are contacted by BEA. Also, a person, or their agent, who is contacted by BEA about reporting in this survey, either by sending them a report form or by written inquiry, must respond in writing pursuant to this section. This may be accomplished by filing the properly completed BE–13 report (BE–13A, BE–13B, BE–13D, BE–13E, or BE–13 Claim for Exemption).

(b) *Who must report.* A BE–13 report is required of any U.S. business enterprise, except certain private funds, see exception in item (b.4.), in which:

(1) A foreign direct investment in the United States relationship is created;

(2) An existing U.S. affiliate of a foreign parent establishes a new U.S. business enterprise, expands its U.S. operations, or acquires a U.S. business enterprise, or;

(3) BEA requests a cost update (Form BE–13E) for a U.S. business enterprise that previously filed Form BE–13B or BE–13D.

(4) Certain private funds are exempt from reporting on the BE–13 survey. If a U.S. business enterprise is a private fund and does not own, directly or indirectly, 10 percent or more of another business enterprise that is not also a private fund or a holding company, it is not required to file any BE–13 report except to indicate exemption from the survey if contacted by BEA.

(c) *Forms to be filed.* Depending on the type of investment transaction, U.S. affiliates would report their information on one of five forms—BE–13A, BE–13B, BE–13D, BE–13E, or BE–13 Claim for Exemption.

(1) Form BE–13A—Report for a U.S. business enterprise when a foreign entity acquires a voting interest (directly, or indirectly through an existing U.S. affiliate) in that U.S. business enterprise including segments, operating units, or real estate; and

(i) The total cost of the acquisition is greater than $3 million; and

(ii) By this acquisition, the foreign entity now owns at least 10 percent of the voting interest (directly, or indirectly through an existing U.S. affiliate) in the acquired U.S. business enterprise.

(2) Form BE–13B—Report for a U.S. business enterprise when it is established by a foreign entity or by an existing U.S. affiliate of a foreign parent; and

(i) The expected total cost to establish the new U.S. business enterprise is greater than $3 million; and

(ii) The foreign entity owns at least 10 percent of the voting interest (directly, or indirectly through an existing U.S. affiliate) in the new U.S. business enterprise.

(3) Form BE–13D—Report for an existing U.S. affiliate of a foreign parent when it expands its operations to include a new facility where business is conducted and the expected total cost of the expansion is greater than $3 million.

(4) Form BE–13E—Report for a U.S. business enterprise that previously filed Form BE–13B or BE–13D. Form BE–13E collects updated cost information and will be collected annually for three years after the year of the establishment or expansion of the U.S. business enterprise.

(5) Form BE–13 Claim for Exemption—Report for a U.S. business enterprise that:

(i) was contacted by BEA but does not meet the requirements for filing Forms BE–13A, BE–13B, or BE–13D; or

(ii) whether or not contacted by BEA, met all requirements for filing Forms BE–13A, BE–13B, or BE–13D except the $3 million reporting threshold.

(d) *Due date.* The BE–13 forms are due no later than 45 calendar days after the acquisition is completed, the new U.S. business enterprise is established, the expansion is begun, the cost update is requested, or a notification letter is received from BEA by a U.S. business enterprise that does not meet the filing requirements for the survey.

[FR Doc. 2022–13713 Filed 6–27–22; 8:45 am]

BILLING CODE 3510–06–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 201 and 314

[Docket No. FDA–2021–N–0862]

RIN 0910–AH62

Nonprescription Drug Product With an Additional Condition for Nonprescription Use

AGENCY: Food and Drug Administration, Department of Health and Human Services (HHS).

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA, the Agency, or we) is proposing to establish requirements for a nonprescription drug product with an additional condition for nonprescription use (ACNU). The proposed rule, if finalized, would establish requirements for a nonprescription drug product that has an ACNU that an applicant must implement to ensure appropriate self-selection or appropriate actual use, or both, by consumers without the supervision of a healthcare practitioner. The proposed rule is intended to increase options for applicants to develop and market safe and effective nonprescription drug products, which could improve public health by broadening the types of nonprescription drug products available to consumers.

DATES: Either electronic or written comments on the proposed rule must be submitted by October 26, 2022. Submit comments (including recommendations) on information collection issues under the Paperwork Reduction Act of 1995 by July 28, 2022.

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. The *https://www.regulations.gov* electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of October 26, 2022. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are received on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

- *Federal eRulemaking Portal: https://www.regulations.gov*. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to *https://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 *https://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):* Dockets Management Staff (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

• For written/paper comments submitted to the Dockets Management Staff, 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–2021–N–0862 for ''Nonprescription Drug Product with an Additional Condition for Nonprescription Use.'' Received comments, those filed in a timely manner (see **ADDRESSES**), will be placed in the docket and, except for those submitted as ''Confidential Submissions,'' publicly viewable at *https://www.regulations.gov* or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240–402–7500.

• 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 *https://www.regulations.gov*. Submit both copies to the Dockets Management Staff. 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: *https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf*.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to *https://www.regulations.gov* and insert the docket number, found in brackets in the heading of this document, into the ''Search'' box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240–402–7500.

Submit comments on information collection issues under the Paperwork Reduction Act of 1995 to the Office of Management and Budget (OMB) at *https://www.reginfo.gov/public/do/PRAMain.* Find this particular information collection by selecting ''Currently Under Review—Open for Public Comments'' or by using the search function. The title of this proposed collection is ''Premarket applications, postmarketing reports and recordkeeping, and labeling for Nonprescription Drug Products With an Additional Condition for Nonprescription Use.''

FOR FURTHER INFORMATION CONTACT:

With regard to the proposed rule: Chris Wheeler, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 3330, Silver Spring, MD 20993–0002, 301–796–0151, *Chris.Wheeler@fda.hhs.gov.*

With regard to the information collection: Domini Bean, Office of Operations, Food and Drug Administration, Three White Flint North, 10A–12M, 11601 Landsdown St., North Bethesda, MD 20852, 301–796–5733, *PRAStaff@fda.hhs.gov.*

SUPPLEMENTARY INFORMATION:

Table of Contents

I. Executive Summary

A. Purpose of the Proposed Rule

FDA is proposing to establish requirements for a nonprescription drug product with an additional condition for nonprescription use (ACNU), which is a drug product that could be marketed without a prescription if an applicant implements an additional condition to ensure appropriate self-selection or appropriate actual use, or both, by consumers without the supervision of a healthcare practitioner. Currently, nonprescription drug products are limited to drugs that can be labeled with sufficient information for consumers to appropriately self-select and use the drug product. For certain drug products, limitations of labeling present challenges for adequate communication of information needed for consumers to appropriately self-select or use the drug product without the supervision of a healthcare practitioner. The proposed rule is intended to increase options for applicants to develop and market safe and effective nonprescription drug products, which could improve public health by broadening the types of nonprescription drug products available to consumers.

B. Summary of the Major Provisions of the Proposed Rule

The proposed rule, if finalized, would establish requirements for a nonprescription drug product with an ACNU. The evidentiary standards that an application must meet under the Federal Food, Drug, and Cosmetic Act (FD&C Act) and current FDA regulations for demonstrating safety and effectiveness would continue to apply to nonprescription drug products approved with an ACNU. This proposed rule would establish additional application requirements, labeling requirements, and postmarketing reporting requirements for a nonprescription drug product with an ACNU.

The proposed rule would establish the requirements for a new drug application (NDA) or abbreviated new drug application (ANDA) for a nonprescription drug product with an ACNU. An applicant would be required

to submit a separate application for the approval of a nonprescription drug product with an ACNU, rather than a supplement to an application approved as a prescription drug product. In addition to applicable existing application requirements, NDA applicants would also be required to describe the ACNU and submit information to support the ACNU.

