



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: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA or Agency) is proposing to amend its nonprescription (over-the-counter or OTC) drug regulations. The proposed rule, if finalized as proposed, would supplement 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). We are also proposing other changes to make the TEA process more efficient.

DATES: Submit either electronic or written comments on the proposed rule by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER]. Submit comments on information collection issues under the Paperwork Reduction Act of 1995 by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER], (see the "Paperwork Reduction Act of 1995" section of this document).

ADDRESSES: You may submit comments as follows:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <http://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <http://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on <http://www.regulations.gov>.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

#### Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Division of Dockets Management, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2016-N-0543 for “Food and Drug Administration Review and Action on Over-the-Counter Time and Extent Applications.” Received comments will be placed in the docket and, except for those submitted as “Confidential Submissions,” publicly viewable at <http://www.regulations.gov> or at the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states “THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.” The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <http://www.regulations.gov>. Submit both copies to the Division of Dockets Management. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as “confidential.” Any information marked as “confidential” will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA’s posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: <http://www.fda.gov/regulatoryinformation/dockets/default.htm>.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to <http://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, 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.

Submit comments on information collection issues to the Office of Management and Budget in the following ways:

- Fax to the Office of Information and Regulatory Affairs, OMB, Attn: FDA Desk Officer, FAX: 202-395-7285, or email to [oir\\_submission@omb.eop.gov](mailto:oir_submission@omb.eop.gov). All comments should be identified with the title, Food and Drug Administration Review and Action on Over-the-Counter Time and Extent Applications.

FOR FURTHER INFORMATION CONTACT: With regard to the proposed rule: Kristin Hardin, Center for Drug Evaluation and Research (CDER), Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993, 240-402-4246, [Kristen.Hardin@fda.hhs.gov](mailto:Kristen.Hardin@fda.hhs.gov).

With regard to the information collection: Ila Mizrachi, Office of Operations, Food and Drug Administration, 8455 Colesville Rd., rm. 14526, Silver Spring, MD 20993-0002, [PRASStaff@fda.hhs.gov](mailto:PRASStaff@fda.hhs.gov).

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## I. Executive Summary

### A. Purpose and Scope of the Proposed Rule

This proposed rule is intended to implement part of the Sunscreen Innovation Act (SIA) (21 U.S.C. Ch. 9 Sub. 5 Part I, enacted November 26, 2014). Among other provisions, the SIA amended the Federal Food, Drug, and Cosmetic Act (FD&C Act) by adding section 586F to the FD&C Act. Section 586F(b) directs FDA to issue regulations establishing timelines and related performance metrics for the review of certain submissions under FDA's regulation governing TEAs, which is codified at 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. If a drug meets 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 be approved in a new drug application (NDA) under section 505 of the FD&C Act. Drugs determined to be not GRASE (or non-monograph) must be approved under section 505 of the FD&C Act before being marketed in the United States (see section II.A. for more detail on the OTC Drug Review and the TEA process).

Section 586F(b) of the FD&C Act specifically 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 proposing to amend the TEA regulation to make the TEA process more efficient and predictable for both product sponsors and FDA by adding filing determination requirements and criteria and by addressing the withdrawal of consideration of TEA and safety and effectiveness data submissions.

The timelines and metrics in this proposed rule would apply to non-sunscreen TEA conditions (see section V.A for more detail). FDA is addressing timelines for review of sunscreen active ingredients and other related topics regarding sunscreens separately, under other provisions of the SIA (see section II.B for more detail).

#### B. Summary of the Major Provisions of the Proposed Rule

The proposed rule implements the SIA requirements for non-sunscreen TEAs by adding proposed new § 330.15 to FDA's OTC drug monograph regulations (21 CFR part 330). The proposed new section has two major provisions regarding actions to be taken by FDA, consistent with requirements in the SIA. In particular, proposed § 330.15(c) establishes timelines for FDA to review and take action on non-sunscreen TEA conditions, and proposed § 330.15(b) describes measurable metrics that FDA will use for tracking the extent to which the timelines set forth in the regulations are met. Proposed § 330.15(a) generally limits the applicability of these timelines to non-sunscreen TEAs submitted after the enactment of the SIA, with one exception.

We are proposing to amend § 330.14 to:

- add provisions concerning filing determinations regarding safety and effectiveness data submissions for eligible TEA conditions (i.e., determinations as to whether such submissions are sufficiently complete to permit a substantive review by FDA) (§ 330.14(j)),

- add provisions regarding the withdrawal of consideration of TEAs and safety and effectiveness data submissions (§ 330.14(k)),
- add certain definitions (§ 330.14(a)), and
- make minor conforming and clarifying changes.

### C. Legal Authority

This rule is proposed 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 22, 2002 (67 FR 3069), in which the final rule establishing the 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, it 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 21 CFR 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 at 21 CFR 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.

Proposed § 330.15 would add timeline and metrics provisions that are intended to implement section 586F of the FD&C Act.

#### D. Costs and Benefits

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

We expect the rule would create a minimal burden on sponsors, 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. 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 would incur one-time costs to read and understand the proposed rule. We also estimate sponsors will submit two additional TEAs annually, and each of these sponsors would also spend time reading and understanding the proposed 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 would 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. FDA Regulation of Over-the-Counter (OTC) Drugs

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 new drug applications (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 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 21 CFR 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.

Initially, OTC drug conditions not marketed in the U.S. 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 (21 CFR 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 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.

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 21 CFR 330.14(g)). The TEA regulation requires multi-step, 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 under section 330.14 (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 proposed 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 proposed rule 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 parties 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 notice of proposed rulemaking to include the condition in § 310.502. The sponsor and other interested parties will have an opportunity to submit comments and new data on FDA's initial determination and proposed rule (§ 330.14(g)(5)). After evaluation of any additional data submitted, FDA will either issue a final rule or a new proposed rule, if necessary, in the Federal Register.

#### B. 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. Proposed § 330.15 addresses section 586F of the FD&C Act, which 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, as amended by the SIA). For FDA review of non-sunscreen TEA conditions, section 586F includes two main requirements, one regarding timelines for review of eligible TEA conditions pending before the date of enactment of the SIA, and the other regarding timelines and performance metrics for the TEA process going forward.

The first general requirement (see FD&C Act section 586F(a)) is that FDA provide the option of selecting one of four frameworks for review to each non-sunscreen TEA sponsor who (1) had submitted a TEA for a condition that had been deemed eligible to be considered for inclusion in the OTC monograph system before the date of enactment of the SIA, and (2) requested the framework option within 180 days after enactment. FDA was required to provide the framework options to requesting sponsors by no later than one year after enactment of the SIA (by November 26, 2015). Before the date of SIA enactment, there were six non-sunscreen TEAs for conditions that had been found eligible to be considered for inclusion in the OTC drug monograph system: (1) piroctone olamine (for dandruff control) (69 FR 7652, 2/18/04; Docket 2004N-0050 (FDA-2004-N-0037)); (2) triclosan (for oral healthcare) (69 FR 40640, 7/6/04; Docket 1981N-0033P (FDA-1981-N-0015)); (3) triclosan (for acne treatment) (70 FR 72447, 12/5/05; Docket 2005N-0445 (FDA-2005-N-0454)); (4) climbazole (for dandruff control) (70 FR 72448, 12/5/05; Docket 2005N-0444 (FDA-2005-N-0021)); (5) sodium picosulfate (for laxative

use) (71 FR 35917, 6/22/06; Docket 2006O-0232 (FDA-2006-O-0057)); and (6) sodium shale oil sulfonate (for dandruff control) (74 FR 15741, 4/7/09; Docket FDA-2009-N-0146).

