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

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Office of Clinical Pharmacology, Guidance and Policy Team at CDER_OCP_GPT@fda.hhs.gov.

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

**May 2018
Clinical Pharmacology/Over-the-Counter (OTC)**

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Contains Nonbinding Recommendations

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1 **Maximal Usage Trials for Topical Active Ingredients Being**
2 **Considered for Inclusion in an Over-The-Counter Monograph:**
3 **Study Elements and Considerations**
4 **Guidance for Industry¹**
5

6
7 This draft guidance, when finalized, will represent the current thinking of the Food and Drug
8 Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is
9 not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements
10 of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff
11 responsible for this guidance as listed on the title page.
12

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14
15
16 **I. INTRODUCTION**
17

18 This guidance provides recommendations for the conduct of in vivo absorption trials for
19 topical active ingredients that are under consideration for inclusion in an over-the-counter
20 (OTC) drug monograph. A Maximal Usage Trial (MUsT) is a standard approach to assess
21 the in vivo bioavailability of topical drug products.² The methodology described in this
22 guidance adapts MUsT principles for active ingredients being considered for inclusion in an
23 over-the-counter (OTC) monograph.³ Because information from a MUsT can help identify
24 the potential for systemic exposure to a topically applied active ingredient, such information
25 can help inform an FDA determination of whether additional safety data are needed to
26 support a finding that an OTC drug containing that active ingredient is generally recognized
27 as safe and effective (GRASE) for its intended use.
28

29 This guidance outlines FDA's recommendations for designing and conducting a MUsT for
30 this purpose, including critical study elements, data analysis, and considerations for special

¹ This guidance has been prepared by the Office of Translational Sciences, Office of Clinical Pharmacology and the Office of New Drugs, Division of Nonprescription Drug Products in the Center for Drug Evaluation and Research at the Food and Drug Administration.

² In this guidance, *drug product* refers to a finished dosage form, which generally includes both inactive and active ingredients. *Active ingredient* refers to a component of the drug product that provides the intended pharmacological activity.

³ See the FDA guidance for industry entitled *Head Lice Infestation: Developing Drugs for Topical Treatment*. See also the FDA draft guidance for industry entitled *Acne Vulgaris: Developing Drugs for Treatment*. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA's Drugs guidance Web Page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

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31 topic areas (e.g., pediatrics, geriatrics). This guidance also encourages study sponsors to seek
32 feedback from the FDA on their overall approach and the design of a particular study.

33
34 In general, FDA's guidance documents do not establish legally enforceable responsibilities.
35 Instead, guidances describe the Agency's current thinking on a topic and should be viewed
36 only as recommendations, unless specific regulatory or statutory requirements are cited. The
37 use of the word *should* in Agency guidances means that something is suggested or
38 recommended, but not required.

39
40

41 **II. BACKGROUND**

42

43 A critical safety consideration for topical drugs is whether applying the drug to the skin
44 results in dermal penetration and systemic exposure to the active ingredient, and, if so, to
45 what extent. This information helps identify potential safety concerns and helps determine
46 whether an adequate safety margin exists for an active ingredient to be included in a relevant
47 OTC monograph.

48

49 The principal barrier to cutaneous dermal penetration is the multilayered, lipid-rich stratum
50 corneum. The passage of any drug through this layer is influenced by many factors,
51 including the drug's physicochemical characteristics, the properties of the formulation and
52 the vehicle, and the condition of the skin (e.g., healthy or diseased). For example, excipients
53 in the drug formulation can act as permeation enhancers directly by having solvent effects on
54 the lipids in the stratum corneum or indirectly through simple hydration of the stratum
55 corneum by occlusive formulations. Products absorbed through the skin have the potential to
56 cause systemic adverse effects, affecting the safety assessment. For drugs that are intended
57 to work at the skin's surface, like sunscreens and pediculicides, systemic absorption may also
58 lower efficacy, affecting the efficacy assessment. Such considerations ultimately weigh into
59 the risk-benefit calculus FDA uses to determine whether an OTC drug product containing a
60 given active ingredient would be GRAS/E.

