



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 330

[Docket No. FDA-2016-N-0543]

RIN 0910-AH30

Food and Drug Administration Review and Action on Over-the-Counter Time and Extent Applications

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA or Agency) is amending its nonprescription (over-the-counter or OTC) drug regulations. This final rule supplements the time and extent application (TEA) process for OTC drugs by establishing timelines and performance metrics for FDA's review of non-sunscreen TEAs, as required by the Sunscreen Innovation Act (SIA). It also amends the existing TEA process to include filing determination and withdrawal provisions to make the TEA process more efficient.

DATES: This rule is effective [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER].

ADDRESSES: For access to the docket to read background documents or the electronic and written/paper comments received, go to <https://www.regulations.gov> and insert the docket number, found in brackets in the heading of this final rule, into the "Search" box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

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I. Executive Summary

A. Purpose and Coverage of the Final Rule

This final rule implements part of the SIA (Pub. L. 113-195) enacted November 26, 2014, by establishing timelines and related performance metrics for the review of certain submissions under FDA's regulation governing TEAs, which is codified in § 330.14 (21 CFR 330.14). The TEA regulation sets forth criteria and procedures by which OTC drugs initially marketed in the United States after the OTC Drug Review began in 1972 and OTC drugs without any U.S. marketing experience can be considered in the OTC drug monograph system. Section 586F(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 360fff-6(b)), which was added by the SIA, requires FDA to issue regulations providing for the timely and efficient review of submissions under the TEA regulation, including establishing: (1) Reasonable timelines for reviewing and acting on such submissions for non-sunscreen OTC active ingredients and other conditions (non-sunscreen TEA conditions) and (2) measurable metrics for tracking the extent to which such timelines are met.

FDA is also amending the TEA regulation to make the TEA process more efficient and predictable for product sponsors, consumers, and FDA by adding filing determination

requirements and criteria, and by addressing the withdrawal of consideration of TEAs and safety and effectiveness data submissions.

The timelines and metrics in this final rule apply to non-sunscreen TEA conditions. FDA is addressing timelines for review of sunscreen active ingredients and other related topics regarding sunscreens separately, under other provisions of the SIA.

B. Summary of the Major Provisions of the Final Rule

This final rule implements the SIA requirements for non-sunscreen TEAs by establishing timelines for FDA to review and take action on non-sunscreen TEA conditions. Timelines are provided for each stage of the TEA process and are intended to be reasonable while taking into consideration FDA public health priorities and available resources. The timelines established by this rule provide sponsors, other interested persons, and the public with consistent time frames for expected Agency action.

This rule also implements the SIA requirements for non-sunscreen TEAs by establishing measurable metrics that FDA will use for tracking the extent to which the timelines set forth in the regulations are met. The Agency anticipates that, among other potential benefits, making the metrics publicly available will improve transparency by providing sponsors, other interested persons, and the public with information that will enable them to quickly find out the number of TEAs that have been submitted to FDA. Over time, these measurements may also assist the Agency with resource planning and use.

The applicability of these metric and timeline provisions are generally limited to non-sunscreen TEAs submitted after the enactment of the SIA.

The final rule also amends the existing TEA regulation to provide for FDA to make filing determinations regarding safety and effectiveness data submissions for eligible TEA conditions.

This additional procedural step provides early notification on whether submissions are sufficiently complete to permit a substantive review by FDA.

In addition, the rule amends the existing TEA regulation to include a provision regarding the withdrawal of consideration of TEAs, and safety and effectiveness data submissions. The withdrawal provision provides clarity on the status of TEAs, and safety and effectiveness data submissions that are no longer being pursued, so that FDA does not spend resources on these submissions.

Finally, the final rule adds certain definitions, and makes minor conforming and clarifying changes to the existing TEA regulation.

C. Legal Authority

This rule is issued under FDA's authority to regulate OTC drug products under the FD&C Act (see sections 201, 501, 502, 503, 505, 510, 586F, and 701(a) of the FD&C Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 360fff-6, and 371(a))). As stated in the Federal Register of January 23, 2002 (67 FR3060), in which the final rule establishing the TEA process was published, submission of a new drug application (NDA) has been required before marketing a new drug since passage of the FD&C Act in 1938 (21 U.S.C. 355). To market a new drug, the drug must first be approved under section 505 of the FD&C Act. Section 701(a) of the FD&C Act authorizes FDA to issue regulations for the efficient enforcement of the FD&C Act. FDA's regulations in part 330 describe the conditions for a drug to be considered GRASE and not misbranded. If a drug meets each of the conditions contained in part 330, as well as each of the conditions contained in any applicable OTC drug monograph, and other applicable regulations, it is considered generally recognized as safe and effective (GRASE) and not misbranded, and is not required by FDA to obtain approval under section 505 of the FD&C Act.

In addition, section 586F of the FD&C Act requires FDA to issue regulations providing for the timely and efficient review of certain submissions under the TEA regulation in § 330.14. Section 586F of the FD&C Act specifically requires these regulations to include timelines and metrics associated with the review of those submissions under the TEA regulation. This rule adds timeline and metrics provisions that are intended to implement section 586F of the FD&C Act.

D. Costs and Benefits

We expect that the final rule will make the TEA process more efficient and predictable, and improve communication between FDA, sponsors, and other interested persons. Sponsors and other interested persons may benefit from knowing whether additional data are needed and what optimal steps to take to receive a GRASE determination, and we will be able to bring resolution to TEA conditions. However, we do not know the monetary value of added predictability.

We expect the rule will create a minimal burden on persons that submit safety and effectiveness data submissions, primarily when they send a letter to request a meeting with us. Thus, we anticipate no increase in annual recurring costs for either small or large sponsors or other interested persons. We expect the six current sponsors of non-sunscreen TEAs covering conditions that have been found eligible to be considered for inclusion in the OTC drug monograph system will incur one-time costs to read and understand the rule.

We also estimate sponsors will submit two additional TEAs annually, and each of these sponsors will also spend time reading and understanding the rule. The present value of the total costs over 10 years ranges from about \$17,000 to \$35,000 with a 7 percent discount rate and from about \$19,000 to \$38,000 with a 3 percent discount rate. With a discount rate of 7 percent

and 3 percent, we estimate that on average affected sponsors will incur less than \$150 of annualized costs per year.

II. Table of Abbreviations and Acronyms Commonly Used in This Document

Abbreviation/Acronym	What It Means
ANDA	Abbreviated New Drug Application
FDA	Food and Drug Administration
FD&C Act	Federal Food, Drug, and Cosmetic Act
GRASE	Generally Recognized as Safe and Effective
HHS	U.S. Department of Health and Human Services
NDA	New Drug Application
NOE	Notice of Eligibility
NPRM	Notice of Proposed Rulemaking
OMB	Office of Management and Budget
OTC	Over-the-Counter
PRA	Paperwork Reduction Act
SIA	Sunscreen Innovation Act of 2014
TEA	Time and Extent Application

III. Background

A. Need for the Regulation/History of This Rulemaking

1. Overview of the OTC Drug Monograph System

The OTC drug monograph system was established to evaluate the safety and effectiveness of all OTC drug products marketed in the United States before May 11, 1972, that were not covered by NDAs and all OTC drug products covered by “safety” NDAs that were marketed in the United States before enactment of the 1962 drug amendments to the FD&C Act. In 1972, FDA began its OTC Drug Review to evaluate OTC drugs by therapeutic categories or classes (e.g., sunscreens, antacids), rather than on a product-by-product basis, and to develop “conditions” under which classes of OTC drugs are GRASE and not misbranded.

FDA publishes these conditions in the Federal Register in the form of OTC drug monographs, which consist primarily of active ingredients, labeling, and other general requirements. Final monographs for OTC drugs that are GRASE and not misbranded are codified in part 330. Manufacturers of drugs that meet each of the conditions contained in part

330, including each of the conditions contained in any applicable OTC drug monograph, and other applicable regulations, need not seek FDA clearance before marketing.