The sponsors of three of those TEAs requested that FDA provide a review framework by the deadline established in section 586F(a) of the FD&C Act. The three TEAs are for: (1) piroctone olamine (for dandruff control) (69 FR 7652, 2/18/04; Docket 2004N-0050 (FDA-2004-N-0037)); (2) sodium picosulfate (for laxative use) (71 FR 35917, 6/22/06; Docket 2006O-0232 (FDA-2006-O-0057)); and (3) sodium shale oil sulfonate (for dandruff control) (74 FR 15741, 4/7/09; Docket FDA-2009-N-0146). FDA provided the review framework options to the requesting sponsors on November 24, 2015. With regard to the three sponsors who did not request or elect a framework in accordance with section 586F(a) of the FD&C Act, the eligible conditions addressed by their TEAs will be reviewed under the timelines set forth in proposed § 330.15 (if finalized as proposed).

The second general requirement (see FD&C Act section 586F(b)) is that FDA issue a regulation that includes (1) timelines for review of non-sunscreen TEA conditions and (2) measurable metrics for tracking the extent to which the timelines are met. This proposed rule includes both timelines and metrics, as required by the SIA.

FDA has 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 is to (1) establish a new section (proposed § 330.15) that is specific to non-sunscreen TEA conditions, 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).

In addition to developing new § 330.15, which implements SIA requirements with regard to the TEA process for non-sunscreens, FDA proposes to make certain changes to the process set forth in § 330.14 that we believe will make the TEA process more clear and efficient for both sponsors and FDA. These proposed changes to § 330.14 are discussed in more detail in this document, but notably include provisions that address filing determination requirements with regard to safety and effectiveness data submissions (to allow FDA to determine, and sponsors to know, early on whether a submission is sufficiently complete to permit a substantive review) and provisions regarding withdrawal of consideration of a TEA or safety and effectiveness data submission.

#### IV. Legal Authority

This rule is being proposed under FDA's authority to regulate OTC drug products under the FD&C Act (see sections 201, 501, 502, 503, 505, 586F, and 701(a) of the FD&C Act (21 U.S.C. 321, 351, 352, 353, 355, 360fff-6, and 371(a))). As stated in the Federal Register of January 22, 2002 (67 FR 3069), in which the final rule establishing the 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, it 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 21 CFR 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 at 21 CFR 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. Proposed § 330.15 would add timeline and metrics provisions that are intended to implement section 586F of the FD&C Act.

#### V. Description of the Proposed Rule

In this rule, we are proposing to establish new § 330.15 and to amend current § 330.14. In particular, we are proposing to: (1) establish timelines and metrics for review of non-sunscreen TEA conditions, (2) add provisions concerning filing determination requirements with regard to the content and format of safety and effectiveness data submissions under § 330.14(f), (3) address withdrawal of consideration of TEAs and safety and effectiveness data submissions, (4v) add related definitions, and (5) make clarifying and conforming changes to the TEA regulation. These proposed changes are discussed in detail in this section.

##### A. Timelines for FDA Review and Action on Time and Extent Applications and Safety and Effectiveness Data Submissions (proposed § 330.15)

The SIA mandates that FDA issue regulations to establish timelines and metrics regarding the review of non-sunscreen TEA conditions, and provides that the proposed timelines may vary based on the content, complexity, and format of the submission, and that they must (1) reflect FDA's public health priorities, including the potential public health benefits posed by the inclusion of additional drugs in the OTC drug monograph system, (2) take into consideration the availability of FDA resources for carrying out such priorities and the relevant review processes and procedures, and (3) be reasonable, taking into account the required consideration of priorities

and resources (FD&C Act section 586F(b)(2)). Proposed § 330.15 is intended to implement these requirements.

1. Applicability (see proposed § 330.15(a))

As a general matter, the timeline provisions in proposed § 330.15 apply to FDA and are triggered by specific actions by sponsors, such as submission of a TEA or submission of a safety and effectiveness data submission (as defined in proposed § 330.14(a)) and, in some cases, FDA (e.g., the date of filing). The metrics provisions also apply to FDA.

Proposed § 330.15(a) describes which TEA conditions are subject to the timelines for FDA review and action in this section and which are not. We invite comment on the proposed applicability of this section. In particular, FDA is proposing that the review of an active ingredient or other condition in a TEA submitted under § 330.14 for consideration in the OTC drug monograph system would be subject to the proposed timelines, with two exceptions.

First, in § 330.15(a)(1), FDA proposes that § 330.15 does not apply to a sunscreen active ingredient or a combination of sunscreen active ingredients or other conditions for such ingredients. Section 586F(b) of the FD&C Act directs the Agency to issue regulations establishing timelines for drugs other than nonprescription sunscreen active ingredients or combinations of nonprescription sunscreen active ingredients. The SIA recognizes that active ingredients can only be GRASE under specified conditions. For example, section 586A of the FD&C Act, which was added by the SIA to provide an alternative route for inclusion in the sunscreen monograph, states that a person may submit a request to FDA for a determination of whether a nonprescription sunscreen active ingredient or combination of ingredients, for use under specified conditions, to be prescribed, recommended, or suggested in the labeling thereof (including dosage form, dosage strength, and route of administration) is GRASE. Because the

TEA regulation addresses active ingredients and other conditions, including dosage forms, and an active ingredient can only be GRASE under specified conditions, we understand the reference to TEAs for drugs other than sunscreen active ingredients in section 586F(b) of the FD&C Act to be distinguishing sunscreen active ingredients and related conditions from non-sunscreen active ingredients and related conditions. Furthermore, “pending requests” for sunscreen active ingredients under the SIA are subject to the provisions of section 586C(b) of the FD&C Act, as amended by the SIA (21 U.S.C. 360fff-3(b)), which include timeframes for FDA review and action. Therefore, under proposed § 330.15(a), § 330.15 would not apply to sunscreen active ingredients and related conditions.

Second, in § 330.15(a)(2), FDA proposes that § 330.15 generally does not apply to non-sunscreen active ingredients or other conditions submitted in TEAs under § 330.14 on or before the date of enactment of the SIA. Section 586F(b)(1) of the FD&C Act directs the Agency to issue regulations establishing timelines for the review of TEA conditions submitted after the date of enactment of the SIA. However, as provided in the SIA, any non-sunscreen TEA conditions determined to be eligible to be considered for inclusion in the OTC drug monograph system before the date of enactment of the SIA, for which the sponsor did not request a framework for review under section 586F(a)(1), will also be reviewed under the timelines set forth in § 330.15(c) of this proposed rule (see FD&C Act section 586F(a)(1)(C)) (if finalized as proposed). Accordingly, the scope of the exclusion in proposed § 330.15(a)(2) references section 586F(a)(1)(C) of the FD&C Act to account for such TEA conditions.

For sponsors of TEAs covering conditions that had been found eligible to be considered for inclusion in the OTC drug monograph system before the date of enactment of the SIA who elected to choose a framework for review, FDA was required to provide four optional

frameworks that set forth timelines for FDA review (FD&C Act section 586F(a)((2)). The frameworks included timelines for review if the sponsors choose an order process with or without a filing determination, or a rulemaking process with or without a filing determination. A notification of optional frameworks was provided to each requesting sponsor on November 24, 2015. Before the date of enactment of the SIA, there were six non-sunscreen TEA conditions that were found by FDA to be eligible to be considered for inclusion in the OTC drug monograph system (listed in section II.B). Of these, three sponsors elected a framework for review, and three did not (listed in section II.B).

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

As discussed in the introduction to section V.A, section 586F(b) of the FD&C Act, as amended by the SIA, directs FDA to establish timelines for the review of certain TEA conditions. As also discussed in section V.A.1, in addition to applying to new non-sunscreen TEAs, these timelines would apply to certain non-sunscreen TEA conditions that were found to be eligible before November 26, 2014. Section 586F(b) of the FD&C Act also requires timelines for internal procedures related to the review of safety and effectiveness data submissions.

FDA is proposing to establish the timelines described in this section of the document for FDA review and action, as described in proposed new § 330.15(c).