The proposed rule would clarify that an ACNU would constitute a meaningful difference between a prescription drug product and a nonprescription drug product that makes the nonprescription drug product safe and effective for use without the supervision of a healthcare practitioner licensed by law to administer the drug. For instance, two drug products could have the same active ingredient, dosage form, strength, route of administration, and indication, with one made available as a nonprescription drug product with an ACNU and the other product made available only by prescription.

The proposed rule would specify that FDA would refuse to approve an NDA or ANDA for a nonprescription drug product with an ACNU if the application fails to meet the applicable requirements of proposed § 314.56 (21 CFR 314.56).

The proposed rule would establish postmarketing reporting requirements for a nonprescription drug product with an ACNU. NDA and ANDA applicants would be required to submit a report with information concerning any incident of failure in the implementation of an ACNU, such as a consumer gaining access to the drug product without fulfilling the ACNU.

C. Legal Authority

FDA's proposal to establish requirements for a nonprescription drug product with an ACNU is authorized by sections 201(n), 502, 503(b), 505, and 701(a) of the FD&C Act (21 U.S.C. 321(n), 352, 353(b), 355, and 371(a)).

D. Costs and Benefits

The proposed rule, if finalized, would establish, for any applicant, the requirements for a nonprescription drug product with an ACNU. Compared to the traditional labeling paradigm of nonprescription drug products, this approved ACNU in addition to the labeling would ensure the appropriate self-selection, appropriate use, or both, of a drug product. We expect that this proposed rule, if finalized, would expand consumer access to certain drug products in a nonprescription setting.

Greater access to drug products would allow consumers to treat certain medical conditions using nonprescription drug products with an ACNU without the supervision of a healthcare practitioner. We estimate a reduction in access costs to consumers who could transfer from a prescription to a nonprescription drug product with an ACNU. Our primary estimate for this item is $26.70 with a range of $0 to $53.40 per consumer per purchase. There may also be cost savings associated with a potential reduction in the number of repetitive meetings between FDA and industry. Our primary estimate is $55,469 per applicant with a range of $45,260 to $66,174. Government and private insurance payers may also experience cost savings because the availability of nonprescription drug products with an ACNU may decrease future medical costs and the number of submitted insurance claims. In addition, we assume that applicants would submit applications when they believe that the profits from a potential approval would exceed the costs of the application. We lack information to monetize these potential profits and costs. We do not monetize our estimates of benefits over a 10-year horizon because of the high uncertainty about the number of applicants, applications, potential approvals, the number of purchases that might occur, and consumer preferences to switch products. For details, see the Preliminary Regulatory Impact Analysis (PRIA), the Uncertainty and Sensitivity section, as well as the Appendix of the same document.

Monetized costs include a one-time cost of reading and understanding the rule for those applicants potentially interested in submitting applications for their nonprescription drug products with an ACNU. Our primary estimate of these costs equals $821 with a range of $379 and $1,264 using a 7-percent discount rate annualized over a ten-year horizon.

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

Abbreviation/acronym	What it means
ACNU	Additional Condition for Nonprescription Use.
ANDA	Abbreviated New Drug Application.
DFL	Drug Facts Labeling.
FAERS	FDA Adverse Event Reporting System.
FD&C Act	Federal Food, Drug, and Cosmetic Act.
FDA	Food and Drug Administration.
ICSR	Individual Case Safety Report.
NDA	New Drug Application.
NDC	National Drug Code.
OMB	Office of Management and Budget.
OTC	Over-the-Counter.
PDP	Principal Display Panel.
RLD	Reference Listed Drug.

III. Background

A. Need for the Regulation

Nonprescription drug products are important for the treatment of many conditions and diseases, although at present most nonprescription drug products are intended to provide temporary relief of minor symptoms or self-diagnosable, self-limited conditions and diseases, rather than chronic diseases. Unlike prescription drug products, nonprescription drug products may be accessed and used safely and effectively by consumers without the supervision of a healthcare practitioner when certain conditions are met. Currently, nonprescription drug products are limited to drugs that can be labeled with sufficient information to enable consumers to appropriately self-select and use the drug product without the supervision of a healthcare practitioner. Self-selection is the decision consumers make to use or not to use a drug product based on reading the information on the drug product labeling and applying knowledge of their personal medical history (Ref. 1). Nonprescription drug products are usually available for consumers to purchase at pharmacies, supermarkets,

or other retail locations, and from online retailers.

FDA recognizes the potential benefit of providing consumers with access to additional types of nonprescription drug products, such as some drug products that are currently available only by prescription and that treat chronic diseases or conditions. However, there are certain drug products that an applicant may seek to market on a nonprescription basis where labeling alone cannot adequately communicate the information needed for consumers to appropriately self-select, use, or both self-select and use the drug product safely and effectively without the supervision of a healthcare practitioner.

The proposed rule has the potential to broaden the types of drug products that FDA could approve as nonprescription. Under the proposed rule, when labeling alone is not sufficient to ensure that the consumer can appropriately self-select or appropriately actually use, or both, a drug product correctly in a nonprescription setting, an applicant may submit an application proposing an ACNU that a consumer must successfully fulfill to obtain the nonprescription drug product with an ACNU. For example, an applicant may submit an application for a nonprescription drug product with an ACNU that enables a consumer to treat a chronic condition that currently does not have a nonprescription treatment. The availability of nonprescription drug products with an ACNU may provide public health benefits by facilitating consumers' self-care and autonomy over their medical treatment (Ref. 2).

B. FDA's Current Regulatory Framework

There are two regulatory pathways to bring a nonprescription drug product to market in the United States: (1) the over-the-counter (OTC) drug review process under section 505G of the FD&C Act (21 U.S.C. 355h); and (2) the new drug application process under section 505 of the FD&C Act. Under the OTC drug review process, a nonprescription drug product may be marketed without an approved NDA or ANDA under section 505 of the FD&C Act if the nonprescription drug product meets the requirements of section 505G of the FD&C Act, and other applicable requirements.

FDA approves drugs as either prescription or nonprescription drug products under section 505 of the FD&C Act. A drug must be dispensed by prescription when it is not safe for use except under the supervision of a healthcare practitioner licensed by law to administer such drug product because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use (see section 503(b)(1) of the FD&C Act). If the approved drug does not meet the criteria for prescription-only dispensing, it may be marketed as nonprescription.

Section 503(b)(4)(B) of the FD&C Act provides that a drug product to which the prescription provisions of the FD&C Act do not apply (*i.e.,* a nonprescription drug product) will be deemed to be misbranded if at any time before dispensing, the label of the drug bears the ''Rx only'' symbol. Read together with section 503(b)(4)(A) of the FD&C Act, which requires prescription drug products to bear the ''Rx only'' symbol, this effectively means that absent a meaningful difference between the products, simultaneous marketing of two drug products with the same active ingredient as both a prescription and a nonprescription drug would result in one of the two products being misbranded. Examples of meaningful differences that can make a prescription drug product safe and effective only under the supervision of a healthcare practitioner licensed by law to administer such drug include the indication, strength, route of administration, dosage form, or patient population (see 83 FR 13994 at 13995, April 2, 2018; see also 70 FR 52050, September 1, 2005).