2. Overview of the TEA Process Prior to This Rulemaking

Initially, OTC drug conditions not marketed in the United States prior to the inception of the OTC Drug Review were not eligible for review under the OTC drug monograph process. The TEA process, established by regulations finalized in 2002 (§ 330.14), expanded the scope of the OTC Drug Review. A “condition,” for purposes of the TEA regulation, is an active ingredient or botanical drug substance (or a combination of active ingredients or botanical drug substances), dosage form, dosage strength, or route of administration marketed for a specific OTC use. The TEA process provides a potential pathway for OTC conditions, including new active ingredients or dosage forms that previously had no U.S. marketing history or that were marketed in the United States after the OTC Drug Review began, to be marketed under an OTC drug monograph.

Active ingredients and other conditions that satisfy the TEA eligibility requirements are subject to the same safety, effectiveness, and labeling standards that apply to other conditions under the OTC monograph process (see § 330.14(g)). The TEA regulation requires multistep, notice-and-comment rulemaking procedures before an active ingredient or other condition is added to an OTC drug monograph.

The TEA process begins with the submission of a TEA containing data documenting the OTC marketing history of the active ingredient, combination of active ingredients, or other condition(s) (e.g., a new dosage strength for an active ingredient already included in an OTC drug monograph). FDA reviews the application and determines whether the sponsor’s marketing data establish that the condition or conditions have been marketed to a material extent and for a

material time, as set forth in the TEA regulation's eligibility requirements. If the condition is not found eligible, FDA will send a letter to the sponsor explaining why the condition was not found acceptable. If the marketing data satisfy the TEA regulation's eligibility criteria, FDA publishes a notice of eligibility (NOE) in the Federal Register announcing that the active ingredient or other condition is being considered for inclusion in an OTC drug monograph and calling for submissions of safety and efficacy data for the proposed OTC use.

We note that although a TEA is the application regarding the time and extent of marketing, which leads to an eligibility determination (resulting in publication of an NOE or a letter of ineligibility), references to TEAs or applications (including in the SIA) sometimes encompass FDA's review of the condition's eligibility and the GRASE determination for the condition. Thus, these references may be used to mean the TEA itself, the safety and effectiveness data submission, FDA's GRASE determination, associated order or rulemaking actions, or all of these. In this rule and preamble, the terms "TEA" and "safety and effectiveness data submission" are used, where appropriate, to describe the two distinct submissions under the TEA regulation. However, the term "TEA process" may be used when referring to one or more actions under the TEA regulation.

If, after FDA reviews the safety and effectiveness data, the Agency initially determines that the active ingredient or other condition is GRASE, it will publish a notice of proposed rulemaking (NPRM) to include the condition in an appropriate OTC drug monograph.

If the condition is initially determined not to be GRASE, FDA will inform the sponsor and other interested persons that submitted data of its decision by letter, and will include the letter in the relevant public docket (§ 330.14(g)(4)). The Agency will also publish a NPRM to include the condition in § 310.502 (21 CFR 310.502). The sponsor and other interested persons

will have an opportunity to submit comments and new data on FDA's initial determination and NPRM (§ 330.14(g)(5)). After evaluation of any additional data submitted, FDA will either issue a final rule or a new NPRM, if necessary, in the Federal Register.

3. The Sunscreen Innovation Act (SIA)

In November 2014, Congress passed the SIA to supplement the TEA process with regard to both sunscreen and non-sunscreen OTC drug products. Section 586F of the FD&C Act was added by the SIA and only applies to TEAs for drugs other than nonprescription sunscreen active ingredients or combinations of nonprescription sunscreen active ingredients (see sections 586 and 586F of the FD&C Act (21 U.S.C. 360fff and 360fff-6) as amended by the SIA). For FDA review of non-sunscreen TEA conditions, section 586F includes two main requirements. The first requirement (see section 586F(a) of the FD&C Act), which is generally outside the scope of this rule, is regarding a framework and timelines for review of certain eligible TEA conditions pending before the date of enactment of the SIA. The second general requirement (see section 586F(b) of the FD&C Act) is that FDA issue a regulation that includes: (1) Timelines for review of new non-sunscreen TEA conditions (with certain exceptions noted in sections 586F(a)(1) and (3)) and (2) measurable metrics for tracking the extent to which the timelines are met.

Accordingly, FDA published a proposed rule on April 4, 2016, to address both timelines and metrics, as required by the SIA.

4. Brief Summary of the Proposed Rule

As described in the proposed rule "Food and Drug Administration Review and Action on Over-the-Counter Time and Extent Applications" (81 FR 19069, April 4, 2016) (Proposed Rule), FDA had determined that with regard to non-sunscreen TEAs, the best way to both address the statutory requirements of the SIA and to make certain FDA-initiated modifications to the TEA

process set forth in § 330.14 was to: (1) Propose a new section (§ 330.15) that is specific to non-sunscreen TEA conditions and establishes the SIA-required timelines and metrics and (2) amend § 330.14 with regard to process improvements for TEAs for all OTC drugs (such as providing format and content criteria for a filing determination and addressing withdrawal of consideration).

We refer readers to the preamble of the Proposed Rule for additional information about the development of the Proposed Rule. The Agency requested public comments on the Proposed Rule, and the comment period closed June 3, 2016.

B. Summary of Comments on the Proposed Rule

We received comments from a trade association and several individual citizens. The comments were generally supportive. In addition to a few general comments, we received comments specific to the proposed timeline provision as well as on the format and content of the safety and effectiveness submissions.

C. General Overview of the Final Rule

This rule finalizes the Proposed Rule. The following subsections give a brief summary of the proposed provisions we are finalizing, including a summary of the key changes between the proposed and final rules.

1. Applicability (§ 330.15(a))

We proposed that a condition in a TEA submitted under § 330.14 would be subject to the timelines for FDA review and action except for: (1) A sunscreen active ingredient or a combination of sunscreen active ingredients, or other conditions for sunscreen ingredients or (2) a non-sunscreen active ingredient or combination of non-sunscreen active ingredients, and other conditions for such ingredients submitted in a TEA under § 330.14 before November 27, 2014,

subject to section 586F(a)(1)(C) of the FD&C Act. The exceptions are based on provisions of the SIA, including section 586F(b) of the FD&C Act, which directs the Agency to issue regulations establishing timelines for drugs other than nonprescription sunscreen active ingredients or combinations of nonprescription active ingredients. For additional discussion on the development of this provision see the preamble (81 FR 19069 at 19073) of the Proposed Rule.

We are finalizing this provision without change.

2. Timelines for FDA Review and Action (§ 330.15(c))

In accordance with section 586F(b) of the FD&C Act, FDA proposed timelines for each of the various stages of the TEA process for conditions within the scope of the rule. The proposed timelines for each stage take into consideration factors set forth under the SIA. For additional discussion on the development of this provision, see the preamble (81 FR 19069 at 19073 to 19077) of the Proposed Rule.

We are finalizing this provision with one clarifying change to acknowledge that, with respect to the 90-day timeline for FDA to issue a filing determination, a safety and effectiveness data submission can be submitted by a person other than the sponsor of the TEA.

3. Metrics (§ 330.15(b))

Section 586F(b) of the FD&C Act requires FDA to establish measurable metrics for tracking the extent to which the timelines set forth in the regulations are met. We proposed to maintain a publicly available posting of metrics for the review of TEAs and safety and effectiveness data submissions submitted under § 330.14 that are subject to the timelines, and update the posting annually. The proposed metrics, when publically posted, should provide sponsors and the public with information that will enable them to quickly ascertain the number

of TEAs that have been submitted to FDA, and the Agency's performance in meeting the proposed timelines. For additional discussion on the development of this provision, see the preamble (81 FR 19069 at 19077) of the Proposed Rule.