Note that terms for certain actions that begin review timelines for FDA are defined in proposed amendments to § 330.14 (e.g., “date of filing”). In addition to clarifying that its definitions apply to proposed § 330.15, proposed § 330.14(a) would clarify the applicability of the definitions in section 201 of the FD&C Act by expressly stating that any relevant definitions in that section, such as the definition of “person” at section 201(e), would apply to §§ 330.14 and 330.15.

a. Proposed timelines

The proposed timelines are:

- FDA will issue a notice of eligibility or post to the docket a letter of ineligibility, in accordance with § 330.14(d) and (e), within 180 days of submission of a TEA under § 330.14(c).
- FDA will issue a filing determination in accordance with § 330.14(j) within 90 days of receipt by FDA of a safety and effectiveness data submission from the sponsor under § 330.14(f). Under proposed § 330.14(a)(5), a safety and effectiveness data submission is defined as a data package submitted by a sponsor that includes safety and effectiveness data and information under § 330.14(f) and that is represented by the sponsor as being a complete submission. Therefore, FDA will not start the 90-day filing determination period until the sponsor has confirmed that it considers the submission to contain all data and information required under § 330.14(f) by providing a statement that the submission is a complete safety and effectiveness data submission. If the sponsor submitted such a safety and effectiveness data submission at the same time as the sponsor submitted the TEA, and the condition addressed in the TEA is deemed eligible for consideration, FDA will issue a filing determination within 90 days after issuing the notice of eligibility.
- If the active ingredient or other condition is initially determined not to be GRASE, FDA will inform the sponsor and other interested parties who have submitted data of its determination by feedback letter in accordance with § 330.14(g)(4), within 730 days (generally 24 months) from the date of filing. FDA is considering whether to add a codified provision to address sponsor requests for additional time in response to a feedback letter and how that would affect the timeline for review. We welcome comments on this issue.

- FDA will issue a notice of proposed rulemaking within 1,095 days (generally 36 months) from the date of filing to either:
  - include the active ingredient or other condition in an appropriate OTC monograph(s), either by amending an existing monograph(s) or establishing a new monograph(s), if necessary; or
  - include the active ingredient or other condition in § 310.502 (which would require the sponsor to seek approval under section 505 of the FD&C Act before marketing).
- FDA will issue a final rule within 912 days (generally 30 months) of the closing of the docket of the proposed rulemaking under § 330.15(c)(4). If the docket is reopened, the final rule will be issued within 912 days of the closing of the re-opened docket.

For non-sunscreen TEA conditions that were found to be eligible before enactment of the SIA and that would be subject to the timelines in proposed § 330.15, FDA intends to treat the date of publication of the final rule for § 330.15 to be the date of filing for purposes of §§ 330.14 and 330.15. Therefore, upon the publication of the final rule, the timelines in proposed § 330.15(c)(3), if applicable, and § 330.15(c)(4) would begin for these eligible TEA conditions.

b. Development of timelines

As required by the SIA (section 586F(b)(2) of the FD&C Act), FDA considered specific factors in developing the timelines in proposed new § 330.15(c). In particular, the SIA provides that the timelines for the review of non-sunscreen TEA conditions may vary based on the content, complexity, and format of the submission, and 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 just described (section 586F(b)(2)(A) and (B) of the FD&C Act).

FDA is allowed (for the “may” factors) or required (for the “shall” factors) to take these factors into account in the timelines for review of non-sunscreen TEAs and related submissions. These SIA provisions recognized factors that could possibly affect how long it may take FDA to complete review of a particular TEA and related submissions. The timelines proposed in § 330.15 factored in the considerations that are required under the SIA; they reflect the projected time necessary for FDA to complete its review of marketing, filing, and scientific data and other information, as well as to make tentative and final determinations about the adequacy of the submissions to ultimately support a finding that the active ingredient or other condition is or is not GRASE and not misbranded for nonprescription use, based on the Agency’s public health priorities and the resources available to carry them out. The timelines also include the projected time necessary to draft and finalize the letters or rules (proposed and final), and when applicable, prepare the document for publication in the Federal Register. In addition, the timelines take into account other activities that may occur during the review, such as convening an advisory committee meeting, meeting with sponsors, or both. FDA believes that the proposed timelines are reasonable, taking into consideration FDA’s priorities and resources. More detail on how FDA took these factors into account is provided in this section.

i. FDA public health priorities

Under section 586F(b)(2)(B)(i) of the FD&C Act, the timelines must reflect FDA's public health priorities, including the potential public health benefits posed by the inclusion of additional drugs in the OTC drug monograph system. FDA has a very broad mandate and multiple public health priorities, with limited resources to address these priorities.

FDA's Center for Drug Evaluation and Research (CDER) is responsible for regulating the safety and efficacy of both prescription and nonprescription human drugs. Like FDA as a whole, CDER must continually balance multiple important public health priorities, of which the OTC Drug Review is one. CDER does, and will continue to, consider the OTC Drug Review among its priorities as it endeavors to appropriately allocate staff and resources within the context of all CDER responsibilities.

Examples of how FDA public health priorities may affect the time required for the review of non-sunscreen TEA conditions under the proposed timelines include situations such as a public health emergency or competing high priority work that requires diversion of the staff assigned to a TEA or safety and effectiveness data submission.

ii. Resources available for carrying out such priorities

Under section 586F(b)(2)(B)(ii), the timelines must take into consideration Agency resources available for carrying out its public health priorities and the processes and procedures related to the review of TEA conditions. Examples of resource constraints that may affect the time required for review include, but are not limited to: multiple TEAs arriving at or near the same time; general expected staff and budget constraints; unexpected staff and budget constraints; personnel turnover and lag times in hiring new staff; etc. For example, FDA has only a certain number of trained staff available to assign to TEA review work, and these staff generally have other assigned work in addition to TEA reviews.

iii. Reasonableness, taking into consideration Agency priorities and resources

In developing the timelines set forth in proposed new § 330.15(c), FDA has attempted to set reasonable timelines that will be achievable in most circumstances, given our experience to date with TEAs and related safety and effectiveness data submissions. While FDA expects that the filing determination requirements we propose adding to § 330.14(j) will help to avoid major content and format deficiencies in incoming safety and effectiveness data submissions, there is likely still to be some variation in the formatting of incoming TEAs and safety and effectiveness data submissions, and a related variation in the ease and efficiency of review.

In determining reasonable timelines, FDA also considered the potential effect on stakeholders, including TEA sponsors and the public. In addition to considering the benefits that the proposed timelines and related metrics would provide to sponsors (e.g., more transparency regarding the TEA review process, increased predictability regarding how long each major process step is expected to take, and metrics on how long each step actually takes), FDA also considered other potential impacts of the proposed timelines on sponsors, including concerns regarding the time required to complete the review and rulemaking process. For each step in the TEA process, FDA attempted to determine a timeline that is achievable, consistent with timelines for similar FDA activities in other contexts to the extent possible (e.g., NDA process timelines, general rulemaking experience), consistent with the Agency's priorities and resources, and that reasonably takes into consideration the interests of the public (in safe and effective OTC drug products) and sponsors (in a timely and efficient review process). For some steps, this resulted in FDA setting a shorter timeline than it had previously estimated for the step. For example, the proposed timeline for the eligibility determination step (proposed new

§ 330.15(c)(1)) is 180 days from receipt of a TEA, which is roughly half the time estimated by FDA for this step in a 2011 guidance to industry (Ref. 1).

#### Eligibility Determination

With respect to the eligibility determination (§ 330.15(c)(1)), FDA is proposing to review and issue a notice of eligibility or post to the docket a letter of ineligibility within 180 days of receipt of a TEA, which FDA considers to be a reasonable timeline, taking into consideration Agency priorities and resources. As stated previously, in a 2011 final guidance to industry, FDA previously estimated a 1-year timeframe for taking this action (Ref. 1).