An applicant may submit an NDA for a nonprescription drug product using the pathways described in section 505(b)(1) or (2) of the FD&C Act to market a new drug product. A 505(b)(1) NDA includes full reports of investigations to demonstrate that the proposed drug product is safe and effective under the conditions prescribed, recommended, or suggested in its proposed labeling (see sections 505(d) and (b)(1) of the FD&C Act). Thus, an NDA for a nonprescription drug product must include, among other things, information to demonstrate that consumers can appropriately self-select and use the proposed drug product safely and effectively without the supervision of a healthcare practitioner. An NDA submitted under section 505(b)(2) of the FD&C Act also includes information to demonstrate that the proposed drug product is safe and effective under the conditions prescribed, recommended, or suggested in its proposed labeling, but at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use (21 U.S.C. 355(b)(2)).

Applicants may submit an ANDA using the pathway described in section 505(j) of the FD&C Act for a drug product that is a generic version of a previously approved drug product. An ANDA for a nonprescription drug product generally references a nonprescription drug product previously approved under section 505(c) of the FD&C Act (known as the RLD) and relies on the Agency's finding that the RLD is safe and effective. An ANDA generally must contain information to show that the proposed generic product (1) is the same as the RLD with respect to the active ingredient(s), conditions of use, route of administration, dosage form, strength, labeling (with certain permissible differences) and (2) is bioequivalent to the RLD. The procedures and requirements for the submission and approval of NDAs, ANDAs, and supplements to those applications are provided in part 314 (21 CFR part 314).

Generally, nonprescription drug products must be labeled with adequate directions for use so the consumer: (1) can use the drug product safely and for the purposes for which it is intended and (2) make an appropriate self-selection decision and appropriately use the nonprescription drug product (see section 502(f)(1) of the FD&C Act and § 201.5 (21 CFR 201.5)). Consumer studies can help demonstrate that the requirement for adequate directions for use is met. These studies may include label comprehension studies (Ref. 3), self-selection studies (Ref. 1), actual-use studies, and other human factors studies.

Nonprescription drug products must also comply with applicable labeling requirements under part 201 (21 CFR part 201), including the format and content requirements for OTC drug product labeling under § 201.66. Labeling created to satisfy the requirements in § 201.66 is commonly referred to as the Drug Facts labeling (DFL). The DFL is intended to enable consumers to appropriately self-select and use the nonprescription drug product safely and effectively. In addition to the DFL, FDA may approve additional labeling for nonprescription drug products.

C. History of the Rulemaking

FDA has received a number of inquiries from stakeholders about whether applications may be submitted for nonprescription drug products with one or more additional conditions that consumers must fulfill to ensure that the drug product is safe and effective for nonprescription use. As explained in detail below, FDA held a public hearing

and participated in a series of workshops convened by the Engelberg Center for Health Care Reform at the Brookings Institution (Brookings Institution) to solicit public input on expanding the approval of nonprescription drug products. FDA used stakeholder input from the public hearing and the workshops to develop the proposed rule.

1. FDA 2012 Public Hearing

In the **Federal Register** of February 28, 2012 (77 FR 12059), FDA announced a public hearing under part 15 (21 CFR part 15) entitled ''Using Innovative Technologies and Other Conditions of Safe Use to Expand Which Drug Products Can Be Considered Nonprescription'' (2012 public hearing). FDA held this public hearing on March 22 and 23, 2012, to: (1) seek input from interested stakeholders on a potential new paradigm where FDA would approve certain drug products for nonprescription use with certain conditions specific to a drug product that would otherwise require a prescription and (2) obtain information and comments on the feasibility of this paradigm and its potential benefits and costs. As part of the public hearing, FDA requested information and public comment on the types of technology that could be used; the types of conditions of safe use; and the potential impacts on pharmacies, consumers, and healthcare practitioners, as well as other issues that might arise under the paradigm. FDA received comments from various stakeholders, including consumers, private industry, healthcare professional associations, academic institutions, and patient advocacy organizations, on a broad range of topics such as: (1) access to care, (2) medication nonadherence, (3) practitioner oversight, (4) potential effect on healthcare and healthcare costs, (5) potential impact on medical conditions or diseases, (6) use of diagnostic aids and technologies as possible conditions of safe use, and (7) potential barriers to successful implementation and adoption (see Docket No. FDA–2012–N–0171).

2. Brookings Institution Workshops

The Brookings Institution convened a series of three expert workshops, based on a cooperative agreement with FDA, to seek stakeholder feedback on practical considerations for the development of a new paradigm focused on developing innovative approaches for consumers to self-select nonprescription drug products appropriately and maintain their safe and effective use and to explore potential practical strategies. Participants included a diverse set of stakeholders from both public and private sectors, including FDA and other Government agencies, healthcare professional associations, trade associations, technology developers, pharmaceutical manufacturers, healthcare professionals, academic institutions, retail pharmacy representatives, and patient advocacy organizations.

On November 8, 2012, the Brookings Institution convened the first expert workshop, ''Nonprescription Medications With Conditions of Safe Use as a Novel Solution for Undertreated Diseases or Conditions.'' This workshop explored issues and practical considerations for the development of this new paradigm (Ref. 4).

On May 9, 2013, the Brookings Institution held the second expert workshop, ''Innovative Technologies and Nonprescription Medications: Addressing Undertreated Diseases and Conditions Through Technology Enabled Self-Care.'' This workshop explored the potential for innovative technologies to facilitate safe and effective use of nonprescription drug products (Ref. 5).

On November 4, 2013, the Brookings Institution held the final expert workshop, ''Exploring Implications of the Nonprescription Drug Safe Use Regulatory Expansion Initiative on Reimbursement and Access.'' This workshop focused on assessing this paradigm's potential impact on consumer access and reimbursement (Ref. 6).

3. Innovative Approaches for Nonprescription Drug Products; Draft Guidance for Industry

In the **Federal Register** of July 18, 2018 (83 FR 33938), FDA published a notice of availability of a draft guidance entitled ''Innovative Approaches for Nonprescription Drug Products'' and established Docket No. FDA–2018–D–2281. This draft guidance describes two innovative approaches that may be useful for applicants to consider in cases where the DFL alone is not sufficient to ensure that a drug product can be used safely and effectively in a nonprescription setting. These approaches include the development of labeling in addition to the DFL and the implementation of additional conditions so that consumers can appropriately self-select and use the product.

IV. Legal Authority

FDA's proposal to establish requirements for a nonprescription drug product with an ACNU is authorized by sections 201(n), 502, 503(b), 505, and 701(a) of the FD&C Act (21 U.S.C. 321(n), 352, 353(b), 355, and 371(a)). Section 502(f) of the FD&C Act deems a drug to be misbranded unless its labeling bears adequate directions for use and adequate warnings against use in those conditions where its use may be dangerous to health, as well as adequate warnings against unsafe dosage or methods or duration of administration or application, in such manner and form, as are necessary for the protection of users. Section 502(f) also authorizes the promulgation of regulations exempting a drug or device from the requirement to bear adequate directions for use upon a determination that such directions are not necessary for the protection of public health.

We are proposing to add an exemption for human nonprescription drug products approved with an ACNU from the requirement in section 502(f)(1) of the FD&C Act for drug products to have labeling that provides adequate directions for use (see proposed § 201.130). When labeling alone cannot provide adequate directions for use for a human nonprescription drug product, FDA may approve the nonprescription drug product with an ACNU under proposed § 314.56.

In addition, section 502(a) of the FD&C Act deems a drug to be misbranded if its labeling is false or misleading in any particular. Under section 201(n) of the FD&C Act, in determining whether labeling is misleading, there shall be taken into account (among other things), not only representations made or suggested but also the extent to which the labeling fails to reveal facts material in the light of such representations or material with respect to consequences that may result from the use of the drug under the conditions of use prescribed in the labeling or under usual or customary conditions of use.