We are finalizing this provision without change.

4. Definitions (§ 330.14(a))

We proposed additional definitions that, in general, are intended to clarify the beginning or ending of the timelines for FDA review and action. We proposed to add these definitions to § 330.14 instead of § 330.15 because § 330.14 describes the TEA process to which these definitions apply. For additional discussion on the development of this provision, see the preamble (81 FR 19069 at 19077 to 19078) of the Proposed Rule.

We are finalizing this provision with clarifying changes to the definition of "Date of filing" and "Safety and effectiveness data submission" to acknowledge that a safety and effectiveness data submission can be submitted by a person other than the sponsor of the TEA.

5. Filing Determination (§ 330.14(j))

We proposed certain filing determination requirements to help improve the content and format of a safety and effectiveness data submission. We also proposed timelines related to these proposed new requirements and proposed processes that apply whether the submission is accepted for filing, refused, or filed over protest. The proposed requirement and related timelines were developed, in part, to provide a clear pathway for the Agency to indicate when a submission does not contain the information necessary for a complete review and what additional information is needed. For additional discussion on the development of this provision, see the preamble (81 FR 19069 at 19078 to 19079) of the Proposed Rule.

We are finalizing the provision with several changes to the Proposed Rule for clarification purposes (for additional details on the changes, see section V.E):

- Throughout the provision, we have made clarifying changes to acknowledge that a safety and effectiveness data submission can be submitted by a person other than the sponsor of the TEA.
- With respect to § 330.14(j)(2), we are clarifying in this final rule that data submitted after a submission has been filed will be reviewed as part of the proposed rulemaking if there is adequate time before the NPRM will publish, or if there is not adequate time, the data will be evaluated as comments to the NPRM.
- In § 330.14(j)(3), we are changing the proposed term “informal conference” to “meeting” to use consistent terminology with the SIA.
- In both § 330.14(j)(2) and (3), we clarify that a copy of the notice will be posted to the docket.
- In § 330.14(j)(3), we originally proposed the process that a person that submitted a safety and effectiveness data submission must follow to request that FDA file a submission over protest. To avoid potential ambiguity, we are modifying § 330.14(j)(3) to clarify that the submitter cannot request to file over protest without first having a meeting with FDA. In addition, this final rule clarifies the status of the submission and the TEA condition once FDA has refused to file a submission.

6. Withdrawal of Consideration of a TEA or Safety and Effectiveness Data Submission

(§ 330.14(k))

We proposed to add a withdrawal provision to new § 330.14(k). The proposed provision allowed a sponsor to request withdrawal of consideration of a TEA or safety and effectiveness

data submission. In addition, we also proposed (§ 330.14(k)(1)(ii)) that inaction by a sponsor in certain circumstances may be deemed by FDA as a withdrawal of consideration. The proposed § 330.14(k)(2) also included a provision that FDA would give notice to the sponsor before deeming the submission withdrawn from consideration to give the sponsor an opportunity to provide an update and request FDA not withdraw the submission. Another proposed provision, § 330.14(k)(3), provided that the notice of withdrawal of consideration would be posted to the docket. In addition, we proposed in § 330.14(k)(4) that if the TEA or safety and effectiveness data submission is deemed withdrawn, the timelines under § 330.15(c) and the metrics under § 330.15(b) no longer apply. The provisions were proposed in part to enable the Agency to better allocate resources by providing a process for the Agency to suspend work on TEAs or safety and effectiveness data submissions that are no longer being pursued by the sponsor. For additional discussion on the development of these provisions see the preamble (81 FR 19069 at 19079 to 19080) of the Proposed Rule.

We are finalizing the provision with several clarifying changes to the Proposed Rule (for additional details on the changes, see section V.E):

- Throughout the provision, we have made clarifying changes to acknowledge that a safety and effectiveness data submission can be submitted by a person other than the sponsor of the TEA.
- Under § 330.14(k)(1)(ii), we no longer include that a sponsor's failure to act on a submission is a reason for FDA's deeming the submission withdrawn because until the sponsor or other interested person acts and files a TEA submission or safety and effectiveness data submission, there is nothing for FDA to deem withdrawn from consideration. For example, once a notice of eligibility is issued, the TEA is no longer

under consideration and the eligible condition is not deemed under consideration until a safety and effectiveness data submission is filed.

- We have revised the proposed § 330.14(k)(2) to extend the time period to make a request that FDA not deem a submission withdrawn from consideration.
- The final rule makes a technical change to proposed § 330.14(k)(3) to account for the situation in which an NOE for a TEA has not been issued and the TEA therefore is not in the public docket.
- The final rule also clarifies in § 330.14(k)(3) that if FDA deems a submission withdrawn from consideration, the condition still remains eligible for consideration if an NOE was issued, and the sponsor or any interested person can pursue consideration of the condition in the future by submitting a new safety and effectiveness data submission.

7. Minor Changes to § 330.14 for Clarity and Consistency

We proposed minor changes to § 330.14 for clarity and consistency purposes. These changes included adding definitions to proposed new paragraph (a). We proposed several minor amendments to § 330.14(f) for clarity and for consistency with the OTC monograph regulations under § 330.10. We also revised § 330.14(f) to use terminology consistent with the new definition in § 330.14(a)(5) for “safety and effectiveness data submission” when referring to a data package submitted for an eligible TEA condition. We also proposed to add the word “feedback” prior to the word “letter” in the first sentence of § 330.14(g)(4) to use terminology consistent with the proposed new definition for “feedback letter” in § 330.14(a)(7). For additional discussion on the development of this provision, see the preamble (81 FR 19069 at 19080) of the Proposed Rule.

We are finalizing this provision with changes to § 330.14(f) in order to clarify that a safety and effectiveness data submission can be submitted by a person other than the sponsor of the TEA.

IV. Legal Authority

This rule is issued under FDA's authority to regulate OTC drug products under the FD&C Act (see sections 201, 501, 502, 503, 505, 510, 586F, and 701(a) of the FD&C Act). As stated in the Federal Register of January 23, 2002, in which the final rule establishing the original TEA process was published, submission of an NDA has been required before marketing a new drug since passage of the FD&C Act in 1938 (21 U.S.C. 355). To market a new drug, the drug must first be approved under section 505 of the FD&C Act. Section 701(a) of the FD&C Act authorizes FDA to issue regulations for the efficient enforcement of the FD&C Act. FDA's regulations in part 330 describe the conditions for a drug to be considered GRASE and not misbranded. If a drug meets each of the conditions contained in part 330, as well as each of the conditions contained in any applicable OTC drug monograph, and other applicable regulations, it is considered GRASE and not misbranded, and is not required by FDA to obtain approval under section 505 of the FD&C Act.

In addition, section 586F of the FD&C Act requires FDA to issue regulations providing for the timely and efficient review of certain submissions under the TEA regulation in § 330.14. Section 586F of the FD&C Act specifically requires these regulations to include timelines and metrics associated with the review of certain submissions under the TEA regulation. Therefore, § 330.15 adds timeline and metrics provisions that are intended to implement section 586F of the FD&C Act.

V. Comments on the Proposed Rule and FDA Response

A. Introduction

We received three comment letters on the Proposed Rule, each containing one or more comments on one or more issues. The comments were submitted by a trade association and individual consumers. The submissions overall support the objectives of the rule. None of the comments suggested changes to specific provisions of the Proposed Rule.

We describe and respond to the comments in sections V.B. through V.D. We have numbered each comment to help distinguish between different comments. The number assigned to each comment or comment topic is purely for organizational purposes and does not signify the comment's value or importance or the order in which comments were received.