61

62 Historically, topical treatments were commonly believed not to result in clinically relevant
63 systemic drug absorption.⁴ Even when the potential for systemic absorption of topically
64 applied OTC products was recognized,⁵ the in vivo bioavailability of such products could not
65 always be measured because of limitations in analytical methods. As analytical methods
66 advanced, however, the FDA started to request pharmacokinetic (PK) trials under maximal-
67 use conditions as part of the systemic safety evaluation for topical products developed under
68 the New Drug Application (NDA) process. The MU_sT, also referred to as a maximal-use PK
69 trial, was described in the FDA draft guidance for industry *Acne Vulgaris: Developing Drugs*

⁴ Bashaw ED, DC Tran, CG Shukla, X Liu, 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.

⁵ See, e.g., Benson HA, 2000, Assessment and Clinical Implications of Absorption of Sunscreens Across Skin, *Am J Clin Dermatol*, 1 (4):217-24; Lin YJ, 2000, Buccal Absorption of Triclosan Following Topical Mouthrinse Application, *Am J Dent*, 13 (4):215-7.

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70 *for Treatment*⁶ in 2005, again in 2015 in the FDA draft guidance for industry *Head Lice*
71 *Infestation: Developing Drugs for Topical Treatment*, and in the 2016 final guidance of the
72 same title. The MUsT paradigm is now a recommended assessment for topical drug products
73 developed under an NDA.

74
75 Unlike the MUsT paradigm in the NDA context, a MUsT conducted in the OTC monograph
76 context evaluates an active ingredient in a range of formulations. This is because an NDA
77 review focuses on the safety and effectiveness of a single drug product, i.e., a specified
78 formulation of active and inactive ingredients, while the review to establish an OTC
79 monograph necessitates determining the conditions under which any of multiple drug
80 products would be generally recognized as safe and effective. The resulting monograph
81 authorizes marketing of every formulation that meets each of its conditions and complies
82 with other applicable regulatory requirements.⁷ Active ingredient(s) are key conditions in
83 any OTC monograph. However, the choice of inactive ingredients, also called excipients, in
84 a finished drug product can affect the absorption of the active ingredient. Therefore, before
85 including an active ingredient in an OTC monograph, it is important to evaluate the
86 absorption of a representative range of formulations.

87
88 In 2014, the FDA asked the Nonprescription Drugs Advisory Committee (NDAC) to address
89 the concerns of dermal absorption for sunscreens⁸ and healthcare antiseptics⁹ to assist with
90 ongoing rulemaking for these topical OTC drugs. Based in part on the committee's input and
91 recommendations, the FDA determined that, in general, results from MUsTs are important to
92 support a GRASE determination for topical drugs regulated under an OTC monograph.

93

III. MAXIMAL USAGE TRIAL

94

A. Overview

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96
97
98 To evaluate an active ingredient proposed for use in any topical drug product under the OTC
99 monograph system, the underlying goal of the MUsT is to evaluate systemic exposure levels
100 under conditions relevant to real-world use that maximize the potential for dermal
101 absorption. Accordingly, the conduct of a MUsT should be consistent with maximal use of
102 the product as specified by existing or anticipated labeling. Testing should be conducted
103 using multiple formulations, including formulations designed for maximum absorption. The

⁶ When final, this guidance will represent the FDA's current thinking on this topic.

⁷ See 21 CFR § 330.1.