In addition, under section 505 of the FD&C Act, FDA will approve an NDA only if the drug is shown to be both safe and effective for use under the conditions prescribed, recommended, or suggested in the proposed labeling for the product. See section 505(c)(1) and (d) of the FD&C Act. If, for example, on the basis of information submitted as part of the application or on the basis of any other information before the Agency with respect to such drug, there is insufficient information to determine whether such drug is safe for use under such conditions, the Agency will not approve the drug. Section 505(j) of the FD&C Act describes the requirements

for ANDAs. In particular, section 505(j)(2)(A) specifies the information that must be included in an ANDA, and section 505(j)(4) describes the approval standard for an ANDA.

In addition, section 503(b) of the FD&C Act contains provisions regarding the marketing of a drug as either a prescription drug product or a nonprescription drug product.

Finally, section 701(a) of the FD&C Act authorizes FDA to issue regulations for the efficient enforcement of the FD&C Act.

V. Description of the Proposed Rule

We are proposing to add § 314.56 to part 314, subpart B, to establish additional application requirements for a nonprescription drug product with an ACNU under an NDA or an ANDA. The evidentiary standards that an NDA for a nonprescription drug product must meet under the FD&C Act and current FDA regulations to demonstrate the safety and effectiveness of the drug product would apply to a nonprescription drug product approved with an ACNU. An ANDA referencing a nonprescription drug product with an ACNU previously approved under an NDA may rely on FDA's finding that the listed drug product is safe and effective for use under the conditions described in the labeling. We are proposing to add § 314.125(b)(20) to part 314, subpart D, to specify that FDA would refuse to approve an NDA for a nonprescription drug product with an ACNU that does not meet the applicable requirements established in § 314.56. We are also proposing to add § 314.127(a)(15) to part 314, subpart D, to specify that FDA would refuse to approve an ANDA for a nonprescription drug product with an ACNU that does not meet the applicable requirements established in § 314.56. We are proposing to add § 314.81(b)(3)(v) to part 314, subpart B, to establish postmarketing reporting requirements for a nonprescription drug product with an ACNU. We are also proposing to add § 201.67 to part 201, subpart C, to establish labeling requirements for a nonprescription drug product with an ACNU. We are proposing to add § 201.130 to part 201, subpart D, to establish an exemption from the statutory requirement for adequate directions for use for a nonprescription drug product with an ACNU. The proposed rule is intended to increase options for applicants to develop and market safe and effective nonprescription drug products, which could improve public health by broadening the types of nonprescription drug products available to consumers. For example, FDA may approve a nonprescription drug product with an ACNU to treat a chronic condition that currently does not have nonprescription treatments.

A detailed description of each proposed section is provided in sections V.A through V.K of this document.

A. Applicability

The proposed rule would apply to NDAs and ANDAs for nonprescription drug products with an ACNU (see proposed §§ 314.56, 314.81, 314.125, 314.127, 201.67, and 201.130). Nonprescription drug products currently marketed under an approved application do not need an ACNU to ensure appropriate self-selection and appropriate actual use because FDA previously determined that labeling alone is sufficient for these drugs to be used safely and effectively without a prescription. The proposed rule would not apply to nonprescription drugs marketed under section 505G of the FD&C Act. Therefore, a requestor (as defined in section 505G(q)(3) of the FD&C Act) cannot submit a request under section 505G(b) of the FD&C Act for a nonprescription drug product with an ACNU.

B. Definitions (Proposed §§ 314.56(a) and 201.67(b))

We are proposing to define the term ''additional condition for nonprescription use'' (ACNU) as one or more FDA-approved conditions that an applicant of a nonprescription drug product must implement to ensure consumers' appropriate self-selection or appropriate actual use, or both, of the nonprescription drug product without the supervision of a healthcare practitioner if the applicant demonstrates and FDA determines that labeling alone is insufficient to ensure appropriate self-selection or appropriate actual use, or both (see proposed §§ 314.56(a) and 201.67(b)). If the ACNU is intended to address appropriate self-selection only, the labeling must enable appropriate actual use of the nonprescription drug product by consumers. Alternatively, if the ACNU is intended to address appropriate actual use only, the labeling must enable consumers to appropriately self-select the nonprescription drug product.

The proposed definition for an ACNU is intentionally broad to give applicants flexibility regarding the types of additional conditions applicants may propose and how those additional conditions can be implemented. For example, an applicant could propose an ACNU that requires a consumer, in order to purchase the nonprescription drug product, to respond with specific answers to a set of questions on a self-selection test available by either a mobile application or an automated telephone response system. An applicant may also propose that before purchasing the nonprescription drug product with an ACNU, a consumer be required to view labeling (for example, text or images in a video), that describes how to appropriately use the nonprescription drug product and to respond to questions to confirm understanding.

C. Separate Application Required for a Nonprescription Drug Product With an ACNU (Proposed § 314.56(b))

The proposed rule would not require a nonprescription drug product with an ACNU to be first marketed as a prescription drug product. However, in cases where there is an approved prescription drug product, the proposed rule would establish the requirement that a nonprescription drug product with an ACNU cannot be approved through a supplement to the approved prescription application. Rather, an applicant must submit a separate application for a nonprescription drug product with an ACNU. Although a separate application would be required, an applicant may cross reference information in its approved NDA for the prescription product and would not need to duplicate studies already conducted for and submitted in its NDA for the prescription product. As explained in Section III.B., a different applicant may submit an NDA under section 505(b)(2) of the FD&C Act, where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use. This is provided the 505(b)(2) applicant establishes that the relied upon NDA or literature is relevant to its nonprescription drug product with an ACNU and its application includes support for any differences between the applicant's proposed drug product and the listed drug on which the applicant is relying to demonstrate the safety and effectiveness of the proposed nonprescription drug product with an ACNU.

As explained in section V.E of this document, the approved prescription drug product and the approved nonprescription drug product with an ACNU are two different products and could be simultaneously marketed.

Requiring a separate application for the nonprescription drug product with an ACNU would enable continued marketing of the prescription product under the original NDA and would

allow it to serve as an RLD for ANDAs for the prescription product. Continued access to the prescription drug product, along with availability of the nonprescription drug product approved with an ACNU, would ensure greater access to needed drugs by providing flexibility in how to obtain them. For example, if a nonprescription drug product approved with an ACNU is available through a kiosk in a pharmacy, patients who do not live near a pharmacy with such a kiosk may find it easier to obtain the drug through a prescription.

Additionally, patients who prefer to continue interacting with their healthcare providers and obtain the drug by prescription would have that option. Patients who had not previously used the drug may also feel more comfortable initiating treatment and obtaining the drug with the involvement of their healthcare providers. While FDA would generally expect any technology that is used to operationalize an ACNU to be easily usable to the majority of consumers, there may be some consumers who may not be comfortable using such technology. Continued availability of the prescription drug product would provide greater flexibility in obtaining the drug and enable these patients to continue their care without potential interruption.

An applicant seeking an initial approval of an ANDA to market a nonprescription drug product with an ACNU may submit an ANDA referencing a nonprescription drug product with an ACNU previously approved under an NDA and may rely on FDA's finding that the RLD is safe and effective. This ANDA would also be required to have a separate application from an existing ANDA approved as a prescription drug product. Because the RLD nonprescription drug product with an ACNU would have a separate NDA from the NDA approved as a prescription drug product, the ANDA would be using a different NDA as its RLD from the RLD for the ANDA for the prescription product. Section 505(j)(2)(D) of the FD&C Act prohibits an applicant from amending or supplementing its ANDA to rely on a different listed drug from the listed drug identified in the ANDA submitted to FDA.