B. Description of General Comments and FDA Response

(Comment 1) The comments generally support the TEA process, the establishment of timelines associated with the general steps in that process, and the proposed revisions to the TEA regulation.

(Response 1) We appreciate the support expressed in the comments received. The TEA process is intended to provide a potential pathway for OTC conditions, including newer active ingredients that previously had no U.S. marketing history or that were marketed in the United States after the OTC Drug Review began, to be marketed under an OTC drug monograph. The associated timelines and revisions to the TEA regulation are intended to implement certain requirements in the SIA and to make the TEA process more efficient and predictable.

C. Specific Comments on Timelines for FDA Review and Action and FDA Response

(Comment 2) One comment stated that the explanation for the proposed timelines was clear. However, the comment suggested that additional changes to the monograph system could further streamline the projected TEA timeline.

(Response 2) This final rule establishes timelines within the context of the general OTC monograph process, which involves rulemaking to establish general recognition of safety and effectiveness for conditions in a monograph. Because this rule is limited to the TEA process and not the overall monograph regulatory framework, changes to the OTC monograph process that in turn could affect the timelines established in this rule are outside the scope of this rulemaking.

(Comment 3) One comment expressed concern that factors such as the format and content of the data submission, the complexity of the data, competing Agency priorities, and available Agency resources and reasonableness could delay TEA reviews and actions many years beyond the established timelines.

(Response 3) As explained in the preamble to the Proposed Rule, section 586F(b) of the FD&C Act provides that the timelines for review of non-sunscreen TEA conditions shall: (1) Reflect FDA public health priorities (including potential public health benefits of including additional drugs in the OTC drug monograph system), (2) take into consideration the resources available for carrying out such public health priorities and the relevant review processes and procedures, and (3) be reasonable, taking into account the required consideration of priorities and resources. We accordingly took these factors into consideration when establishing timelines. Furthermore, we determined that instead of setting multiple timelines for submissions of varying content, complexity, and format, it would be more efficient and sensible, for each stage of the TEA process, to set one general timeline for the review of non-sunscreen TEA conditions that

accommodates anticipated variation among submissions. Because anticipated variation is already accounted for, FDA expects the time frames to be achievable in most circumstances.

D. Specific Comments on the Filing Determination and FDA Response

(Comment 4) With respect to the format and content of submissions, one comment seeks FDA guidance on the inclusion of certain information from foreign data sources for non-sunscreen active ingredients. The comment incorporated a comment that was previously submitted to FDA on its draft guidance for industry “Nonprescription Sunscreen Drug Products--Content and Format of Data Submissions To Support a GRASE Determination Under the Sunscreen Innovation Act”¹ (nonprescription sunscreen content and format draft guidance) (Ref. 1).

(Response 4) As explained in the preamble to the Proposed Rule, the general advice provided in the nonprescription sunscreen content and format draft guidance (Ref. 1) may also be useful to persons preparing safety and effectiveness data submissions for non-sunscreen TEAs. The comment’s request for guidance on the inclusion of certain information from foreign data sources in the safety and effectiveness data submission is outside the scope of this rulemaking. However, the Agency will consider providing additional guidance to address this issue.

E. Technical Amendments

The revised regulatory text includes technical amendments that we have made to the proposed provisions in order to clarify requirements. In the following subsections, we summarize the changes that are intended to clarify amendments to the relevant provisions.

¹ When final, this guidance will represent FDA’s current thinking on this topic.

1. Clarifying that the Sponsor or Other Interested Person Can Submit a Safety and Effectiveness Data Submission

We are finalizing §§ 330.14(a), (f), (j), (k), and 330.15(c)(2) with changes to clarify that a safety and effectiveness data submission can be submitted by a person other than the sponsor of the TEA.

In proposed § 330.14(a), we defined the term “Sponsor” to mean the person that submitted the TEA, and we defined “Safety and effectiveness data submission” to mean, in part, a data package submitted by a sponsor. Generally we expect the person submitting the TEA (i.e., the sponsor) will submit a safety and effectiveness data submission upon issuance of a NOE. However, upon issuance of the NOE, the TEA is no longer under consideration, and the sponsor does not necessarily have to be the person that submits the safety and effectiveness data submission. Therefore, while we are not changing the definition of “Sponsor,” we are modifying the definition of “Safety and effectiveness data submission” to clarify that the submission can be submitted by a person other than the sponsor.

Correspondingly, we are clarifying the proposed definition of “Date of filing” under § 330.14(a) and clarifying the proposed §§ 330.14(f) and 330.15(c)(2) by removing references to the “sponsor” in order to acknowledge that the safety and effectiveness data submission can be submitted by a person other than the sponsor. In addition, throughout § 330.14(j) and (k), we have removed references to the “sponsor” in the context of a safety and effectiveness data submission and replaced the term with more general terms, such as “submitter” or “person that submitted the safety and effectiveness submission,” in order to acknowledge that the safety and effectiveness data submission can be submitted by a person other than the sponsor.

2. Filing Determination (§ 330.14(j))

In addition to the changes noted in the previous subsection, we are finalizing the provision with several additional changes for clarification purposes.

In § 330.14(j)(2), FDA proposed that the date of filing will begin the FDA timelines described in § 330.15(c)(3) and (4). Because FDA needs adequate time to review submitted data and the timeline for FDA to review and develop a NPRM begins as soon as the safety and effectiveness data submission has been filed, we are clarifying that data submitted after a submission has been filed will be reviewed before issuance of the NPRM if there is adequate time; otherwise, the data will be evaluated as comments to the NPRM. We note that although other submitted data submissions may be considered under the rulemaking process, they will not be subject to a filing determination. Furthermore, as with comments submitted after the comment period, any data submitted after the comment period for the NPRM may not be considered before issuance of the final rule.

We are also adding language to both § 330.14(j)(2) and (3) to clarify that when FDA sends a notice to the person that submitted a safety and effectiveness data submission informing that person that the submission is filed or filed over protest, a copy of the corresponding notice will be posted to the docket. The posting to the docket, which is public, provides other interested persons notice that a submission is filed and FDA is beginning its review.

Additionally, in proposed § 330.14(j)(3), we described the process for cases in which FDA refuses to file the safety and effectiveness data submission. The Proposed Rule provided that the sponsor (now submitter) can request an informal conference within 30 days of FDA notifying the sponsor that it refuses to file the submission. We are changing the term “informal conference” to “meeting” to be consistent with the SIA. In addition, the proposed provision

explained that a sponsor's request to file over protest must be within 120 days of the meeting with FDA. To avoid potential ambiguity, we are modifying § 330.14(j)(3) to clarify that a sponsor (now submitter) cannot request to file over protest without first meeting with FDA.

Finally, we are clarifying the status of a safety and effectiveness data submission that FDA has refused to file by including at the end of § 330.14(j)(3) that if FDA refuses to file a safety and effectiveness data submission and the submission is not filed over protest, then the submission is no longer deemed under consideration. If the original submitter or other interested person wishes to pursue consideration of an eligible condition at some point in the future, a new safety and effectiveness data submission must be submitted.

3. Withdrawal of Consideration of a TEA or Safety and Effectiveness Data Submission (§ 330.14(k))

We are finalizing the provision with several clarifying changes.