⁸ Food and Drug Administration, Center for Drug Evaluation and Research, Summary Minutes of the Nonprescription Drugs Advisory Committee (NDAC) Meeting, September 4-5, 2014. <https://wayback.archive-it.org/7993/20170404152726/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/NonprescriptionDrugsAdvisoryCommittee/UCM421304.pdf>

⁹ Food and Drug Administration, Center for Drug Evaluation and Research, Summary Minutes of the Nonprescription Drugs Advisory Committee (NDAC) Meeting, September 3, 2014. <https://wayback.archive-it.org/7993/20170404152740/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/NonprescriptionDrugsAdvisoryCommittee/UCM421120.pdf>

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104 collected samples from the MUsT should then be analyzed, and the systemic exposures to the
105 active ingredients of interest should be evaluated using standard PK measures. Routine
106 collection of adverse event data is recommended. The need for targeted safety assessments
107 should be considered in the protocol design phase.

108
109 The FDA expects to use the resulting in vivo PK data, in conjunction with data from animal
110 toxicity studies, to estimate a safety margin for systemic exposure to the active ingredient in
111 the relevant category of OTC monograph drug products.¹⁰ If the overall record supports a
112 finding that a particular category of drugs containing that active ingredient would be GRASE
113 and not misbranded under specified monograph conditions, other details from the MUsT may
114 be used to establish such conditions to ensure that marketed products remain within an
115 acceptable safety margin. For example, if data indicate that there is a need to limit the
116 absorption of a given active ingredient, the FDA may consider establishing monograph
117 conditions for final product formulations containing that active ingredient, such as in vitro
118 permeation testing for final formulations using the formulation that resulted in the greatest
119 absorption in the MUsT for that active ingredient as a benchmark.

120 The FDA recognizes that more than one study design can provide the desired information
121 and that many factors can influence the specific approach to be used. Study sponsors should
122 seek FDA's input on the formulations to be tested and other proposed study elements prior to
123 conducting the MUsT. The following are the FDA's general recommendations for the design
124 and conduct of the MUsT.

125

B. Study Elements and Considerations

126

1. Study Population

127

128
129
130 The study population should be representative of the population expected to use the product.
131 If a topical product has more than one indication with different expected populations, the
132 sponsor should choose the population with the highest potential for dermal absorption. The
133 resulting data may be extrapolable to indications likely to yield lower exposures of the
134 topical drug product. Some factors to consider include:¹¹

135

- 136 • Skin surface area to be exposed
- 137
- 138 • Dosing frequency (if different for different indications)
- 139

¹⁰ For drugs with a known potential for adverse effects based on animal data, the anticipated level of risk for humans may be quantified using a safety margin calculation. A *safety margin calculation* takes the highest no-observed-adverse-effect level in animals and estimates a maximum safe level of exposure for humans. One caveat to the safety margin calculation is that animal studies do not always predict effects in humans, and the actual threshold for an effect in humans may be different (higher or lower) than in the species tested. The human sensitivity to a drug is often unknown. To account for this uncertainty, the predicted safe exposure level in humans that is reflected in the safety margin will be well below the exposure level that causes toxicities in animals.

¹¹ See sections III.B.13 and III.B.14 for discussions of considerations for pediatric and geriatric populations.

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- Factors affecting skin permeability: For example, if the active ingredient will be used to treat a disease where the skin barrier is perturbed (e.g., tinea pedis), the sponsor should enroll subjects with the disease of interest to provide an appropriate in vivo assessment of the topical drug product's absorption. If, on the other hand, the topical drug product is to be used on healthy skin (e.g., sunscreens or certain antiseptics), the sponsor should enroll subjects with healthy, intact skin in the trial.

2. Number of Subjects

When determining the sample size for a MUSt, the sponsor should consider the study design and any potential sources of intersubject and intrasubject variability. The sample size should be large enough to provide an estimate of the maximum exposure. Because OTC monographs allow an active ingredient to be used in diverse formulations (see section III.B.9), the number of subjects needed to create a representative sample will likely be larger than for PK studies designed to support a single drug formulation for an NDA.