An applicant may submit an amendment, supplement, or annual report to an application for a nonprescription drug product with an ACNU, consistent with FDA regulations (§§ 314.60, 314.96, 314.70, and 314.97). An applicant seeking to make changes to an NDA or ANDA submitted for a nonprescription drug product with an ACNU that is under review by FDA would submit an amendment to the application to request a change (§§ 314.60 and 314.96). An applicant seeking to make changes to an FDA-approved NDA or ANDA for a nonprescription drug product with an ACNU would submit a supplement to the approved NDA or ANDA (§§ 314.70 and 314.97).

D. Specific Requirements for an Application for a Nonprescription Drug Product With an ACNU (Proposed § 314.56(c))

The proposed rule would establish the specific NDA and ANDA requirements for a nonprescription drug product with an ACNU (see proposed § 314.56(c)).

1. New Drug Application

In addition to applicable existing application requirements, NDA applicants would also be required to describe the ACNU and submit information to support the ACNU. Specifically, the proposed rule would require that an NDA for a nonprescription drug product with an ACNU must, when fulfilling the content and format requirements under § 314.50, include the following information about the ACNU in the application: (1) a statement regarding the purpose of the ACNU (*i.e.,* appropriate self-selection or appropriate actual use, or both, by consumers of the nonprescription drug product without the supervision of a healthcare practitioner) (see proposed § 314.56(c)(1)(i)); (2) a statement of the necessity of the ACNU (see proposed § 314.56(c)(1)(ii)); (3) a description of how the ACNU ensures appropriate self-selection or appropriate actual use, or both (see proposed § 314.56(c)(1)(iii)); (4) a description of the key elements of the ACNU (see proposed § 314.56(c)(1)(iv)); (5) adequate data or other information that demonstrate the necessity of the ACNU to ensure appropriate self-selection or appropriate actual use, or both (see proposed § 314.56(c)(1)(v)); (6) adequate data or other information that demonstrate the effect of the ACNU on the appropriate self-selection or appropriate actual use, or both (see proposed § 314.56(c)(1)(vi)); and (7) a description of the specific way the ACNU is operationalized (see proposed § 314.56(c)(1)(vii)). The first four requirements for the ACNU in the application (see proposed § 314.56(c)(1)(i) through (iv)) and the last requirement for the ACNU in the application (see proposed § 314.56(c)(1)(vii) provide statements, including explanations, descriptions, and justifications, about the ACNU; the remaining requirements for the ACNU in the application (see proposed § 314.56(c)(1)(v) through (vi)) provide data or other information to support these statements. Each of these seven requirements for the ACNU to be included in the application are further described in this section.

We are providing an example of one fictitious nonprescription drug product with an ACNU, Drug X, to provide a simplified illustration of a product that may potentially be considered under this proposed regulatory framework. We will use Drug X to explain examples of information that the applicant would submit in the NDA for a nonprescription drug product with an ACNU. This is only one type of example; many other types of ACNUs for nonprescription drug products could be possible.

Drug X is proposed as a nonprescription drug product indicated for the treatment of symptom Y in adults who have a disease-specific risk score below the threshold for developing serious side effect E when taking Drug X. As part of the nonprescription development program, the applicant conducted robust self-selection and label comprehension studies. The results of the self-selection and label comprehension studies demonstrated that consumers cannot appropriately self-select Drug X with labeling alone. FDA acknowledges these self-selection and label comprehension studies were well designed and conducted and concurs that consumers cannot self-select Drug X with labeling alone. Results of the self-selection and label comprehension studies show that, although consumers recognize that they have symptom Y, they cannot appropriately calculate their disease-specific risk score for side effect E. Therefore, the applicant proposes an ACNU for Drug X to ensure consumers' appropriate self-selection and now seeks approval of Drug X as a nonprescription drug product with an ACNU. The ACNU requires all consumers to complete a questionnaire located on a secure website created by the applicant to determine whether Drug X is appropriate for the consumer. The questionnaire has a series of questions that the consumer answers. The underlying program or other operating information used by the secure website calculates the risk score for serious side effect E using the consumer's answers and determines if the consumer has an acceptable disease-specific risk score to use Drug X. A consumer with an acceptable risk score can then either: (1) purchase Drug X on the applicant's secure website or (2) purchase Drug X

at a retail site specified by the applicant after presenting a barcoded voucher that can be printed or downloaded onto the consumer's mobile device from the applicant's secure website.

a. Statement regarding the purpose of the ACNU. The proposed rule would require the applicant to provide a statement regarding the purpose of the ACNU (see proposed § 314.56(c)(1)(i)). This statement would indicate whether the ACNU is intended for: (1) appropriate self-selection, (2) appropriate actual use, or (3) both. For example, the purpose of the ACNU for Drug X is to ensure appropriate self-selection by consumers.

b. Statement of the necessity of the ACNU. The proposed rule would require the applicant to explain why the ACNU is necessary to ensure appropriate self-selection or appropriate actual use, or both, by consumers of the nonprescription drug product (see proposed § 314.56(c)(1)(ii)). The applicant must explain why labeling alone cannot be sufficient for the purposes of meeting the approval requirements for a nonprescription drug product. The applicant may include a summary of the adequate data or other information that is submitted as part of an application for a nonprescription drug product with an ACNU, pursuant to proposed § 314.56(c)(1)(v), to explain why labeling alone cannot be sufficient.

c. Description of how the ACNU ensures appropriate self-selection or appropriate actual use, or both. The proposed rule would require the applicant to describe how the ACNU will ensure appropriate self-selection or appropriate actual use, or both, by consumers (see proposed § 314.56(c)(1)(iii)). For example, with Drug X, the applicant would describe that the ACNU requires a consumer to complete a questionnaire, located on a website, created by the applicant, that would assist in calculating a consumer's risk score for developing serious side effect E. This questionnaire would determine whether Drug X is appropriate for the consumer. The applicant may be expected, among other things, to justify the appropriateness of the self-selection questions, including the criteria and/or considerations used in calculating the risk score for a particular consumer. This may include a description of the algorithm in the underlying program or other operating information used by the website that calculates the risk score for serious side effect E to determine if the consumer has an acceptable risk score to use Drug X. The applicant would also describe how a consumer with an acceptable risk score can then purchase Drug X.

d. Description of key elements of the ACNU. The proposed rule would require the applicant to describe the key elements of the ACNU (see proposed § 314.56(c)(1)(iv)). The description of the key elements must include: (1) the additional condition(s) implemented by the applicant to be fulfilled by the consumer to be able to obtain or use the nonprescription drug product with an ACNU, (2) the labeling specifically associated with the ACNU, and (3) the criteria by which the consumer would successfully fulfill the ACNU, including a description of the specific actions to be taken by a consumer or required responses to be provided by a consumer. Labeling specifically associated with the ACNU should be annotated with each specific element of the ACNU. All labeling, including labeling specifically associated with the ACNU, should be provided in editable documents whenever possible. For example, labeling specifically associated with Drug X would include the carton and container annotated with the elements specific to the ACNU. All questions in the questionnaire would be submitted as labeling. The applicant for Drug X would describe the criteria by which the consumer would fulfill the ACNU including the questions and all potential consumer responses that would determine that Drug X was appropriate or not appropriate for the consumer.

e. Adequate data or other information that demonstrates the necessity of the ACNU to ensure appropriate self-selection or appropriate actual use, or both. The proposed rule would require an applicant to include data or other information that demonstrates the necessity of the ACNU to ensure appropriate self-selection or appropriate actual use, or both (see proposed § 314.56(c)(1)(v)). To do so, the applicant must conduct or reference adequate testing to show that labeling alone would not support the safe and effective use of the nonprescription drug product. For example, the applicant of Drug X would submit adequate data from robust self-selection studies and label comprehension studies that demonstrate that consumers could not appropriately self-select Drug X with labeling alone.