We no longer include failure to act on a submission as a reason that FDA may deem the submission to be withdrawn from consideration, as was proposed under § 330.14(k)(1)(ii). In the preamble to the Proposed Rule, we explained there have been past instances when a NOE was issued but the sponsor never submitted safety and effectiveness data and the TEA condition remained unresolved. We proposed that a failure to act on a submission, which could include a sponsor's failure to file a safety and effectiveness data submission for a TEA-eligible condition, is one reason for FDA to deem the submission withdrawn from consideration and that, for purposes of the provision, this could include deeming a TEA-eligible condition withdrawn from consideration. However, in such a scenario when a condition is found eligible and there has not been a safety and effectiveness data submission, there is no action for FDA to take. Once a NOE is issued, the TEA is no longer under consideration. Also, since the sponsor or any other

interested person is not obligated or under an established deadline for submitting a safety and effectiveness data submission, we do not consider the TEA-eligible condition to be under consideration until such a submission is filed. As a result, a sponsor's failure to act on a submission will not result in the need for FDA to deem a submission or other aspect of the TEA process withdrawn from consideration, and inclusion of this provision is not necessary.

We also proposed in § 330.14(k)(1)(ii) that FDA may deem a submission to be withdrawn from consideration due to the sponsor's failure to respond to communications from FDA. This provision remains, and we note the reference to "communications" encompasses the notice of withdrawal under § 330.14(k)(2) and any preceding communication from FDA that the sponsor failed to respond to.

In § 330.14(k)(2), we proposed that FDA will notify the sponsor of a submission that FDA intends to deem withdrawn under § 330.14(k)(1)(ii), and that the sponsor will then have 30 days from the date of the notice to request that FDA not withdraw consideration of the TEA or safety and effectiveness data submission. We are changing the time provided to request that FDA not withdraw consideration from 30 days to 90 days.

We are also further revising proposed § 330.14(k)(3), in which FDA proposed that a notice of withdrawal will be posted to the docket when FDA deems a submission withdrawn from consideration. We are including a clarification that when a condition has been found eligible, even if the safety and effectiveness data submission is withdrawn, not only does the NOE remain in the public docket but the condition remains eligible for consideration, so that the condition can still be considered in the future if a new safety and effectiveness data submission is received. In addition, we are adding an exception to the notice of withdrawal being posted to the docket. Specifically, when a TEA submission is withdrawn from consideration before the

issuance of an NOE, the notice of withdrawal will not be posted to the public docket and will only be sent to the sponsor because in such an instance the TEA, itself, is not on public display.

Finally, although not a change to the Proposed Rule, we note as we discussed in the preamble to the Proposed Rule, that if a sponsor requests withdrawal of consideration of its TEA or safety and effectiveness data submission, FDA generally intends to stop its review. However, although FDA may withdraw consideration of a TEA or safety and effectiveness determination, we may determine not to withdraw or not to stop review in some cases. For example, if FDA has already issued a NPRM that tentatively determines that the active ingredient or other condition is GRASE for an OTC use or is not GRASE for an OTC use, FDA may continue the rulemaking and proceed to issue a final rule.

VI. Effective Date

The SIA requires that the final rule be published not less than 30 calendar days before the effective date of the regulation. Consequently, this final rule will become effective 30 calendar days after the date of the rule's publication in the Federal Register.

Beginning on that date, the timelines and metrics set forth in this regulation will apply to the review of non-sunscreen TEAs, and safety and effectiveness data submissions to which this regulation is applicable, and any amended provisions of § 330.14 will apply to the TEA process under that regulation.

VII. Economic Analysis of Impacts

A. Introduction

We have examined the impacts of the final rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4). Executive Orders 12866 and 13563 direct us to assess all

costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). We have developed a comprehensive Economic Analysis of Impacts that assesses the impacts of the final rule. We believe that this final rule is not a significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because this final rule does not impose significant new economic burdens on any entity, we certify that the final rule will not have a significant economic impact on a substantial number of small entities.

The Unfunded Mandates Reform Act of 1995 (section 202(a)) requires us to prepare a written statement, which includes an assessment of anticipated costs and benefits, before issuing “any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation) in any one year.” The current threshold after adjustment for inflation is \$146 million, using the most current (2015) Implicit Price Deflator for the Gross Domestic Product. This final rule would not result in an expenditure in any year that meets or exceeds this amount.

In table 1, we provide the Regulatory Information Service Center/Office of Information and Regulatory Affairs Consolidated Information System accounting information.

Table 1.--Economic Data: Costs and Benefits Statement

Category	Primary Estimate	Low Estimate	High Estimate	Units Year Dollars	Discount Rate	Period Covered	Notes
Benefits							
Annualized					7%		
Monetized					3%		
\$ millions/year							
Annualized					7%		
Quantified					3%		
Qualitative	The final rule will improve the TEA review process by establishing timelines and clarifying requirements and will increase the predictability of the process.						
Costs							
Annualized	\$0.026	\$0.017	\$0.035	2015	7%	10 years	
Monetized	\$0.029	\$0.019	\$0.038	2015	3%	10 years	
\$ millions/year							
Annualized					7%		
Quantified					3%		
Qualitative							
Transfers							
Federal					7%		
Annualized					3%		
Monetized							
\$ millions/year							
From/To	From:			To:			
Other					7%		
Annualized					3%		
Monetized							
\$ millions/year							
From/To	From:			To:			
Effects							
State, Local, and/or Tribal Government: No effects							
Small Business: No effects							
Wages: No effect							
Growth: No effect							

B. Summary

1. Baseline Conditions

We regulate nonprescription drug products under two primary pathways: (1) The NDA process, described in 21 CFR part 314 or (2) the nonprescription (over-the-counter or OTC) drug monograph process, described in part 330. There are important differences between these two pathways. Under the NDA process, the sponsor of an application must submit to us nonclinical and clinical data that support the safety and effectiveness of its drug product, and we must review and approve the application before the sponsor can market such product. By contrast,

OTC drug monographs are regulations describing conditions (§ 330.14 defines “condition” as an active ingredient or botanical drug substance (or combination of both), dosage form, dosage strength, or route of administration marketed for a particular specific OTC use) that certain OTC drugs (such as antacids) must meet to be considered GRASE and not misbranded. In contrast with the application pathway, once a sponsor or other interested person submits safety and effectiveness data to amend a monograph (which is posted to a public docket), the data are public. Drug products that comply with an applicable OTC drug monograph and other applicable regulations may be marketed without an NDA.

Initially, active ingredients and other conditions that were not marketed in the United States before the inception of the OTC Drug Review in 1972 were not eligible for review under the OTC drug monograph process. However, the TEA process, established by regulations finalized in 2002 (§ 330.14), expanded the scope of this OTC drug review. The TEA process offers a pathway for OTC conditions to be marketed under an OTC drug monograph. OTC conditions can include newer active ingredients that previously had no U.S. marketing history, or that were marketed in the United States after the OTC drug review began. Active ingredients and other conditions that satisfy the TEA eligibility requirements are subject to the same safety, effectiveness, and labeling standards that apply to other conditions under the OTC monograph process.

The TEA process requires multistep, notice-and-comment rulemaking procedures before a new active ingredient or other condition is added to an OTC drug monograph. After determining that an active ingredient or other condition is eligible for consideration under the OTC monograph process, we issue a notice in the Federal Register announcing the TEA determination and requesting safety and effectiveness data for the proposed OTC use. Next,

after reviewing data submitted to the docket, we issue a NPRM to either include the condition in the appropriate OTC drug monograph or, if the condition is initially determined not to be GRASE for OTC use, include it in § 310.502, which would require the sponsor to seek approval under the NDA pathway to market the condition. NPRMs regarding GRASE determinations allow for public comments and for sponsors and other interested persons to submit additional data for safety and effectiveness. If a monograph is amended, by publishing a final rule, an OTC condition that complies with the OTC monograph and the general requirements for OTC drugs may be marketed in the United States without an NDA (examples of other general requirements include requirements to comply with Current Good Manufacturing Practice, to register and list products, to use drug facts labeling).