If information needed to calculate the number of subjects (such as the expected intersubject and intrasubject variability) is not available, the FDA recommends that the sponsor conduct a pilot study. This pilot study should use the formulation with the highest potential for permeation based on in vitro testing (see section III.B.9). For example, the sponsor could use a formulation containing known permeation enhancers in a pilot study. A pilot study can also be used to validate the analytical methodology, assess the PK variability, evaluate the time intervals for sample collection, and provide other information that can inform the design of the MUSt.¹² While useful in optimizing the study design of a MUSt, a pilot PK study is unlikely to provide sufficient data to substitute for a full-scale MUSt.

3. Amount Applied

The amount of test article applied should be consistent with the existing or proposed directions for use in the applicable OTC monograph. The amount applied should be captured by weighing the container or using another appropriate method.

4. Surface Area Treated

The surface area to be treated should be consistent with the intended monograph directions for use.

a. Individual Lesions

If the drug is proposed for use in skin diseases with specific lesions having defined margins, the maximum number of lesions anticipated to be treated at one time should be reflected in the study design and be consistent with the proposed use and labeling.

¹² See the draft guidance for industry *Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs—General Considerations*. When final, this guidance will represent the FDA's current thinking on this topic.

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b. Partial-Body Exposure

In a MUsT evaluating an active ingredient for use in OTC drug products that are applied only to part of the human body, the test article should be applied to the maximal area proposed in labeling. For example, if the proposed labeling addresses use of the drug product on up to 30 percent of body surface area, 30 percent of the body should be evaluated in the MUsT.¹³ The surface area of application should be recorded so that it can be submitted in support of a monograph determination. For MUsTs evaluating healthcare antiseptics for use as surgical hand scrubs, the exposure should cover the hands and arms up to the elbow.

c. Whole-Body Exposure

If near total-body involvement is a presenting feature of the condition to be treated (e.g., eczema in pediatric patients), or if a preventive therapy is intended to be used over a large portion of the body (e.g., sunscreen), the test article should be applied to as much body surface area as possible and appropriate, and the surface area of application should be recorded. For sunscreens, the exposed area should include at least 75 percent of the body surface area.

5. Frequency of Dosing

In MUsTs evaluating active ingredients for topical products intended for use multiple times in a day, test articles should be administered at the highest frequency sought for inclusion in labeling. If the product is intended for application in the morning and at night, then the MUsT should incorporate dosing at both times. If the potential monograph labeling recommends re-application after specific intervals or activities, the subjects should be redosed accordingly. For example, dosing in a MUsT for an antiseptic handrub could entail 100 applications, given that this is the number of times some health care workers might disinfect their hands in an 8- to 12-hour shift.¹⁴ Dosing in a MUsT for sunscreens should use the same dosing interval as directed in OTC sunscreen labeling, every 2 hours.¹⁵

6. Duration of Dosing

For active ingredients to be included in OTC drugs that are used chronically, the FDA recommends that subjects be dosed until levels of the active ingredient and clinically relevant

¹³ Bashaw ED, DC Tran, CG Shukla, X Liu, 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. See also the draft guidance for industry *Acne Vulgaris: Developing Drugs for Treatment*. When final, this guidance will represent the FDA's current thinking on this topic.

¹⁴ Evans V and P Orris P, 2012, The Use of Alcohol-Based Hand Sanitizers By Pregnant Health Care Workers, *J Occup Environ Med*, 54(1):3.

¹⁵ See 21 CFR 201.327.

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218 metabolites, if any, have reached steady state,¹⁶ both: (1) to ensure that maximum
219 penetration of the active ingredient has occurred; and (2) to optimize its chances of being
220 detected. A pilot PK study can be useful for determining the duration of dosing in the
221 MUsT.

222

223 7. *Method of Application*

224

225 If topical drug products containing the active ingredient of interest bear instructions
226 regarding application or site preparation (e.g., washing), these same instructions and
227 procedures should be incorporated into the MUsT. Likewise, if there are ordinary
228 circumstances surrounding use, such as wearing socks or clothing, those conditions should
229 also be incorporated into the MUsT.