#### Filing Determination

FDA is proposing to issue a filing determination within 90 days of submission by the sponsor of a safety and effectiveness data submission, which is defined in proposed § 330.14(a), in part, as a submission that the sponsor has confirmed it considers to be complete (i.e., contains all data and information required under § 330.14(f)). While this timeline is 30 days longer than the filing provisions in 21 CFR 314.101 for NDAs and ANDAs, we anticipate that the filing review of a safety and effectiveness data submission for a nonprescription active ingredient or other condition may require more time than an NDA or ANDA review because the submission may consist of data and information from a wider variety of sources, with possibly a greater reliance on certain sources (e.g., published literature).

#### Rulemaking and Feedback Letter

Notice and comment rulemaking is generally a lengthy and multistep process (Ref. 2). The timelines in this proposed rule are consistent with the length of time typically required for other rulemaking, and reflect the amount of time FDA anticipates will be required for the reviews of safety and effectiveness data submissions and related rulemaking.

Major steps for FDA rulemaking generally include determination that a rule is needed and what the rule should say; drafting, reviewing, and finalizing the proposed rule; publishing the proposed rule; a public comment period and review of the comments; revising the proposed rule as appropriate; reviewing the draft final rule and finalizing it, and publishing the final rule in the Federal Register.

As noted previously, rulemaking is often a lengthy process, and the OTC Drug Review process (of which the TEA process is a part) offers additional rulemaking challenges, such as were discussed in a public meeting on OTC process reform held by FDA in 2014 (“Over-The-Counter Drug Monograph System--Past, Present and Future; Public Hearing,” 79 FR 10168, February 24, 2014; Docket No. FDA-2014-N-0202). Additional information, such as the hearing transcript, is available at <http://www.fda.gov/Drugs/NewsEvents/ucm380446.htm>. For TEA active ingredients and other conditions, the timelines for rulemaking involve conducting the scientific review, making a GRASE determination, and drafting and finalizing the rule for publication in the Federal Register. FDA estimates that initial scientific review of a complete safety and effectiveness data submission, including for new molecular entities that have never been marketed in the United States, will take approximately 730 days (generally 24 months). In addition to conducting this comprehensive review, the timeline may also include other activities, such as convening an advisory committee (or, under rare circumstances, an advisory review panel under § 330.10) and meeting with sponsors.

If the active ingredient or other condition is initially determined not to be GRASE for OTC use in the United States, FDA will also issue a feedback letter within this 730-day (generally 24-month) timeline. The feedback letter may identify the specific gaps in the data or information necessary to make a GRASE determination, and it provides the sponsor with time

before the NPRM is published that could be used to begin collecting the data or information required for potential inclusion in a monograph. We note that a feedback letter reflects the Agency's initial determination. If FDA does not issue a feedback letter, it does not guarantee that we will ultimately determine that an ingredient is GRASE and not misbranded.

FDA proposes to issue an NPRM within 1,095 days (generally 36 months) from the date of filing (as defined in proposed § 330.15(a)(6)). For an active ingredient or other condition that is initially determined to be GRASE, FDA would issue a proposed rule to include the condition in the appropriate OTC monograph. For an active ingredient or other condition that is initially determined not to be GRASE, FDA would issue a proposed rule to include the condition in 21 CFR 310.502 (the regulation listing drugs that have been accorded new drug status through rulemaking and must be approved under section 505 of the FD&C Act before marketing). In general, FDA intends to close the public comment period for the proposed rule at 90 days, unless a request to defer further rulemaking to allow the submission of new safety or effectiveness data to the record is granted.

FDA is proposing to issue a final rule within 912 days (generally 30 months) of the closing of the comment period for the proposed rule. During this 912-day time period, FDA will review and consider any new data, information, and public comments submitted to the docket and draft and publish a final regulation.

Timelines for FDA review and action for sunscreen active ingredients under sections 586B and 586C of the FD&C Act, as amended by the SIA, are generally shorter than those in this proposed rule. The most notable differences are the timelines for proposed and final GRASE determinations which, under the SIA requirements for sunscreen active ingredients, are

made through an order process rather than a rulemaking process. The order process eliminates some of the requirements of rulemaking that are time-consuming and resource intensive.

A 2009 Government Accountability Office (GAO) report (Ref. 3) examined, among other things, how long agencies, including FDA, take to issue rules. For the 16 case studies, the report found significant variation in time to complete rulemaking, with an average of about four years and a range of one to nearly 14 years. Factors that influenced the time needed to issue a rule included the complexity of the issues, Agency priorities, and the amount of internal and external review required (Ref. 3 at p. 19).

In summary, based on the type of data typically submitted in a TEA, along with the potential variability in the content and formatting of that submission, and because of the complex scientific review required to determine if an active ingredient or other condition is GRASE for OTC use, the possible use of an advisory committee, and the requirements for the rulemaking process itself, FDA considers the timelines put forth in this proposed rule to be reasonable, taking into consideration Agency priorities and resources. As described in further detail in the paragraphs that follow, if a TEA and the related safety and effectiveness data submission are straightforward, well-organized, and complete, FDA may be able to take action within shorter timeframes than proposed in this rule.

As stated previously, under section 586F(b)(2)(A) of the FD&C Act, the timelines established in the regulations required under that section could vary based on the content, complexity, and format of the submission. FDA considered a number of timeline options. Ultimately, FDA determined that instead of setting multiple proposed timelines for submissions of varying content, complexity, and format, it would be more efficient and sensible to set one general timeline for the review of non-sunscreen TEA conditions that accommodates anticipated

variation among submissions. There is likely to be some variation in how quickly each submission is reviewed, because each will present a unique set of data and each review will occur in the context of multiple ongoing FDA activities and priorities. This may result in a review step taking less time than proposed in § 330.15(c) (for example, if a submission is well-organized, complete when submitted, and straightforward). In unusual circumstances, a review or rulemaking step may require a longer time than proposed in § 330.15(c) (e.g., an unusually high volume of TEAs submitted, an especially complex new ingredient or other condition, or a public health emergency that diverts Agency resources). However, FDA would endeavor to meet the proposed timelines in § 330.15(c) for all submissions, and any missed timelines would be reflected in the metrics set forth in proposed § 330.15(b). In summary, the provisions in § 330.15(c) provide sponsors and the public with consistent timeframes for expected Agency action. In the paragraphs that follow, we discuss some practical examples of how certain factors might be expected to impact FDA review of a non-sunscreen TEA condition:

- Content

The quantity and quality of submitted data can generally impact FDA's review. If a TEA or safety and effectiveness data submission includes all the information that is required and all information that the sponsor wishes to have considered in the initial submission to FDA, it is likely possible to complete review of the TEA or safety and effectiveness data submission more quickly than if it has poor quality data, if FDA finds that clarification or additional data is needed, or if the sponsor submits additional spontaneous data supplements during the substantive review.

- Complexity

Complexity, including, among other things, the nature of the active ingredient or other condition that is the subject of the TEA and the status of the monograph for the therapeutic category (i.e., final, tentative, or new) may also impact FDA's review. For example, review of a TEA and safety and effectiveness data submission for an active ingredient that has not previously been evaluated under the monograph for any use would likely be more complex than for an ingredient that is the subject of a GRASE determination in another monograph category. In addition, a review that involves a new technology would be more complex than one that does not.

The OTC monograph status for the therapeutic category (final, tentative, or new) and the U.S. Pharmacopeia (USP) monograph status (whether establishment of a USP monograph is required or not) may each affect the time required for review and rulemaking, in that addition of an active ingredient or other condition to a final OTC monograph once the GRASE determination is made would generally be faster than working with a tentative or new OTC monograph. Also, because a USP monograph for the ingredient is required before FDA can issue a final rule adding an active ingredient to an OTC monograph (§ 330.14(i)), the USP monograph status may lengthen the review and rulemaking time.

Finally, if FDA determines that an advisory committee or an advisory review panel is appropriate (e.g., for a particularly complex new issue), that process could increase the time required to complete the review, particularly if the committee's recommendations raised additional issues to review.