Although our multistep TEA process allows sponsors and other interested persons to learn about the progress of our review of a submission (for example, when an NOE is issued, and if a feedback letter is issued), there are no established timelines to review submissions or for data to be submitted. The lack of timelines can create unpredictability for interested persons because they may lack key information. For example, they may not know: (1) Whether the safety and effectiveness data submitted is sufficient or in the right format for us to conduct a substantive review; (2) when they need to submit new information; or (3) when to expect our determinations regarding eligibility or other feedback. The unpredictability in the process could result in interested persons not performing a required action within reasonable time for our review, performing unnecessary actions (examples of unnecessary actions may include collecting unnecessary or inadequate data, performing tests or studies that do not contribute to data needed by us to make a GRASE determination), or creating unnecessary effort for us and for them. Without specific timelines, persons that submit safety and effectiveness data submissions may

not know whether their initial data submissions were insufficient to review, whether their data submissions were sufficient and are under review, or whether we require additional information. In addition, without specific timelines, we don't know whether interested persons intend to submit additional data or whether they do not intend to pursue a TEA condition any further.

2. Purpose of This Rule

This rule complies with certain mandates of the SIA enacted in November 2014. In particular, the final rule establishes timelines and metrics for review of TEAs for non-sunscreen OTC drug products. Specific timelines applicable to non-sunscreen TEA conditions will be added in a new § 330.15. The first timeline is to issue an NOE or post a letter of ineligibility to the TEA docket within 180 days of submission of a TEA. The second timeline is to issue a filing determination within 90 days of receipt of a complete safety and effectiveness data submission once the submitter has confirmed that it considers the submission to be complete. If we initially determine the active ingredient or other condition not to be GRASE, we will inform sponsors and other interested persons who submitted data within 730 days from the date of filing as defined in § 330.14(a). The next timeline is to issue a NPRM within 1,095 days from the date of filing. Lastly, we will issue a final rule regarding GRASE status within 912 days of the closing of the docket of the proposed rulemaking.

The final rule will also amend the existing § 330.14 by: (1) Setting forth clear filing determination requirements with regard to the content and format of safety and effectiveness data submissions for TEAs and (2) addressing withdrawal of consideration of a TEA or safety and effectiveness data submission. These amendments will apply to all TEAs, and their goal is to provide early notification on whether the submissions meet the filing requirements and to provide more clarity regarding withdrawal of TEA-related submissions. The amendments in this final rule are intended to provide us with feedback from sponsors or other interested persons on

whether they intend to actively pursue their submissions, and specify that we may withdraw consideration of a TEA or safety and effectiveness data submission in certain circumstances (such as at a submitter's request). Finally, this final rule also adds definitions and makes clarifying changes to the TEA regulation in § 330.14.

The clarifications and establishment of timelines for the TEA process seek to dissipate uncertainties that may have prevented interested persons from submitting all the necessary data for us to make final GRASE determinations to existing TEA conditions that have been found to be eligible to be considered for inclusion in the OTC drug monograph system. Since the TEA review process became effective in 2002 (67 FR 3060 at 3074), we have received six TEAs for non-sunscreen active ingredients, including applications for dandruff, laxative, gingivitis, and acne products. Of these six, the sponsors for three of the TEAs have subsequently requested that the Agency withdraw consideration of the conditions that were found eligible for consideration.

3. Benefits

We lack data to quantify the potential benefits of this final rule. With this final rule, we expect the timelines and data submission clarifications will make the TEA process, including establishing a new OTC drug monograph, more efficient and predictable, and improve communication between us and sponsors or other interested persons. Sponsors and other interested persons may benefit from knowing whether additional data are needed and what optimal steps to take to receive a GRASE determination, and we will be able to bring resolution to TEA conditions. However, we do not know the monetary value of added predictability.

4. Costs

We expect this final rule will create a minimal burden on sponsors and other interested persons from the possible cost associated with sending a meeting request letter to us in the event

that we refuse to file a safety and effectiveness data submission and the submitter wants to meet with us to discuss the decision, or the possible cost of calling or writing us to request that we do not withdraw consideration of a submission under § 330.14(k)(2). Therefore, we anticipate no increase in annual recurring costs for either small or large sponsors or other interested persons.

We expect the six current sponsors will spend time reading and understanding the final rule; we estimate this task will take from about 6.5 hours to 13 hours. With an hourly wage rate of \$133 including 100 percent overhead, each sponsor will incur one-time costs ranging from about \$865 to \$1,730. This cost range is an overestimate because most sponsors are already familiar with the rule if they read the Proposed Rule. We also estimate that we will receive 2 additional TEAs annually, and thus during a 10-year horizon we estimate potentially 20 additional applicants will spend the time to read and understand the final rule. This cost is also an overestimate because we assume that future sponsors will be different from sponsors who already have read and understood the rule. The present value of the total costs over 10 years ranges from about \$17,000 to \$35,000 with a 7 percent discount rate and from about \$19,000 to \$38,000 with a 3 percent discount rate. With a discount rate of 7 percent and 3 percent, we estimate that on average, sponsors will incur less than \$150 of annualized costs per year.

5. Impact on Small Entities

The Regulatory Flexibility Act requires a Regulatory Flexibility Analysis unless the Agency can certify that the final rule will have no significant impact on a substantial number of small entities. The final rule will affect few entities. Moreover, we estimate one-time costs under \$2,000 per entity, costs well below 0.01 percent of annual revenues for the smallest entities; thus we certify that the final rule will not have a significant economic impact on a substantial number of small entities.

This is the full economic analysis.

VIII. Analysis of Environmental Impact

We have determined under 21 CFR 25.31(a) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

IX. Paperwork Reduction Act of 1995

This final rule contains information collection requirements that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (the PRA) (44 U.S.C. 3501-3520). The title, description, and respondent description of the information collection provisions are shown below with an estimate of the annual reporting burden. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

Title: Additional Criteria and Procedures for Classifying Over-the-Counter Drugs as Generally Recognized as Safe and Effective and Not Misbranded--OMB Control No. 0910-0688--Revision.

Description: The final rule amends FDA's TEA regulations to establish timelines and performance metrics for FDA's review of non-sunscreen TEAs and safety and effectiveness data submissions, as required by the SIA. FDA is making other changes to make the TEA process more efficient. Accordingly, FDA is revising the information collection currently approved under OMB control number 0910-0688 consistent with the regulations.

FDA has OMB approval (control number 0910-0688) for the information collection in § 330.14, which specifies additional criteria and procedures by which OTC drugs that were

initially marketed in the United States after the OTC Drug Review began and OTC drugs without any U.S. marketing experience may become eligible for consideration in the OTC drug monograph system.

The final rule amends the TEA regulations in §330.14 to make the process more efficient and to make conforming and clarifying changes. Section 330.14(j) clarifies the requirements on content and format criteria for a safety and effectiveness data submission, and provides procedures for FDA's review of the submissions and determination of whether a submission is sufficiently complete to permit a substantive review. Section 330.14(j)(3) describes the process for cases in which FDA refuses to file the safety and effectiveness data submission. Under §330.14(j)(3), if FDA refuses to file the submission, the Agency will notify the submitter in writing, state the reason(s) for the refusal, and provide 30 days in which to submit a written request for a meeting with the Agency about whether the Agency should file the submission. A written request for a meeting is not already approved under OMB control number 0910-0688. We estimate that approximately one person that submits a safety and effectiveness data submission ("Number of Respondents" in table 2, row 1) will annually submit to FDA approximately one request for a meeting ("Total Annual Responses" in table 2, row 1), and preparing and submitting each request will take approximately 1 hour ("Average Burden per Response" in table 2, row 1).

Under §330.14(j)(4)(iii), the safety and effectiveness data submission must contain a signed statement that the submission represents a complete safety and effectiveness data submission and that the submission includes all the safety and effectiveness data and information available to the submitter at the time of the submission, whether positive or negative. A signed statement is not already approved under OMB control number 0910-0688. We estimate that

approximately two persons (“Number of Respondents” in table 2, row 2) will annually submit to FDA approximately two signed statements as described previously (“Total Annual Responses” in table 2, row 2), and that preparing and submitting each signed statement will take approximately one hour (“Average Burden per Response” in table 2, row 2).