230

231 8. *Combinations of Active Ingredients*

232

233 In general, the formulation being evaluated in the MUsT should contain the active ingredient
234 being evaluated for inclusion in an OTC monograph as the only active ingredient. If there is
235 a scientific reason for combining more than one active ingredient, sponsors should seek the
236 FDA's guidance before initiating a MUsT.

237

238 9. *Formulation Considerations*

239

240 Study formulations should have the maximum concentration of the active ingredient
241 proposed for inclusion in the applicable OTC monograph.

242

243 The FDA recommends that sponsors evaluate multiple formulations in MUsTs
244 because: (1) the composition of the formulation may have a large impact on
245 absorption through the skin; and (2) active ingredients in OTC monographs may be
246 marketed in multiple diverse formulations. Multiple formulations may be evaluated
247 in separate or combined studies. The selection of these formulations should be
248 guided by information gained from in vitro skin permeation testing using a human
249 cadaver skin permeation system (e.g., static or flow through cells).¹⁷ Justification for
250 the formulations chosen, including results of the in vitro testing, should be included in
251 the MUsT protocol. The protocol should contain sufficient detail for others to
252 reproduce the formulations.

253

254 In the absence of mitigating safety data or other bioavailability-related information,
255 we recommend MUsT testing of at least four formulations. A sponsor that chooses to
256 study fewer than four formulations should provide a scientific rationale as well as

¹⁶ See the draft guidance for industry *Clinical Lactation Studies – Study Design, Data Analysis, and Recommendations for Labeling*. When final, this guidance will represent the FDA's current thinking on this topic.

¹⁷ Bronaugh, RL and RF Stewart, January 1985, Methods for In Vitro Percutaneous Absorption Studies IV: The Flow-Through Diffusion Cell, J Pharm Sci, 74(1):64-67.

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257 both in vivo MUsT and in vitro skin permeation data. Sponsors are encouraged to
258 discuss this rationale with the FDA in advance of a monograph submission.

259
260 The formulations screened in the in vitro skin permeation system and subsequently
261 selected for evaluation in a MUsT should be *market image* formulations with the
262 highest potential for absorption of the active ingredient at issue. Market image
263 formulations are similar to those that would be suitable for marketing and not, for
264 example, a simple extemporaneous formulation (i.e., a dispersion in a vehicle) that
265 was created without regard to such factors as deployability, spreadability, and shelf-
266 life. These factors, among others, can have a significant impact on absorption.¹⁸ In
267 addition, because marketed product formulations often include excipients that are
268 known permeation enhancers (e.g., alcohol), at least one of the tested formulations
269 should include permeation enhancers at the high end of concentrations typically used
270 in topical OTC drug products.

271
272 If an active ingredient is highly absorbed in the first formulation tested and there are
273 gaps in the preclinical toxicology safety data that FDA recommends be gathered to
274 support the safety of the active ingredient if absorbed, we recommend that individuals
275 fill in the nonclinical safety data gaps before evaluating additional formulations.
276 Once supportive preclinical toxicology safety data are obtained, additional
277 formulations can be tested as necessary to assure that maximum human exposure is
278 adequately defined. On the other hand, if important safety risks are detected in
279 preclinical toxicology testing at feasible levels of absorption, the active ingredient
280 may not be suitable for the OTC monograph system.

281 282 *10. Sample Collection*

283
284 The time points for blood sample collection should adequately capture the C_{max} , T_{max} ¹⁹, and
285 the entire concentration-versus-time profile. The sponsor should choose time intervals for
286 sample collection on the basis of the active ingredient's known disposition parameters or, in
287 the absence of any in vivo information, by using a geometric sampling approach. The time
288 of sample collection, the transportation and storage of the sample, and handling techniques of
289 the sample should be documented.

290
291 In general, PK sampling should be collected both after a single dose and at steady state to
292 evaluate the accumulation potential of the active ingredient. Additional sampling for the
293 active ingredient or metabolite concentrations is also recommended when an adverse event
294 occurs. Additionally, sufficient PK sampling after the final dose should be included to
295 ensure proper characterization of the terminal elimination rate. A pilot PK study can be
296 useful for informing the sample collection considerations for a MUsT.