- Format

The format including, among other things, whether a TEA or safety and effectiveness data submission is well-organized or poorly-organized, whether some or all of the information is

submitted in electronic format, etc., could also impact FDA's review. We note that FDA recently issued draft guidance for industry regarding the format and content of data submissions for nonprescription sunscreen active ingredients (Ref. 4). A well-formatted TEA can generally be reviewed more quickly and efficiently than a poorly-organized TEA. In addition, review could take longer (or result in a refusal to file) if a safety and effectiveness data submission is disorganized with a structure that does not facilitate review for completeness, if there are electronic submissions that cannot be opened or that cannot be readily navigated (e.g., hyperlinks do not operate), or if there are data tabulations or graphic displays that are not interpretable, inadequately labeled, or do not indicate data sources. These issues may arise, in particular, with regard to safety and effectiveness data submissions that are filed over protest.

### 3. Metrics (proposed new § 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 (see proposed timelines under § 330.15(c)). FDA is proposing 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 under proposed § 330.15(a), and update the posting annually. The posting will contain the metrics listed in this section, as proposed in § 330.15(b), for submissions received during the previous calendar year.

- Number and percent of eligibility notices or ineligibility letters issued within 180 days of submission of a TEA (i.e., for new TEAs submitted during the year, the number and percentage for which FDA issued either an eligibility notice or an ineligibility letter within 180 days).

- Number and percent of filing determinations issued within 90 days of submission of a safety and effectiveness data submission (i.e., for safety and effectiveness data submissions received during the year, the number and percentage for which FDA issued a filing determination within 90 days).
- If applicable, number and percent of feedback letters issued within 730 days (generally 24 months) from the date of filing (i.e., the number of feedback letters issued during the year, if any, and the number and percent of these that were issued within 730 days from the date of filing the safety and effectiveness data submission).
- Number and percent of notices for proposed rulemaking issued within 1,095 days (generally 36 months) from the date of filing (i.e., the number of notices of proposed rulemaking issued during the year, if any, and the number and percent of these that were issued within 1,095 days from the date of filing).
- Number and percent of final rules issued within 912 days (generally 30 months) of closing of the docket of the proposed rulemaking (i.e., the number of final rules issued during the year, if any, and the number and percent of these that were issued within 912 days of the closing of the docket of the proposed rulemaking). We note that if the docket is reopened, the 912 days will be measured from the date the reopened docket is closed.
- Total number of TEAs submitted under § 330.14; FDA may also post a total number of TEAs that have been submitted in all previous years.

For purposes of the metrics, a lack of FDA action in response to a triggering event in the previous calendar year will not be factored in unless the response was due in the previous calendar year. In other words, if a sponsor submits a TEA in October of the previous calendar year, and FDA has not yet issued a notice of eligibility or letter of ineligibility because 180 days

has not elapsed by the end of the calendar year, under the proposed metrics, FDA would not consider the lack of response as missing the timeline. Whether FDA met the timeline or not would be reflected in the next year's metrics.

FDA intends to track these metrics and post them publically on the FDA Internet site. The Agency routinely uses its Internet site to post information and track progress and performance metrics on various initiatives (Ref. 5).

The Agency anticipates that the proposed metrics web posting will improve transparency by providing 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. Over time, these measurements may also assist the Agency with resource planning and utilization.

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

FDA is proposing to revise § 330.14 to add new definitions and requirements. The new proposed definitions are primarily meant to clarify the beginning or ending of the timelines for FDA review and action as proposed in new § 330.15. The new proposed requirements include filing determination provisions under proposed new § 330.14(j) and "withdrawal of consideration" provisions under proposed new § 330.14(k), which are intended to make the TEA process more efficient for both sponsors and FDA.

1. Definitions (proposed revised § 330.14(a))

FDA is proposing new definitions that, in general, are intended to clarify the beginning or ending of the timelines for FDA review and action as proposed in § 330.15. FDA is adding these definitions to § 330.14 instead of proposed new § 330.15 because § 330.14 describes the TEA

process to which these definitions apply. The definitions for “condition” and “botanical drug substance,” proposed under § 330.14(a)(1) and (2) respectfully, are unchanged from the current definitions under § 330.14(a). FDA is proposing to add the following new definitions of terms that apply to § 330.14.

- FDA is proposing that the term “sponsor” mean the person (as defined in section 201(e) of the FD&C Act) that submitted a TEA under § 330.14(c). Because the TEA process involves a public rulemaking process, comments from other interested parties, such as additional safety and effectiveness data, may be submitted to the docket for a TEA condition. FDA is proposing this definition to make clear that the sponsor is the person that submitted the TEA and related safety and effectiveness data submission, and will be the recipient of certain letters communicating FDA decisions. Because this is a public process, such letters will also be posted publicly to the relevant docket.
- FDA is proposing that the term “time and extent application (TEA)” mean a submission by a sponsor under § 330.14(c), which will be evaluated by the Agency to determine eligibility of a condition for consideration in the OTC drug monograph system. FDA is proposing this definition to make clear the difference between a submission to FDA for the purposes of establishing that the condition has been marketed for a material time and to a material extent versus a submission to FDA for the purposes of establishing that the condition is GRASE.
- FDA is proposing that the phrase “safety and effectiveness data submission” mean a data package submitted by a sponsor that includes safety and effectiveness data and information under § 330.14(f) and that is represented by the sponsor as being a

complete submission. FDA is proposing this definition to differentiate this type of submission from the TEA. It also clarifies that FDA will not begin its filing determination under § 330.14(j) unless the sponsor first asserts that the submission is complete.

- FDA is proposing that the phrase “date of filing” mean the date of the notice from FDA informing the sponsor that FDA has made a threshold determination that the safety and effectiveness data submission is sufficiently complete to permit a substantive review. For submissions filed over protest in accordance with § 330.14(j)(3), the date of filing is the date of the notice from FDA informing the sponsor that FDA has filed the submission over protest. This date will be no later than 30 days after the sponsor’s request that FDA file the submission over protest. FDA is proposing this definition to make clear the start of the timeframe for FDA review and action under § 330.15(c)(3) and (4).

- FDA is proposing that the term “feedback letter” mean a letter issued by the Agency in accordance with § 330.14(g)(4) that informs the sponsor and other interested parties who have submitted data under paragraph (f) of this section that a condition is initially determined not to be GRASE. FDA is proposing this definition to clarify the FDA action under § 330.14(g)(4) and the timeframe for such action under § 330.15(c)(3).

## 2. Filing Determination (proposed new § 330.14(j))

FDA is proposing new requirements that specify certain filing determination requirements that are intended, in part, to help improve the content and format of a safety and effectiveness data submission. FDA is also proposing timelines related to these proposed new

requirements. For example, submission criteria include factors such as whether the submission includes all required information, whether the submission is organized and formatted in a manner that allows FDA to readily determine if it is sufficiently complete to permit a substantive review, and whether the submission includes all required certifications.

The proposed new section also sets forth processes that apply whether the submission is accepted for filing, refused, or filed over protest. If the submission is filed, the date of filing, as defined in proposed § 330.14(a), represents the start of FDA's initial review for a GRASE determination, and triggers the start of timelines under proposed §§ 330.15(c)(3) and (4).

FDA believes that these proposed requirements would benefit both TEA sponsors and FDA, as well as potentially benefitting other interested parties. In FDA's experience, TEA-related submissions vary widely in their content and format and are sometimes difficult or extremely time-consuming and resource-intensive to review as submitted (e.g., missing data; copies of articles in foreign languages without an accompanying translation; hyperlinks that do not work; data submitted piecemeal; data not organized in any discernable manner, such as a submission with no listing of contents, page numbers, data categories, etc.). The proposed new requirements would provide more clarity and certainty to sponsors as to the content and format of a safety and effectiveness data submission and would provide for FDA to let sponsors know early on in the process if there is missing material or a problematic format that could delay review. For FDA, the proposed new requirements would be expected to result in more complete and clear data submissions from sponsors, to allow FDA to more easily and quickly determine whether the submission is sufficiently complete to permit FDA to go forward with a substantive review, and to ensure that once FDA begins its substantive review, the data and other information necessary for a complete review are available. If the submission is not sufficiently

complete to allow substantive review, the new requirements would provide a clear pathway to communicate this issue to sponsors via a filing determination, and to communicate what additional information or format changes are required. Because safety and effectiveness data submissions are posted to the public docket, once filed, a more complete submission may also benefit other interested parties. Among other things, it may be easier for non-sponsor interested parties to determine whether there is information not otherwise reflected in the docket that they would like to submit for FDA to consider in the GRASE determination.

