-hour period)

• Treatment duration
  – Maximal duration of usage or time to reach steady state
Skin damage by ultra-violet (UV) rays and Benefits of sunscreen

Benefits of Sunscreen

• Decrease in skin aging
• Decrease in sunburn
• May reduce potential risks of skin cancer
Sunscreen Active Ingredients

Category I (GRASE)
- Zinc Oxide
- Titanium Dioxide

Category II (Non-GRASE)
- Aminobenzoic acid (PABA)
- Trolamine salicylate

Category III (Insufficient data for GRASE determination)

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<tr>
<th>No.</th>
<th>Ingredient</th>
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<tr>
<td>1</td>
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<tr>
<td>2</td>
<td>Oxybenzone</td>
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<tr>
<td>3</td>
<td>Ensulizole</td>
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<td>11</td>
<td>Dioxybenzone</td>
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<tr>
<td>12</td>
<td>Cinoxate</td>
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Not deferred
Sunscreen Final Rule Deferral

• Sunscreen final rule has been deferred till Nov. 29. 2020
• The sunscreen industry has submitted the deferral request of 8 active ingredients in Category III.
  – The industry needs to provide a pharmacokinetic (PK) assessment of active ingredients following repeated topical applications under maximal use conditions.
  – Depending on the level of systemic exposure of active ingredients, additional nonclinical studies may be necessary to support the systemic safety of the active ingredients.
  – The FDA is working with the industry to set the Master protocol with standardization of key elements.
Dermal absorption of sunscreen

• Sunscreen ingredients were found in systemic circulation and tissue in humans (Schlumpf, 2010; Krause, 2012, ...), etc.

• In vivo permeation studies show detectable systemic exposure of a sunscreen ingredient following topical application of sunscreen (Janjua, 2008; Gonzalez, 2006; Gulson, 2012, ...).

(adapted from Janjua et al., 2008)

(Gulson et al., 2012)

(Gonzalez et al., 2006)
Insufficient dermal absorption data in literature

• Common issues in publication
  – Extemporaneous formulations
  – Sub-maximal use conditions

• Recommended criteria of maximal use conditions
  – Application every 2 hours 4 times a day
  – Duration to reach steady state (to be informed by a pilot study)
  – Body surface area – minimum 75%
  – Dose per topical application: 2 mg/cm²
Considerations for MUst

**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.
Considerations for MUst

Sample Collection & Analytical Testing

The time points for blood sample collection should adequately capture 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.
A pilot study is to obtain initial PK data to design the confirmatory pivotal study.

The subject number should be able to address the anticipated inter-subject and intra-subject variability.

At least 4 market-image formulations should be tested including one formulation with permeation enhancer.

PK sample collection needs to adequately capture the Cmax, Tmax, and the entire concentration-versus-time profile.
• Pivotal MUsT study should be conducted in a sufficiently large number of subjects given the large target population and variation in skin permeation within it

• Elements including dose, dosing regimen, and BSA are standardized. The current label recommends the application of sunscreen 2 mg/cm² every 2 hours.

• At least 4 market-image formulations should be tested including one formulation with permeation enhancer.
Master Key Elements for Sunscreen

• Demographics of subjects
  – Pilot study: To understand inter-subject and intra-subject variability
  – Pivotal study: Sufficient number of subjects representing general US demographics across sex, ages, and races.

• Body surface area
  – 75% body surface area is considered as the maximal skin area for sunscreen.

• Frequency of application
  – Every 2 hours per day (4 applications per 8 hours)

• Treatment duration
  – 5 days or to achieve steady state
Regulatory action and advice

• Publication of *Proposed Rule, Sunscreen Drug Products for Over-the-Counter Human use* (02/26/2019)

• Publication of *guidance, Maximal usage trial (MUsT) for Topical Active ingredients being considered for inclusion in an over-the-counter monograph: Study elements and considerations* (Draft 05/21/2018, Final 02/2019)
Summary

- With the final rule deferral, 8 sunscreen active ingredients have been proposed for evaluation within a MUsT program by an industry trade group.
- Master MUsT protocol is
  - To standardize the MUsT study design elements.
  - To develop topical OTC product in a time- and budget- efficient manner.
- There are key elements for Sunscreen Master protocol: dose and dosing regimen, BSA, and treatment duration.
- The FDA encourages the industry to discuss both pilot and pivotal study design with the FDA prior to the initiation of the study.
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