297

¹⁸ Benson HA, 2000, Assessment and Clinical Implications of Absorption of Sunscreens Across Skin, AmJ Clin Dermatol, 1 (4):217-24.

¹⁹ C_{max} is the peak plasma concentration, and T_{max} is the time to peak plasma concentration.

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298 11. *Sensitive and Validated Analytical Method*

299
300 The use of a validated and sensitive analytical method is scientifically critical. The assay
301 used in the MUsT should be validated according to current good laboratory practices (21
302 CFR part 58). Additionally, sponsors should consider the Agency’s most current guidance
303 on bioanalytical method validation, which may be found by searching
304 <https://www.fda.gov/RegulatoryInformation/Guidances/>. The assay’s limit of quantitation-
305 limit of detection should be sufficiently low to allow a signal-to-noise ratio that ensures
306 confidence in detection of a concentration of 0.5 nanogram (ng)/milliliter (mL) for the
307 compound of interest (i.e., the lower limit of quantification should extend below the 0.5
308 ng/mL level to ensure the analytical accuracy and precision of the assay at the 0.5 ng/mL
309 level).²⁰ To be scientifically sound, the assay needs to be validated before study initiation,
310 and the validation results should be part of the study report. If an active ingredient has
311 clinically relevant metabolites, an assay should also be developed and validated to test for
312 those metabolites.

313 314 12. *Safety Data*

315
316 Study protocols should evaluate the safety and tolerability of the drug product. Because the
317 subjects in a MUsT represent an enriched dataset in the upper range of exposures, the FDA
318 recommends that the sponsor collect safety-related data (e.g., vital signs, adverse skin events,
319 other adverse events) from the study’s regularly scheduled physical examinations and study
320 visits.

321 322 13. *Pediatrics*

323
324 To assure the safety of pediatric populations, MUsT data should generally be collected in
325 adults first before considering whether a MUsT is also necessary in pediatrics. Physiologic
326 and development differences between pediatric and adult patients can lead to differences in
327 systemic exposure from topically applied products. For example, young children have a
328 larger ratio of skin surface-to-body volume compared to adults, which can result in increased
329 systemic exposure compared to adults. The skin of young children has significant differences
330 in skin capacitance and transepidermal water loss, along with a thinner stratum corneum
331 which can also affect systemic absorption.²¹ In addition to the potential for increased
332 exposure compared to adults, there may be different or more severe adverse effects in
333 children at any given exposure level compared to adults because of the effect of a drug on a
334 developing or immature organ system.

²⁰ The threshold value of 0.5 ng/mL is based on the principle that that level would approximate the highest plasma level below which the carcinogenic risk of any unknown compound would be less than 1 in 100,000 after a single dose. This threshold value is consistent with the *Threshold of Toxicological Concern* concept, which was applied to impurities in the International Council for Harmonization (ICH) guidance for industry entitled, *M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk*.

²¹ Nikolovski J, GN Stamatias, N Kollias, and BC Wiegand, 2008, Barrier Function and Water-Holding and Transport Properties of Infant Stratum Corneum Are Different From Adult and Continue to Develop Through the First Year of Life. *J Invest Dermatol*, 128 (7):1728–36.

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335
336 If the calculated safety margin for a proposed monograph active ingredient (based on
337 nonclinical results and human MUsT) is relatively small for an adult population, the FDA
338 will determine if an additional MUsT in young children or other studies are warranted for
339 any specific pediatric age range. There may be other reasons why conducting a MUsT in a
340 pediatric population may be needed to support the safety of a proposed monograph active
341 ingredient. Study sponsors considering whether to conduct pediatric studies should consult
342 with the FDA.