We note that while the SIA did not require FDA to issue a regulation regarding filing determination criteria for safety and effectiveness data submissions under § 330.14, it did require FDA to issue draft and final guidance on the format and content of information submitted by a sponsor in support of a “request” under section 586A of the FD&C Act and a “pending request,” which are related to sunscreens (see FD&C Act section 586D(a)(1)(A) and (B)). A notice of availability of the draft guidance on this topic was published in the Federal Register on November 23, 2015 (Ref. 4). When final, this guidance will provide the Agency’s current thinking about the criteria for the content and format of the safety and effectiveness data submitted by the sponsor of a TEA for a nonprescription sunscreen active ingredient or related condition. As noted in the draft guidance, when finalized, parts of the general advice in that guidance about the content and format of sunscreen safety and effectiveness data submissions may also be useful to persons preparing submissions for non-sunscreen TEA conditions.

As stated earlier in this section, proposed § 330.14(j) sets forth criteria FDA would use in making a filing determination for a safety and effectiveness data submission, as well as timing and processes related to the determination. In particular, in § 330.14(j)(1), FDA proposes that after FDA receives a safety and effectiveness data submission, the Agency will determine

whether the submission may be filed. The determination would be whether or not to accept the submission for filing, after an initial review of the submission regarding whether the submission contains the data and information required under § 330.14(f) in an acceptable format, and satisfies the other filing criteria under § 330.14(j)(4). The filing of a submission under proposed § 330.14(j)(2) would mean that FDA has made a threshold determination that the submission is sufficiently complete to permit a substantive review.

In § 330.14(j)(2), FDA proposes that the date of filing will begin the FDA timelines described in § 330.15(c)(3) and (4).

In § 330.14(j)(3), FDA proposes to describe the process for cases in which FDA refuses to file the safety and effectiveness data submission. If this happens, the Agency would notify the sponsor in writing and state the reason for the refusal under proposed § 330.14(j)(4). Proposed § 330.14(j)(3) provides the sponsor 30 days in which to request an informal conference with the Agency about whether the Agency should file the submission and sets forth the procedures if the sponsor wishes to file the submission over protest following the informal conference. Proposed § 330.14(j)(3) further provides that FDA will convene the informal conference within 30 days of the request from the sponsor. It also provides that if, within 120 days after the informal conference, the sponsor 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 § 330.14(j)(2), notify the sponsor in writing, and review it as filed. The sponsor need not resubmit a copy of a safety and effectiveness data submission that is filed over protest.

In proposed § 330.14(j)(4), FDA describes the conditions under which FDA may refuse to file a safety and effectiveness data submission. These include a submission that:

- is incomplete because it does not contain information required under § 330.14(f) (if such information is not provided because it is not relevant, the submission must clearly identify and explain the omission);
- is not organized or formatted in a manner to enable the Agency to readily determine if it is sufficiently complete to permit a substantive review;
- 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 sponsor at the time of the submission, whether positive or negative;
- does not contain an analysis and summary of the data and other supporting information, organized by clinical or nonclinical area;
- does not contain a supporting document summarizing the strategy used for literature searches, including search terms, sources, dates accessed and years reviewed;
- does not contain a reference list and copy of supporting information; or
- includes data or information relevant to the GRASE determination that is marked as confidential without a statement that the information may be released to the public (if the relevant data was produced and marked confidential by a third party, the sponsor would need to include a statement that the sponsor is authorized to make the information publicly available or include an authorization from the third party permitting the information to be publicly disclosed).

In addition, the following four filing determination factors relate to requirements under other sections of the regulations. FDA may refuse to file a safety and effectiveness data submission if the submission:

- does not contain either a complete environmental assessment or information supporting a categorical exclusion under part 25 (see 21 CFR part 25, “Environmental impact considerations”);
- does not contain a statement for each nonclinical laboratory study that it was conducted in compliance with part 58 requirements (see 21 CFR part 58, “Good laboratory practice for nonclinical laboratory studies”) (or a statement of reasons for the noncompliance);
- does not contain a statement for each clinical investigation involving human subjects that it was conducted in compliance with part 56 institutional review board regulations (see 21 CFR part 56, “Institutional Review Boards”) or was not subject to those regulations, and that it was conducted in compliance with part 50 informed consent regulations (see 21 CFR part 50, “Protection of human subjects”); or
- does not include required part 54 financial certification and disclosure statements (see 21 CFR part 54, “Financial disclosure by clinical investigators”).

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

The Agency is also proposing to add withdrawal provisions to new § 330.14(k). These proposed provisions acknowledge that a sponsor may request withdrawal of consideration of a TEA or safety and effectiveness data submission. In addition, inaction by a sponsor in certain

circumstances may be deemed by FDA as a request for withdrawal of consideration (e.g., prolonged failure of a sponsor to submit any safety and effectiveness data after receipt of an NOE, failure of a sponsor to respond to FDA communications). These proposed requirements are expected to help provide clarity on the status of TEAs and safety and effectiveness data submissions, and the effect of a withdrawal of consideration on the docket. They would also permit FDA to suspend work on those TEAs or safety and effectiveness data submissions that are no longer being pursued by the sponsor and for which FDA does not believe that the GRASE determination should go forward.

The Agency believes that the proposed provisions on withdrawal of consideration would allow the Agency to better allocate resources for the review of TEA conditions than the current process. Based on past experience with the OTC monograph process, FDA has found that following an Agency action, a sponsor may not respond to a request for data from FDA. For example, the Agency issued an NOE and request for safety and effectiveness data in 2005 for a TEA active ingredient (70 FR 72447, December 5, 2005) and to date, FDA has not received data or a response from the sponsor. Without an established deadline for submitting data or otherwise responding to an Agency request, a sponsor may never submit the requested data and a TEA condition may remain unresolved. To better utilize FDA resources as well as to address the withdrawal of consideration of a TEA or a safety and effectiveness data submission, the Agency is proposing to amend § 330.14 to add paragraph (k) to address such withdrawal of consideration.

In § 330.14(k)(1), we propose that FDA may withdraw consideration of a TEA or safety and effectiveness data submission if: (1) the sponsor requests that its submission be withdrawn from consideration, or (2) FDA deems the submission to be withdrawn from consideration due to

the sponsor's failure to act on the submission or failure to respond to communications from FDA. For purposes of this provision, withdrawal of consideration of a TEA would include the withdrawal of consideration of a TEA condition that had been found to be eligible, but for which a safety and effectiveness data submission is not received by the Agency. If a sponsor requests withdrawal of consideration for its TEA or safety and effectiveness data submission, FDA generally intends to stop its review. However, we note that while FDA may withdraw consideration of a TEA or safety and effectiveness determination, we may determine not to do so in some cases. For example, if FDA has already issued a proposed rule that tentatively determines that the active ingredient or other condition is GRASE for OTC use, or is not GRASE for OTC use, FDA may continue to rely on the information submitted to the docket and proceed to issue a final rule.

