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DRAFT GUIDANCE

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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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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)

Draft Guidance Temp
05/21/18

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Maximal Usage Trials for Topical Active Ingredients Being Considered for Inclusion in an Over-The-Counter Monograph: Study Elements and Considerations Guidance for Industry[1]

I. INTRODUCTION

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

This guidance outlines FDA's recommendations for designing and conducting a MUsT for 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.

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

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

II. BACKGROUND

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

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

Historically, topical treatments were commonly believed not to result in clinically relevant systemic drug absorption.[4] Even when the potential for systemic absorption of topically applied OTC products was recognized,[5] the in vivo bioavailability of such products could not always be measured because of limitations in analytical methods. As analytical methods advanced, however, the FDA started to request pharmacokinetic (PK) trials under maximal-use conditions as part of the systemic safety evaluation for topical products developed under the New Drug Application (NDA) process. The MUsT, also referred to as a maximal-use PK 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.

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

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

In 2014, the FDA asked the Nonprescription Drugs Advisory Committee (NDAC) to address the concerns of dermal absorption for sunscreens[8] and healthcare antiseptics[9] to assist with ongoing rulemaking for these topical OTC drugs. Based in part on the committee's input and recommendations, the FDA determined that, in general, results from MUsTs are important to support a GRASE determination for topical drugs regulated under an OTC monograph.

III. MAXIMAL USAGE TRIAL

A. Overview

To evaluate an active ingredient proposed for use in any topical drug product under the OTC monograph system, the underlying goal of the MUsT is to evaluate systemic exposure levels under conditions relevant to real-world use that maximize the potential for dermal absorption. Accordingly, the conduct of a MUsT should be consistent with maximal use of the product as specified by existing or anticipated labeling. Testing should be conducted 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

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. Routine collection of adverse event data is recommended. The need for targeted safety assessments should be considered in the protocol design phase.

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.[10] If the overall record supports a finding that a particular category of drugs containing that active ingredient would be GRASE and not misbranded under specified monograph conditions, other details from the MUsT may be used to establish such conditions to ensure that marketed products remain within an acceptable safety margin. For example, if data indicate that there is a need to limit the absorption of a given active ingredient, the FDA may consider establishing monograph conditions for final product formulations containing that active ingredient, such as in vitro permeation testing for final formulations using the formulation that resulted in the greatest absorption in the MUsT for that active ingredient as a benchmark.

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

B. Study Elements and Considerations

1. Study Population

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

- Skin surface area to be exposed
- Dosing frequency (if different for different indications)

[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.

- 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.

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.

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

7. Method of Application

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

8. Combinations of Active Ingredients

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

9. Formulation Considerations

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

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

In the absence of mitigating safety data or other bioavailability-related information, we recommend MUsT testing of at least four formulations. A sponsor that chooses to 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.

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

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

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

10. Sample Collection

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

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

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

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

11. Sensitive and Validated Analytical Method

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

12. Safety Data

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

13. Pediatrics

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

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[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 Stamatas, 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.

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

14. Geriatrics

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

IV. DATA ANALYSIS

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

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

V. CONSULTATION WITH THE FDA

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

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[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, Am J Clin Dermatol, 10 (2):73-86.

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

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