Alternatively, the applicant can submit information explaining the necessity of the ACNU for appropriate self-selection or appropriate actual use, or both, when FDA has previously signaled that labeling alone is not sufficient to ensure appropriate self-selection or appropriate actual use, or both. For example, this might apply if FDA has previously approved multiple nonprescription drug products for the same indication with a similar ACNU. The applicant is encouraged to discuss its drug development plans with FDA if the applicant has questions about whether an ACNU would be appropriate.

f. Adequate data or other information that demonstrates the effect of the ACNU on the appropriate self-selection or appropriate actual use, or both. The applicant must also submit adequate data or information that demonstrates the effect of the ACNU on the appropriate self-selection or appropriate actual use, or both, by the consumer of the nonprescription drug product (see proposed § 314.56(c)(1)(vi)). The data must show that consumers can appropriately self-select or use the drug product safely and effectively, or both, with the ACNU. For example, the applicant of Drug X would submit adequate data from robust self-selection studies that demonstrate that consumers could appropriately self-select Drug X with the ACNU.

g. Description of how the applicant will operationalize the ACNU. The proposed rule would require that the applicant describe the specific way the ACNU is operationalized (see proposed § 314.56(c)(1)(vii)). While it is important for FDA to understand how the ACNU is operationalized because this is part of achieving appropriate self-selection or use, the specific way an ACNU is operationalized is not a key element of the ACNU. The purpose of the ACNU is to enable self-selection and appropriate use without the oversight of a healthcare practitioner. The ACNU can be operationalized in different ways provided it reliably meets the objective. Alternatives to the way the ACNU is operationalized in the previous example, which involves administration of a questionnaire using a website, might include: (1) administering the questionnaire using a display screen at a pharmacy kiosk, (2) administering the questionnaire using a mobile application, and (3) administering the questionnaire using an automated telephone response system. These examples differ in the way the ACNU is operationalized (*i.e.,* how the questionnaire is being administered), but the key elements (including the questions in the questionnaire and responses that ensure appropriate self-selection) remain the same. FDA seeks comment on any unique issues that might arise for retailers or consumers based on the way the applicant operationalizes the ACNU in the previous examples, *e.g.,* in a store kiosk, online, or otherwise.

h. Additional considerations. If an NDA applicant submits an application

for a nonprescription drug product with an ACNU that proposes to use certain technologies, but FDA determines that labeling alone is sufficient to enable appropriate self-selection and appropriate actual use, FDA would refuse to approve the application for the nonprescription drug product with the ACNU (see proposed §§ 314.125(b)(20) and 314.127(a)(15)). However, FDA may approve an application for a nonprescription drug product with technologies that do not meet the definition of an ACNU. In cases where FDA determines that labeling alone is sufficient to enable appropriate self-selection and appropriate actual use, the labeling statements specifically required for a nonprescription drug product with an ACNU under this proposed rule (see proposed § 201.130) must not appear on the drug product labeling.

2. Abbreviated New Drug Application

Applicants may submit an ANDA referencing a listed drug that has been approved with an ACNU under section 505(c) of the FD&C Act and rely on FDA's previous finding that the RLD is safe and effective. The proposed rule would require that an ANDA for a nonprescription drug product with an ACNU must, when fulfilling the content and format requirements under § 314.94: (1) state the purpose of the ACNU (the same purpose as the ACNU for the RLD), (2) include information demonstrating that the key elements of the proposed ACNU are the same as the key elements of the ACNU for its RLD, and (3) include information on the way the ANDA applicant intends to operationalize the proposed ACNU. If an applicant believes the ACNU is operationalized in the same way as the RLD (*e.g.,* both use a mobile application), the ANDA must include information demonstrating the operationalization of the ACNU is the same as the RLD. If the ANDA proposes a different way to operationalize the proposed ACNU, the ANDA must include information to show that this different operationalization of the proposed ACNU achieves the same purpose as the ACNU for its RLD and the differences from the RLD are otherwise acceptable in an ANDA (see proposed § 314.56(c)(2)). As with all ANDAs, an ANDA for a nonprescription drug product with an ACNU also would be expected to be pharmaceutically equivalent and bioequivalent to its RLD and to have the same clinical effect and safety profile as its RLD when administered to patients under the conditions specified in the labeling. Information concerning the purpose of the reference product's ACNU and the description of the key elements should be available in the approval letter for the reference product or in the publicly available approval package.

The labeling for the ANDA drug product must be the same as the labeling for its RLD at the time of the ANDA's approval, except for changes required because of differences approved under a petition filed under § 314.93 or because the drug product for which an ANDA is submitted and the RLD are produced or distributed by different manufacturers (see sections 505(j)(2)(A) and (j)(4) of the FD&C Act) and §§ 314.94(a)(8) and 314.127(a)(7)).

a. Statement regarding the purpose of the ACNU. As part of the submission, an ANDA applicant would state the purpose of the ACNU (the same purpose as the ACNU for the RLD) (see proposed § 314.56(c)(2)(i)). Although an ANDA must state the purpose of the ACNU, an ANDA would not be required to include the explanation of the necessity for the ACNU or how the ACNU would ensure appropriate self-selection, appropriate actual use, or both. As a general matter, the ANDA would rely on FDA's findings of safety and effectiveness for an RLD with an ACNU.

b. Description of key elements of the ACNU. An ANDA applicant would also provide information to show that the key elements of the proposed ACNU are the same as the key elements of the ACNU approved for its RLD (see proposed § 314.56(c)(2)(ii)).

c. Description of how the applicant will operationalize the ACNU. An ANDA applicant would include information on how the ACNU would be operationalized. The proposed rule would allow ANDA applicants to operationalize its ACNU in a different way from its RLD. For instance, an ANDA applicant may consider proposing to make available on the internet a self-selection aid for its nonprescription drug product with an ACNU, whereas the self-selection aid for its RLD is made available at a physical retail store via an electronic display. Consistent with section 505(j) of the FD&C Act and our general approach to ANDAs, an ANDA would have a variety of ways to achieve the same purpose as the ACNU for its RLD. The ANDA would contain information to support that the way in which it is operationalized, as proposed, achieves the same purpose as the ACNU for its RLD and the differences from the RLD are otherwise acceptable in an ANDA (see proposed § 314.56(c)(2)(iii)). As with all ANDAs, an ANDA for a nonprescription drug product with an ACNU also would be expected to be pharmaceutically equivalent and bioequivalent to its RLD and have the same clinical effect and safety profile as its RLD when administered to patients under the conditions specified in the labeling.

FDA requests comment on the proposal to allow potential permissible differences between the NDA and the ANDA in the ways to operationalize the ACNU and how an applicant would demonstrate that the ACNU for the ANDA achieves the same purpose as the ACNU for its RLD.

As stated earlier in this proposed rule, the specific ways to operationalize the ACNU are not considered key elements of the ACNU and otherwise are not considered a condition of use of the drug product. For example, to the extent NDA applicants operationalize their ACNUs using proprietary means, ANDA applicants can use different ways than their RLD for operationalizing the ACNU (provided that the purpose of the ACNU is achieved through the same key elements).