Under § 330.14(k)(1), FDA, in response to a written request, may withdraw consideration of a TEA submitted under § 330.14(c) or a safety and effectiveness data submission submitted under § 330.14(f). A request that FDA withdraw consideration of a TEA or safety and effectiveness data submission is not already approved under OMB control number 0910-0688. We estimate that approximately one person that submitted a safety and effectiveness data submission (“Number of Respondents” in table 2, row 3) will annually submit to FDA approximately one request (“Total Annual Responses” in table 2, row 3), and that preparing and submitting each request will take approximately 1 hour (“Average Burden per Response” in table 2, row 3).

Under § 330.14(k)(2), a person that submitted the submission may request that FDA not withdraw consideration of a TEA or safety and effectiveness data submission. A request for FDA to not deem its submission withdrawn from consideration is not already approved under OMB control number 0910-0688. We estimate that approximately one person that submitted a TEA or safety and effectiveness data submission (“Number of Respondents” in table 2, row 4) will annually submit to FDA approximately one request (“Total Annual Responses” in table 2, row 4), and that preparing and submitting each request will take approximately two hours (“Average Burden per Response” in table 2, row 4).

FDA estimates the burden of this information collection as follows:

Table 2.--Estimated Annual Reporting Burden¹

21 CFR Section	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
330.14(j)(3)--Request for a meeting on FDA's refusal to file	1	1	1	1	1
330.14(j)(4)(iii)--Signed statement that the submission is complete	2	1	2	1	2
330.14(k)(1)--Request for FDA to withdraw consideration of a TEA or safety and effectiveness data submission	1	1	1	1	1
330.14(k)(2)--Request for FDA to not deem its submission withdrawn from consideration	1	1	1	2	2
Total					6

¹There are no capital costs or operating and maintenance costs associated with this collection of information.

The information collection provisions of this final rule have been submitted to the OMB for review, as required by section 3507(d) of the PRA. FDA will publish a subsequent notice in the Federal Register announcing OMB's decision to approve, modify, or disapprove the information collection provisions in this final rule. An Agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

X. Federalism

We have analyzed this final rule in accordance with the principles set forth in Executive Order 13132. Section 4(a) of the Executive order requires agencies to “construe ... a Federal statute to preempt State law only where the statute contains an express preemption provision or there is some other clear evidence that the Congress intended preemption of State law, or where the exercise of State authority conflicts with the exercise of Federal authority under the Federal statute.” The sole statutory provision giving preemptive effect to the final rule is section 751 of the FD&C Act (21 U.S.C. 379r). We have complied with all of the applicable requirements under the Executive order and have determined that the preemptive effects of this rule are consistent with Executive Order 13132.

XI. Reference

The following reference is on display in the Division of Dockets Management (see ADDRESSES) and is available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; it is also available electronically at <https://www.regulations.gov>. FDA has verified the Web site address, as of the date this document publishes in the Federal Register, but Web sites are subject to change over time.

1. FDA, Draft Guidance for Industry, “Nonprescription Sunscreen Drug Products: Content and Format of Data Submissions To Support a GRASE Determination Under the Sunscreen Innovation Act,” November 2015, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM473772.pdf>.

List of Subjects in 21 CFR Part 330

Over-the-counter drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 330 is amended as follows:

PART 330--OVER-THE-COUNTER (OTC) HUMAN DRUGS WHICH ARE GENERALLY RECOGNIZED AS SAFE AND EFFECTIVE AND NOT MISBRANDED

1. The authority citation for part 330 is revised to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 360fff-6, 371.

2. Section 330.14 is amended as follows:

- a. Redesignate paragraph (a) as introductory text, revise the newly redesignated introductory text, and add new paragraph (a);
- b. Revise paragraphs (f) heading and introductory text and (g)(4); and

c. Add paragraphs (j) and (k).

The revisions and additions read as follows:

§ 330.14 Additional criteria and procedures for classifying OTC drugs as generally recognized as safe and effective and not misbranded.

This section sets forth additional criteria and procedures by which over-the-counter (OTC) drugs initially marketed in the United States after the OTC drug review began in 1972 and OTC drugs without any U.S. marketing experience can be considered in the OTC drug monograph system. This section also addresses conditions regulated as a cosmetic or dietary supplement in a foreign country that would be regulated as OTC drugs in the United States. Section 330.15 sets forth timelines for FDA review and action.

(a) Definitions. The definitions and interpretations contained in section 201 of the Federal Food, Drug, and Cosmetic Act and the following definitions of terms apply to this section and to § 330.15.

(1) Botanical drug substance means a drug substance derived from one or more plants, algae, or macroscopic fungi, but does not include a highly purified or chemically modified substance derived from such a source.

(2) Condition means an active ingredient or botanical drug substance (or a combination of active ingredients or botanical drug substances), dosage form, dosage strength, or route of administration, marketed for a specific OTC use, except as excluded in paragraph (b)(2) of this section.

(3) Date of filing means the date of the notice from FDA stating that FDA has made a threshold determination that the safety and effectiveness data submission is sufficiently complete to permit a substantive review; or, if the submission is filed over protest in accordance with

paragraph (j)(3) of this section, the date of filing is the date of the notice from FDA stating that FDA has filed the submission over protest (this date will be no later than 30 days after the request that FDA file the submission over protest).

(4) Feedback letter means a letter issued by the agency in accordance with paragraph (g)(4) of this section that informs the sponsor and other interested persons who have submitted data under paragraph (f) of this section that a condition is initially determined not to be generally recognized as safe and effective (GRASE).

(5) Safety and effectiveness data submission means a data package submitted by a sponsor or other interested person that includes safety and effectiveness data and information under paragraph (f) of this section and that is represented by the submitter as being a complete submission.

(6) Sponsor means the person that submitted a time and extent application (TEA) under paragraph (c) of this section.

(7) Time and extent application (TEA) means a submission by a sponsor under paragraph (c) of this section, which will be evaluated by the agency to determine eligibility of a condition for consideration in the OTC drug monograph system.

* * * * *

(f) Safety and effectiveness data submission. The notice of eligibility will request a safety and effectiveness data submission that includes published and unpublished data to demonstrate the safety and effectiveness of the condition for its intended OTC use(s), as well as the submission of any other relevant data and views. These data will be submitted to a docket established in the Division of Dockets Management and will be publicly available for viewing at that office, except data deemed confidential under 18 U.S.C. 1905, 5 U.S.C. 552(b), or 21 U.S.C.

331(j). Data considered confidential under these provisions must be clearly identified. Any proposed compendial standards for the condition will not be considered confidential. The safety and effectiveness data submission must be sufficiently complete to be filed by the agency under paragraph (j)(2) of this section. Safety and effectiveness data and other information submitted under this paragraph are subject to the requirements in § 330.10(c), (e), and (f). The safety and effectiveness data submission must include the following:

* * * * *

(g) * * *

(4) If the condition is initially determined not to be GRASE for OTC use in the United States, the agency will inform the sponsor and other interested persons who have submitted data of its determination by feedback letter, a copy of which will be placed on public display in the docket established in the Division of Dockets Management. The agency will publish a notice of proposed rulemaking to include the condition in § 310.502 of this chapter.

* * * * *

(j) Filing determination. (1) After FDA receives a safety and effectiveness data submission, the agency will determine whether the submission may be filed. The filing of a submission means that FDA has made a threshold determination that the submission is sufficiently complete to permit a substantive review.