In § 330.14(k)(2), we propose that FDA will notify the sponsor of a submission that FDA intends to deem withdrawn under paragraph (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 and request additional time needed to submit relevant data and information. For example, a sponsor may request that FDA not withdraw consideration of a safety and effectiveness data submission to allow the submission of new safety or effectiveness data to the record if the sponsor needs additional time to conduct a study and submit the data. If, within 30 days of FDA's notice, the sponsor requests that FDA not withdraw consideration under proposed § 330.14(k)(1)(ii), we will continue to consider the submission. If we continue to consider the submission, that does not preclude the possibility of withdrawing consideration under § 330.14(k)(1) at a later time. FDA recommends that sponsors keep FDA

apprised of the anticipated timing for submission of requested data to facilitate the review process and better utilize FDA resources.

In § 330.14(k)(3), FDA proposes to clarify that if consideration of a TEA or safety and effectiveness data submission is withdrawn, information that has been posted to the public docket for the TEA at the time of the withdrawal (such as an NOE or a safety and effectiveness data submission that has been accepted for filing and posted to the docket) will remain on the public docket. The TEA process is primarily a public process and withdrawal of consideration of a TEA or safety and effectiveness data submission will not cause previously public information to be removed from the docket. We also note that the original sponsor or other interested parties may wish to pursue review of the active ingredient or other condition at some point in the future. In that case, a new safety and effectiveness data submission may be submitted for the same active ingredient or other condition after consideration of the original submission has been withdrawn. If the Agency has already issued an NOE that determined that the active ingredient or other condition is eligible for review under the TEA process, another interested party may submit safety and effectiveness data for the eligible condition for the Agency's review.

In § 330.14(k)(4), FDA proposes that if a TEA or safety and effectiveness data submission being reviewed in accordance with § 330.15 is withdrawn, the timelines under § 330.15(c) and the metrics under § 330.15(b) no longer apply.

#### 4. Minor Changes to § 330.14 for Clarity and Consistency

FDA is proposing to reorganize paragraph (a) of § 330.14 to create an introductory paragraph that includes the current text under § 330.14(a), except for the definitions of “condition” and “botanical drug substance,” which would be moved to the proposed definitions section in § 330.14(a). FDA is proposing to eliminate the paragraph heading “introduction,” and

in its place, propose the paragraph heading “definitions” and a statement that the definitions that follow apply to this section and § 330.15. Under this new heading, FDA is proposing to include the definitions and current text for the terms “condition” and “botanical drug substance.” FDA is also proposing to add to the end of the introductory paragraph of § 330.14 a sentence stating that § 330.15 sets forth timelines for FDA review and action.

FDA is proposing several minor amendments to § 330.14(f) for clarity and for consistency with the OTC monograph regulations under § 330.10.

- FDA is proposing to revise paragraph (f) to use terminology consistent with the new definition in § 330.14(a)(5) for “safety and effectiveness data submission” when referring to the data package submitted by the sponsor.
- FDA is proposing to revise the first sentence and add the second sentence to differentiate between, in the NOE, requesting the safety and effectiveness data submission from the sponsor, and requesting data and views from other interested parties.
- FDA is proposing to add a sentence that references the new filing determination requirements at proposed new § 330.14(j) and makes clear that the safety and effectiveness data submission must be sufficiently complete to be filed by the Agency under proposed paragraph (j)(2).
- FDA is proposing to add a sentence that references the requirements for compliance with good laboratory practices, institutional review board, informed consent, and financial certification or disclosure statement requirements, under § 330.10(c), (e), and (f), and makes clear that those requirements also apply to the safety and effectiveness data and information submitted under this paragraph.

This proposed sentence does not impose new requirements. The sentence was added for clarity and consistency with § 330.10.

FDA is proposing 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).

## VI. Proposed Effective Date

The SIA directs the Agency to issue a final rule regarding the timelines and metrics described in section 586F(b) of the FD&C Act within 27 months after the enactment of the SIA (by February 26, 2017). The SIA also requires that the final rule be published not less than 30 calendar days before the effective date of the regulation. Consequently, the final rule implementing the timeline and metrics provisions of section 586F(b) will become effective 30 calendar days after the date of the final rule’s publication in the Federal Register.

Beginning on that date, the timelines and metrics set forth in the regulation will apply to the review of TEAs and safety and effectiveness data submissions to which that 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 proposed 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 proposed rule. We believe that this proposed 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 proposed rule does not impose significant new economic burdens on any entity, we propose to certify that the proposed 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 proposing “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 \$144 million, using the most current (2014) Implicit Price Deflator for the Gross Domestic Product. This proposed 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 proposed rule would improve the TEA review process by establishing timelines and clarifying requirements and increase the predictability of the process.						
Costs							
Annualized	\$0.00	\$0.00	\$0.00	2015	7%	10 years	
Monetized	\$0.00	\$0.00	\$0.00	2015	3%	10 years	
\$millions/year							
Annualized					7%		
Quantified					3%		
Qualitative							
Transfers							
Federal					7%		
Annualized Monetized					3%		
\$millions/year							
From/To	From:			To:			
Other					7%		
Annualized Monetized					3%		
\$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 new drug application (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 supports 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 as GRASE and not misbranded. In contrast with the application pathway, once a sponsor 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 (21 CFR 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 multi-step, 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 proposed rule 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. The proposed rule allows for public comments and for sponsors and other interested parties 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, etc.).

Although our multi-step TEA process allows sponsors to learn about the progress of our review of an application (for example when an NOE is issued, and if a feedback letter is issued), there are no established timelines to review applications or for sponsors to submit data. The lack of timelines can create unpredictability for interested parties 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 sponsors 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. For example, if a TEA remains inactive for a significant amount of time, scientific knowledge may evolve thus creating the need to amend the original TEA. Without specific timelines sponsors may not know whether their initial data submission was insufficient to review, was sufficient but is under review, or whether we require additional information. In addition, without specific timelines, we don't know if sponsors intend to submit additional data or whether they do not intend to pursue their application any further.

## 2. Purpose of this Proposed Rule

This proposed rule complies with certain mandates of the Sunscreen Innovation Act (Pub. L. 113-195), enacted in November 2014. In particular, the proposed rule would establish

timelines and metrics for review of TEAs for non-sunscreen OTC drug products. Specific timelines applicable to non-sunscreen TEA conditions would be added in a new section to Title 21 of the CFR, § 330.15. The first proposed timeline is to issue a Notice of Eligibility or a post a letter of ineligibility to the TEA docket within 180 days of submission of a TEA. The second proposed timeline is to issue a filing determination within 90 days of receipt of a complete safety and effectiveness data submission from the sponsor once such sponsor 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 interested parties within 730 days from the date of filing as defined in proposed § 330.14(a). The next proposed timeline is to issue a notice of proposed rulemaking (NPRM) within 1,095 days from the date of filing. Lastly, we propose to issue a final rule within 912 days of the closing of the docket of the proposed rulemaking.

The proposed rule would 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 by (2) addressing withdrawal of consideration of a TEA or safety and effectiveness data submission. These amendments would apply to all TEAs, and their goal is to provide early notification to sponsors whether their applications meet the filing requirements and to provide more clarity regarding withdrawal of a TEA-related submissions. The proposed amendments are intended to provide us with feedback from sponsors whether they intend to actively pursue their applications, and specify that we may withdraw consideration of a TEA or safety and effectiveness data submission in certain circumstances (such as at a sponsor's request or after prolonged inaction and lack of response to FDA

communications). Finally, the proposed rule would also add definitions and make clarifying changes to the TEA regulation in § 330.14.

The proposed clarifications and establishment of timelines for the TEA process seek to dissipate uncertainties that may be preventing interested parties from submitting all the necessary data for us to grant final GRASE determination 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, January 23, 2002), we have received six TEAs for non-sunscreen active ingredients, including applications for dandruff, laxative, anti-gingivitis, and anti-acne products. However, we have not yet issued a proposed rule regarding whether any of these ingredients are GRASE under specified conditions of use. In fact, as of December 2015, the sponsor of one of these TEAs has not yet submitted safety and effectiveness data for our review.