Although FDA plays a ministerial role in listing patents in the publication ''Approved Drug Products with Therapeutic Equivalence Evaluations'' (commonly known as the Orange Book), FDA seeks comment on whether patents claiming aspects of the ACNU for the nonprescription drug product may be submitted for listing consistent with § 314.53 and section 505(b)(1)(A)(viii) and (c)(2) of the FD&C Act. FDA seeks comments on this topic and other issues FDA should consider in implementing this proposal that will help avoid unnecessarily delaying the entry of ANDA nonprescription drug products with an ACNU to the drug market.

E. Nonprescription and Prescription Approval and Simultaneous Marketing (Proposed § 314.56(d))

FDA has interpreted the language in section 503(b)(4) of the FD&C Act to allow simultaneous marketing of drug products with the same active ingredient as prescription and nonprescription if some meaningful difference, such as indication, strength, route of administration, dosage form, or patient population, exists between the drug products that makes the prescription product safe and effective only under the supervision of a healthcare practitioner licensed by law to administer the drug (see 83 FR 13994, April 2, 2018; see also 70 FR 52050, September 1, 2005). Section 503(b)(1) of the FD&C Act requires a drug which: (1) because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, is not safe for use except under the supervision of

a practitioner licensed by law to dispense such drug or (2) is limited by an approved application under section 505 of the FD&C Act to use under the professional supervision of a practitioner licensed by law to administer such drug, to be dispensed only upon prescription of a practitioner licensed to administer such drug. Under section 503(b)(4)(B) of the FD&C Act, a drug, for which the prescription dispensing provisions of section 503(b)(1) of the FD&C Act do not apply, shall be deemed to be misbranded if at any time before dispensing, the label of the drug bears the ''Rx only'' symbol. Likewise, under section 503(b)(4)(A), drugs that are subject to the prescription dispensing provisions of section 503(b)(1) must bear the ''Rx only'' symbol, or else they are misbranded. This effectively means that, absent a meaningful difference between the products, simultaneous marketing of two drug products with the same active ingredient as both a prescription and a nonprescription drug product would result in one of the two products being misbranded.

Under this proposed rule, the additional condition(s) that allow a nonprescription drug product to be safely used without the supervision of a healthcare practitioner would be a meaningful difference between the prescription drug product and the nonprescription drug product with an ACNU. Therefore, under the proposed rule, a prescription drug product and a nonprescription drug product with an ACNU that contain the same active ingredient can be simultaneously marketed even if they do not have other meaningful differences, such as different indications or strengths (see proposed § 314.56(d)).

The proposed rule would require applicants seeking approval for the first time of an NDA for a nonprescription drug product with an ACNU to submit a separate NDA, rather than a supplement to an approved NDA (see proposed § 314.56(b)). The approval of a separate NDA would permit simultaneous marketing and access to the drug as both a prescription drug product and a nonprescription drug product with an ACNU. Consistent with FDA's goal of increasing options for applicants to develop and market safe and effective drugs for consumers, this proposed rule would enable continued access to the drug product as a prescription drug product, while also extending access to the drug product in the nonprescription setting with the ACNU. Even if the application holder of the NDA for the prescription drug product decides to discontinue marketing of the NDA for the prescription drug product, generic versions of the prescription drug product would be eligible for approval relying on the discontinued NDA for the prescription product as an RLD, so long as FDA determines that the NDA for the prescription product was not discontinued for reasons of safety or effectiveness (see § 314.161).

F. Refusal To Approve an Application With an ACNU (Proposed §§ 314.125(b)(20) and 314.127(a)(15))

The proposed rule would specify that FDA would refuse to approve an NDA for a nonprescription drug product with an ACNU if FDA has determined the NDA failed to meet the requirements in § 314.56 applicable to NDAs (see proposed § 314.125(b)(20)). Similarly, the proposed rule would specify that FDA would refuse to approve an ANDA for a nonprescription drug product with an ACNU that fails to meet the requirements in § 314.56 applicable to ANDAs (see proposed § 314.127(a)(15)). In addition to other reasons cited in § 314.125 or § 314.127, FDA would refuse to approve an application for a nonprescription drug product with an ACNU if FDA has determined that the applicant failed to demonstrate that labeling is insufficient to ensure consumers' appropriate self-selection or appropriate actual use, or both, of the nonprescription drug product without the supervision of a healthcare practitioner or if the applicant failed to demonstrate that its proposed ACNU is adequate to ensure appropriate self-selection or appropriate actual use, or both, by consumers without the supervision of a healthcare practitioner. We also note that under current § 314.125(b)(8), FDA may refuse to approve an NDA if the drug product's proposed labeling does not comply with the requirements for labels and labeling in part 201. This authority would permit FDA to refuse to approve an NDA with an ACNU if the labeling does not comply with labeling requirements specific to such NDAs, such as proposed §§ 201.67 and 201.130. Similarly, under current § 314.127(a)(7), FDA will refuse to approve an ANDA if its labeling is not the same as the labeling of its RLD, with certain permitted exceptions. Thus, FDA may refuse to approve an ANDA with an ACNU if its proposed labeling does not comply with labeling requirements specific to nonprescription products with an ACNU, such as proposed §§ 201.67 and 201.130.

G. Other Postmarketing Reports (Proposed § 314.81(b)(3)(v))

The proposed rule would require NDA and ANDA applicants to report to FDA information concerning any incident of failure in the implementation of an ACNU using the FDA Adverse Event Reporting System (FAERS) (see proposed § 314.81(b)(3)(v)). A failure in implementation of an ACNU would include any event that results from a deviation in an applicant's implementation of the ACNU that may cause or lead to inappropriate medication use or consumer harm, such as a consumer gaining access to the drug product without fulfilling all necessary conditions for the nonprescription drug product with an ACNU. A failure in implementation of an ACNU must be reported by the applicant whether or not the failure is associated with an adverse event. To meet these reporting requirements, applicants will likely need quality assurance systems in place to capture instances where failures in implementation of an ACNU occur. A failure in implementation of an ACNU includes the following circumstances: (1) the consumer accessed or used the drug product without successfully fulfilling the ACNU, (2) the consumer successfully fulfilled the ACNU but could not access or appropriately use the drug product in the nonprescription setting, or (3) the consumer was unable to make an attempt to fulfill the ACNU due to systematic, technological, or mechanical errors in the implementation of the ACNU. For example, for the fictitious nonprescription drug product with an ACNU Drug X (as discussed in section V.D of this document), a report would be required to be submitted to FDA if the consumer with an acceptable risk score, was unable to purchase Drug X on the applicant's website or receive a voucher from the applicant's website in order to purchase Drug X at a retail site specified by the applicant. Failure to access the drug product could result in the consumer missing doses of the drug product.

The applicant must submit a single report (an individual case safety report (ICSR) of an adverse event) describing both the failure in implementation of an ACNU and an associated adverse event when both occur and the applicant is aware of both before submitting a report. If the applicant determines that a failure of implementation of an ACNU occurred that is associated with a previously submitted ICSR of an adverse event, a followup report must be submitted to FAERS using the same unique

identification number as the original ICSR of an adverse event and must include the information concerning the failure in implementation of an ACNU as required by proposed § 314.81(b)(3)(v)(A). If the applicant receives information of an adverse event associated with a previously submitted report in FAERS of a failure in implementation of an ACNU, a followup report must be submitted to FAERS as an ICSR of an adverse event. Such followup report must use the same unique identification number as the original report in FAERS of a failure in implementation of an ACNU and must include the information concerning the adverse event as required in § 314.80(f).