(2) If FDA finds that none of the reasons in paragraph (j)(4) of this section for refusing to file the safety and effectiveness data submission apply, the agency will file the submission and notify the submitter in writing. FDA will post a copy of the notice to the docket. The date of filing begins the FDA timelines described in § 330.15(c)(3) and (4). Data submitted after the date of filing will be considered before the issuance of a notice of proposed rulemaking if there is

adequate time for review; otherwise, the data will be considered as comments to the proposed rule after issuance of a notice of proposed rulemaking.

(3) If FDA refuses to file the safety and effectiveness data submission, the agency will notify the submitter in writing and state the reason(s) under paragraph (j)(4) of this section for the refusal. The submitter may request in writing, within 30 days of the date of the agency's notification, a meeting with the agency about whether the agency should file the submission, and FDA will convene the meeting within 30 days of the request. If, within 120 days after the meeting, the submitter requests that FDA file the submission (with or without correcting the deficiencies), the agency will file the safety and effectiveness data submission over protest under paragraph (j)(2) of this section, notify the submitter in writing and post a copy to the docket, and review the submission as filed. The submitter must have a meeting before requesting that FDA file the submission over protest but need not resubmit a copy of a safety and effectiveness data submission that is filed over protest. A safety and effectiveness data submission and the corresponding TEA-eligible condition are both not deemed under consideration if FDA refuses to file the safety and effectiveness data submission, and it is not filed over protest; the condition remains eligible for consideration and the sponsor or any interested person can pursue consideration of the condition in the future by submitting a new safety and effectiveness data submission.

(4) FDA may refuse to file a safety and effectiveness data submission if any of the following applies:

(i) The submission is incomplete because it does not contain information required under paragraph (f) of this section. If the submission does not contain required information because

such information or data are not relevant to the condition, the submission must clearly identify and provide an explanation for the omission.

(ii) The submission is not organized or formatted in a manner to enable the agency to readily determine whether it is sufficiently complete to permit a substantive review.

(iii) The submission does not contain a signed statement that the submission represents a complete safety and effectiveness data submission and that the submission includes all the safety and effectiveness data and information available to the submitter at the time of the submission, whether positive or negative.

(iv) The submission does not contain an analysis and summary of the data and other supporting information, organized by clinical or nonclinical area, such as clinical efficacy data, clinical safety data, clinical pharmacology, adverse event reports, animal toxicology, chemistry data, and compendial status.

(v) The submission does not contain a supporting document summarizing the strategy used for literature searches, including search terms, sources, dates accessed, and years reviewed.

(vi) The submission does not contain a reference list of supporting information, such as published literature, unpublished information, abstracts and case reports, and a copy of the supporting information.

(vii) The submission includes data or information relevant for making a GRASE determination marked as confidential without a statement that the information may be released to the public.

(viii) The submission does not contain a complete environmental assessment under § 25.40 of this chapter or fails to provide sufficient information to establish that the requested action is subject to categorical exclusion under § 25.30 or § 25.31 of this chapter.

(ix) The submission does not contain a statement for each nonclinical laboratory study that the study was conducted in compliance with the requirements set forth in part 58 of this chapter, or, if it was not conducted in compliance with part 58 of this chapter, a brief statement of the reason for the noncompliance.

(x) The submission does not contain a statement for each clinical investigation involving human subjects that the investigation was conducted in compliance with the institutional review board regulations in part 56 of this chapter, or was not subject to those regulations, and that the investigation was conducted in compliance with the informed consent regulations in part 50 of this chapter.

(xi) The submission does not include financial certification or disclosure statements, or both, as required by part 54 of this chapter, accompanying any clinical data submitted.

(k) Withdrawal of consideration. (1) Notwithstanding paragraph (g) of this section, FDA may withdraw consideration of a TEA submission or a safety and effectiveness data submission if:

(i) The person that submitted the submission requests that its submission be withdrawn from consideration; or

(ii) FDA deems the submission to be withdrawn from consideration due to the submitter's failure to respond to communications from FDA.

(2) Before FDA deems a submission withdrawn under paragraph (k)(1)(ii) of this section, FDA will notify the person that submitted the submission. If, within 90 days from the date of the notice from FDA, the submitter requests that FDA not withdraw consideration of the submission, FDA will not deem the submission to be withdrawn.

(3) If FDA withdraws consideration of a submission under paragraph (k)(1) of this section, FDA will post a notice of withdrawal to the docket, except in the case of a TEA submission that is withdrawn from consideration before issuance of a notice of eligibility, in which case, the notice of withdrawal will only be provided to the sponsor. Information that has been posted to the public docket for the condition at the time of the withdrawal (such as a notice of eligibility or a safety and effectiveness data submission that has been accepted for filing and posted to the docket) will remain in the public docket. If the condition has been found eligible through issuance of a notice of eligibility, the condition remains eligible for consideration and the sponsor or any interested person can pursue consideration of the condition in the future by submitting a new safety and effectiveness data submission.

(4) If FDA withdraws consideration of a submission under paragraph (k)(1) of this section, the timelines under § 330.15(c) will no longer apply as of the date of withdrawal, and the submission will not be included in the metrics under § 330.15(b).

3. Add § 330.15 to subpart B to read as follows:

§ 330.15 Timelines for FDA review and action on time and extent applications and safety and effectiveness data submissions.

(a) Applicability. This section applies to the review of a condition in a time and extent application (TEA) submitted under § 330.14 for consideration in the over-the-counter (OTC) drug monograph system. This section does not apply to:

(1) A sunscreen active ingredient or combination of sunscreen active ingredients, and other conditions for such ingredients; or

(2) A non-sunscreen active ingredient or combination of non-sunscreen active ingredients, and other conditions for such ingredients submitted in a TEA under § 330.14 before

November 27, 2014, subject to section 586F(a)(1)(C) of the Federal Food, Drug, and Cosmetic Act.

(b) Metrics. FDA will maintain and update annually, a publicly available posting of metrics for the review of TEAs and safety and effectiveness data submissions that are subject to the timelines in this section. The posting will contain the following information for tracking the extent to which the timelines set forth in paragraph (c) of this section were met during the previous calendar year.

(1) Number and percent of eligibility notices or ineligibility letters issued within 180 days of submission of a TEA;

(2) Number and percent of filing determinations issued within 90 days of submission of a safety and effectiveness data submission;

(3) If applicable, number and percent of feedback letters issued within 730 days from the date of filing;

(4) Number and percent of notices for proposed rulemaking issued within 1,095 days from the date of filing;

(5) Number and percent of final rules issued within 912 days of closing of the docket of the proposed rulemaking; and

(6) Total number of TEAs submitted under § 330.14.

(c) Timelines for FDA review and action. FDA will review and take an action within the following timelines:

(1) Within 180 days of submission of a TEA under § 330.14(c), FDA will issue a notice of eligibility or post to the docket a letter of ineligibility, in accordance with § 330.14(d) and (e).

(2) Within 90 days of submission of a safety and effectiveness data submission, in accordance with § 330.14(j), FDA will issue a filing determination. The date of filing begins the FDA timelines in paragraphs (c)(3) and (4) of this section.

(3) Within 730 days from the date of filing, if the condition is initially determined not to be GRASE for OTC use in the United States, FDA will inform the sponsor and other interested persons who have submitted data of its determination by feedback letter in accordance with § 330.14(g)(4).

(4) Within 1,095 days from the date of filing of a safety and effectiveness data submission, FDA will issue a notice of proposed rulemaking to either:

(i) Include the condition in an appropriate OTC monograph(s), either by amending an existing monograph(s) or establishing a new monograph(s), if necessary; or

(ii) Include the condition in § 310.502 of this chapter.

(5) Within 912 days of the closing of the docket of the proposed rulemaking under paragraph (c)(4) of this section, FDA will issue a final rule.

Dated: November 17, 2016.

Leslie Kux,

Associate Commissioner for Policy.

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