### 3. Benefits

We lack data to quantify the potential benefits of the proposed rule. With the proposed rule, we expect the proposed timelines and data submission clarifications would make the TEA process, including establishing a new OTC drug monograph, more efficient and predictable, and improve communication between us and sponsors. Sponsors may benefit from knowing if additional data is needed and what optimal steps to take to receive a GRASE determination, and we would be able to bring resolution to TEA conditions. However, we do not know the monetary value of added predictability to sponsors. Also, because we have not yet issued tentative GRASE determinations for any of the non-sunscreen TEA conditions under review, as of December 2015, and because we do not know the increase in the probability of granting

tentative GRASE determinations resulting from the proposed rule, we request comment on the potential benefits of the proposed rule.

#### 4. Costs

This proposed rule supplements the TEA process. We expect the rule would create a minimal burden on sponsors 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 sponsor would like to meet with us to discuss the decision, or the possible cost of calling or writing FDA to request that we not withdraw consideration of a submission in the event that we deem a submission withdrawn under proposed 330.14(k)(ii). Therefore, we anticipate no increase in annual recurring costs for either small or large sponsors.

We expect the six current sponsors would spend time reading and understanding the proposed rule, and this would take from about 6.5 hours to 13 hours. With an hourly wage rate of \$133 including 100 percent overhead, each sponsor would incur one-time costs ranging from about \$865 to \$1,730. We also estimate that we would receive two additional TEAs annually, and thus during a 10-year horizon we estimate potentially twenty additional applicants would spend the time to read and understand the proposed 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 would incur less than \$150 of annualized costs per year.

#### 5. Impact on Small Entities

The Regulatory Flexibility Act requires a Regulatory Flexibility Analysis (RFA) unless the Agency can certify that the proposed rule would have no significant impact on a substantial

number of small entities. The proposed rule would 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, and we propose to certify that the rule would not have a significant economic impact on a substantial number of small entities.

We invite comments on this 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 proposed rule contains information collection provisions that are subject to review by OMB under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). The title, description, and respondent description of the information collection are given under this section 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 the collection of information.

We invite comments on these topics: (1) Whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the

use of automated collection techniques, when appropriate, and other forms of information technology.

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

Description: The proposed rule would amend 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 also proposes other changes to make the TEA process more efficient.

FDA has OMB approval (Control Number 0910-0688) for the information collection in 21 CFR 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 proposed rule would amend the TEA regulations in §330.14 to make the process more efficient and to make conforming and clarifying changes. Proposed §330.14(j) would clarify the requirements on content and format criteria for a safety and effectiveness data submission, and would provide procedures for FDA's review of the submissions and determination of whether a submission is sufficiently complete to permit a substantive review. Proposed §330.14(j)(3) would describe the process for cases in which FDA refuses to file the safety and effectiveness data submission. Under proposed §330.14(j)(3), if FDA refuses to file the submission, the Agency will notify the sponsor in writing, state the reason(s) for the refusal, and provide the sponsor with 30 days in which to submit a written request for an informal conference with the Agency about whether the Agency should file the submission. A sponsor's

submission of a written request for an informal conference is not already approved under OMB Control Number 0910-0688. We estimate that approximately one sponsor (“number of respondents” in table 2, row 1) will annually submit to FDA approximately one request for an informal conference (“total annual responses” in table 2, row 1), and that preparing and submitting each request will take approximately one hour for each sponsor (“average burden per response” in table 2, row 1).

Under proposed §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 sponsor at the time of the submission, whether positive or negative. A sponsor’s signed statement is not already approved under OMB Control Number 0910-0688. We estimate that approximately two sponsors (“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 for each sponsor (“average burden per response” in table 2, row 2).

Under proposed § 330.14(k)(1), FDA, in response to a written request from a sponsor, may withdraw consideration of a TEA submitted under § 330.14(c) or a safety and effectiveness data submission submitted under § 330.14(f). A sponsor’s 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 sponsor (“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 one hour for each sponsor (“average burden per response” in table 2, row 3).

Under proposed § 330.14(k)(2), a sponsor may request that FDA not withdraw consideration of a TEA or safety and effectiveness data submission. A sponsor’s 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 sponsor (“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 for each sponsor (“average burden per response” in table 2, row 4).

FDA estimates the burden of this information collection as follows:

Table 2.--Estimated Annual Reporting Burden<sup>1</sup>

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

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

In compliance with the PRA (44 U.S.C. 3507(d)), we have submitted the information collection requirements of this proposed rule to OMB for review. Interested persons are requested to send comments on this information collection to the Office of Information and Regulatory Affairs, OMB (see ADDRESSES).

## X. Federalism

We have analyzed this proposed 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 proposed rule is section 751 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 379r).

We believe that the preemptive effect of this proposed rule, if finalized, would be consistent with Executive Order 13132. Through the publication of this proposed rule, we are providing notice and an opportunity for State and local officials to comment on this rulemaking.

## XI. References

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

1. FDA, Guidance for Industry, “Time and Extent Applications for Nonprescription Drug Products,” September 2011, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078902.pdf>.
2. Office of the Federal Register, “A Guide to the Rulemaking Process,” 2011, available at [https://www.federalregister.gov/uploads/2011/01/the\\_rulemaking\\_process.pdf](https://www.federalregister.gov/uploads/2011/01/the_rulemaking_process.pdf).
3. GAO, “Federal Rulemaking, Improvements Needed to Monitoring and Evaluation of Rules Development as Well as to the Transparency of OMB Regulatory Reviews,” April 2009 (GAO-09-205), available at <http://www.gao.gov/assets/290/288538.pdf>.
4. 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>.
5. Examples of FDA internet pages that include progress reports or other metrics include: FDA’s FDA-TRACK webpage, <http://www.fda.gov/AboutFDA/Transparency/track/ucm195010.htm>; FDA’s “Sunscreen Innovation Act (SIA)” webpage, <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ucm434782.htm> , and FDA’s “Rulemaking History for OTC Time and Extent Applications” webpage, <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Over-the-CounterOTCDrugs/StatusofOTCRulemakings/ucm072455.htm>.

Over-the-counter drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, we propose that 21 CFR part 330 be 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) introductory text and (g)(4);
- 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) 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.

(2) 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.

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

(4) 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.

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

(6) Date of filing means the date of the notice from FDA informing the sponsor 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 informing the sponsor that FDA has filed the submission over protest (this date will be no later than 30 days after the sponsor's request that FDA file the submission over protest).

(7) 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 parties 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).

\* \* \* \* \*

(f) Safety and effectiveness data submission. The notice of eligibility shall request that the sponsor submit 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). The notice of eligibility will also request data and views from other interested parties. These data shall be submitted to a docket established in the Division of Dockets Management and shall 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 shall 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 parties 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 sponsor in writing. The date of filing begins the FDA timelines described in § 330.15(c)(3) and (4).

(3) If FDA refuses to file the safety and effectiveness data submission, the agency will notify the sponsor in writing and state the reason(s) under paragraph (j)(4) of this section for the refusal. The sponsor may request in writing, within 30 days of the date of the agency's notification, an informal conference 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 informal conference, the sponsor 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 sponsor in writing, and

review it as filed. The sponsor need not resubmit a copy of a safety and effectiveness data submission that is filed over protest.

(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 if 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 sponsor 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 it 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 it 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 it 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) FDA may withdraw consideration of a TEA submission or a safety and effectiveness data submission if:

(i) The sponsor requests that its submission be withdrawn from consideration, or  
(ii) FDA deems the submission to be withdrawn from consideration due to the sponsor's failure to act on the submission or 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 sponsor of the submission. If, within 30 days from the date of the notice

from FDA, the sponsor 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. Information that has been posted to the public docket for the TEA 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 on the public docket.

(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 prior to 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 by the sponsor of a safety and effectiveness data submission, FDA will issue a filing determination in accordance with § 330.14(j). 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 parties 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: March 29, 2016.

Leslie Kux,

Associate Commissioner for Policy.

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