343 344 *14. Geriatrics*

345
346 When the topical drug product is expected to be used in the geriatric population, a sufficient
347 number of geriatric subjects should be enrolled in the adult MUsT, ensuring adequate
348 representation of the entire age range. Geriatric skin is morphologically different from
349 younger skin and has less elasticity, moisture content, cellularity, and vascularity.^{22, 23, 24}
350

351 352 **IV. DATA ANALYSIS**

353
354 If the systemic exposure to the active ingredient is quantifiable, the PK data should be
355 analyzed using standard PK metrics for plasma, serum, or blood, such as C_{max} , T_{max} , area
356 under the curve (AUC), half-life, and clearance, which are descriptive of the concentration of
357 the active ingredient or its clinically relevant metabolites over time. The accumulation
358 potential of the active ingredient should be assessed based on the exposures after single and
359 multiple doses.
360

361 The upper range of the systemic exposure (e.g., C_{max} , AUC) and their interindividual
362 variances among the study population should be reported and will be used to calculate the
363 safety margin based on animal toxicity studies. A sufficient number of subjects to give an
364 estimate of the maximum exposure is important, as discussed in section III.B.
365
366

367 **V. CONSULTATION WITH THE FDA**

368
369 We recognize that testing programs are influenced by the specifics of the ingredient,
370 indication, prior knowledge, and other factors that cannot be fully addressed in this
371 document. Therefore, we encourage study sponsors to seek our advice before initiating a
372 MUsT to support OTC monograph status for a particular active ingredient.
373

²² Luebberding S, N Krueger, and M Kerscher, 2013, Age-Related Changes in Skin Barrier Function — Quantitative Evaluation of 150 Female Subjects, *Int J Cosmet Sci*, 35 (2):183-90.

²³ Luebberding S, N Krueger, and M Kerscher, 2014, Age-Related Changes in Male Skin: Quantitative Evaluation of One Hundred and Fifty Male Subjects, *Skin Pharmacol Physiol*, 27 (1):9-17.

²⁴ Farage MA, KW Miller, E Berardesca, and HI Maibach, 2009, Clinical Implications of Aging Skin: Cutaneous Disorders in the Elderly, *AmJ Clin Dermatol*, 10 (2):73-86.

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374 The OTC Drug Review is a public process, culminating in the establishment of OTC drug
375 monographs that embody FDA's finding that any drug that meets the conditions of that
376 monograph and those in 21 CFR 330.1 is GRASE and not misbranded. Such a finding of
377 general recognition needs to be based on data that is generally available, which is ensured by
378 its inclusion in the public docket. For this reason, we anticipate that for the FDA to consider
379 a MUsT as potential support for the safety of a particular active ingredient, and for its
380 inclusion in an OTC drug monograph, that study would need to be included in the public
381 docket for the relevant monograph.

382
383 We recognize that sponsors have expressed concern about making certain information about
384 the development of their MUsT programs public prematurely, while they are still considering
385 whether and how to begin such testing. To address this concern, the FDA may hold private
386 meetings with sponsors who request them if they would like to discuss specific potential
387 MUsT protocol details that are not yet part of the public record. Notwithstanding the
388 availability of such private preliminary meetings, minutes from these meetings are
389 subsequently submitted to the public docket and documents submitted for these meetings
390 may be subject to disclosure under the Freedom of Information Act. We anticipate that
391 meeting minutes will provide a summary of general concepts that were discussed, while
392 excluding information to the extent that it contains confidential commercial information,
393 trade secrets, and other types of information at this stage of testing that study sponsors
394 generally do not publicly disclose, such as chemistry data and detailed protocols. This model
395 gives sponsors the opportunity to privately discuss and receive input from the FDA about
396 their preliminary plans to generate the MUsT data needed for the FDA to include an active
397 ingredient in a given OTC drug monograph. If a sponsor ultimately submits data to support a
398 GRASE determination in an OTC monograph, nothing here will alter the obligation to make
399 data that is necessary to support a general recognition determination publicly available.