A report to FAERS for a failure in implementation of an ACNU would be submitted when the applicant has at least the minimum dataset for a failure in implementation, which includes the following three elements: (1) an identifiable reporter, (2) the drug product name, and (3) a description of the failure in implementation of the ACNU. The proposed rule would require the report to include certain information that the applicant is aware of about the drug product and the initial reporter, as well as a narrative summary of the failure in implementation of an ACNU and a description of the action initiated or completed to address the failure in implementation of an ACNU. The applicant would be required to submit a report for each failure in implementation of an ACNU as soon as possible but no later than 15 calendar days from the date when the applicant has acquired the minimum dataset for a report of a failure in implementation of an ACNU. Additionally, if an applicant obtains or otherwise receives any new information about previously submitted reports about the failure in implementation of an ACNU, the applicant would be required to investigate the new information, assess the relationship or impact of the new information on the initial report, and submit followup reports as soon as possible but no later than 15 calendar days after obtaining the new information. Proposed § 314.81(b)(3)(v)(C) would require the report to be submitted to FDA in an electronic format that FDA can process, review, and archive unless a waiver has been requested and granted. To better enable FDA to assess compliance with reporting requirements and to facilitate FDA's inspection of related records, we are proposing to require an applicant to maintain for a period of 10 years the records of all reports of failures in implementations of an ACNU and associated adverse events known to the applicant (proposed § 314.81(b)(3)(v)(D)).

FDA seeks specific comment on the burden and benefits of submitting an individual report to FDA for each individual failure in implementation of an ACNU encountered by a consumer resulting from the same cause of failure, as opposed to a single, consolidated report for all such failures. For example, there could be a situation where an ACNU involves administration of a questionnaire using a pharmacy kiosk, and the kiosk screen malfunctions, preventing multiple consumers from fulfilling the ACNU because they cannot complete the questionnaire on the kiosk screen. We are seeking comment on the benefits and burdens in this type of situation of submitting individual reports for each consumer affected by the malfunction versus one single, consolidated report for all consumers affected.

H. General Labeling Requirements (Proposed § 201.67(c))

The proposed rule would clarify that a nonprescription drug product with an ACNU must comply with all applicable regulatory requirements for nonprescription drug products, including those under part 201. Specifically, the applicant must comply with the existing content and format requirements for nonprescription drug products in § 201.66, known as the DFL (see proposed § 201.67(c)(1)). As required in § 201.66(c)(6), the labeling for all nonprescription drug products must contain directions for use under the heading ''Directions.'' The proposed rule would require the labeling for all nonprescription drug products approved with an ACNU to include the following statement, as specified in proposed § 201.130(a)(1), as the first statement under the heading ''Directions'': ''To check if this drug is safe for you, go to [insert where or how consumers can find information about the ACNU; for example, applicant's website, applicant's phone number, or specific retail location] and [insert action to be taken by consumer]. Do not take this drug without completing this step.'' This initial statement would be followed by the other required information in § 201.66(c)(6). This proposed statement would alert consumers that the nonprescription drug product with an ACNU has a requirement that must be fulfilled to ensure safe and effective use. The proposed statement would further remind the original purchaser and alert persons other than the original purchaser that the product is not suitable for all individuals and that consumers should carefully examine any labeling accompanying the nonprescription product with an ACNU before using the product.

As stated previously, FDA may currently approve labeling for nonprescription drug products in addition to the DFL, and this would continue if the proposed rule is finalized (see proposed § 201.67(c)(2)). For example, FDA could approve information leaflets or other documents contained inside the carton or container for a nonprescription drug product, including for a nonprescription drug product with an ACNU.

A list of questions to be answered by the consumer in a self-selection aid could be labeling necessary to effectively implement the ACNU. All labels and other written, printed, or graphic matter that are necessary to effectively implement the ACNU (*e.g.,* questions associated with a self-selection aid) would be considered to accompany the nonprescription drug product and, therefore, would meet the definition of labeling under the FD&C Act.

Approved labeling for a nonprescription drug product with an ACNU must be available to consumers at the time of purchase and use as required in section 502(c) of the FD&C Act. In general, we believe that the applicant should describe in their application the process for ensuring consumers have access to the approved labeling prior to fulfilling the ACNU.

I. Format Requirements for Required ACNU Statement (Proposed § 201.67(d))

The proposed rule would require that the statement specified in § 201.130(a)(2) meet specific format requirements (see proposed § 201.67(d)). This statement must be visible to consumers at the time of purchase and use. Additionally, the statement would alert persons that may have access to the drug product (*e.g.,* family members in the purchaser's home), including the individual who originally purchased the product, that these nonprescription drug products are not suitable for all individuals and should only be used after fulfilling the ACNU. The proposed rule would require that the statement appear on the principal display panel (see § 201.60) and the immediate container surface that the consumer is most likely to view when seeking information about the drug product (see proposed § 201.67(d)(1)). If the immediate container is a bottle, the statement must appear on the surface that the consumer would most likely consider to be the front of the bottle. If

the immediate container is a blister card, the statement must appear on the blister card surface that the consumer would most likely view when removing the drug product from the blister card. If the blister card contains more than one blister unit, the statement would not need to be included on each blister unit of a blister card. However, the statement must remain intact and be readable on the blister card when the drug product is removed from each blister unit.

The proposed rule would require that the statement be prominently presented in boldface and black type in a yellow background banner (see proposed § 201.67(d)(2) and (3)). No other information or statement may be included in the yellow background banner. The hue of the yellow color in the background banner must be a shade that provides a high contrast with the black type of the statement. The font size of the statement would be at least 25 percent as large as the font size of the largest printed words on the container surface that the consumer would most likely view when seeking information about the drug product; in no case could the font size be smaller than 12 point type (1 point = 0.0138 inches) (see proposed § 201.67(d)(4)). For containers where the size would render compliance with this requirement impractical, the applicant would be able to request an exception to the minimum font size requirement (see proposed § 201.67(d)(5)). However, FDA would not determine an exception is warranted if the statement is not prominent in relation to other elements on the container surface containing the statement.

J. Exemption From Adequate Directions for Use (Proposed § 201.130)

Consistent with the proposed definition of ACNU, a drug product can only be approved with an ACNU if the applicant demonstrates and FDA determines that labeling alone is insufficient to ensure appropriate self-selection or appropriate actual use, or both. Therefore, it is not possible for these products to be labeled with adequate directions for use under section 502(f)(1) of the FD&C Act, as defined in § 201.5. The proposed rule would exempt a nonprescription drug product with an ACNU from the statutory requirement to be labeled with adequate directions for use, provided that certain conditions are met. Specifically, a nonprescription drug product approved with an ACNU under section 505(c) or (j) of the FD&C Act would be exempt from section 502(f)(1) if the product contains the labeling required under proposed § 201.130(a) and the ACNU is implemented by the applicant as approved by FDA in the application (see proposed § 201.130). FDA is proposing this exemption to the requirement for adequate directions for use for a nonprescription drug product with an ACNU because we have determined that the labeling and the ACNU are sufficient to ensure consumers' appropriate self-selection and actual use of the nonprescription product without the supervision of a healthcare practitioner. Therefore, adequate directions for use, as required by section 502(f)(1) of the FD&C Act and § 201.5, would not be necessary for the protection of the public health.

The proposed rule would require that the following statement appear as the first direction under the heading ''Directions'' in the labeling, as required in § 201.66(c)(6): ''To check if this drug is safe for you, go to [insert where or how consumers can find information about the ACNU; for example, applicant's website, phone number, or specific retail location] and [insert action to be taken by consumer]. Do not take this drug without completing this step.'' (See proposed § 201.130(a)(1).) The applicant would include information to inform consumers where the additional condition would be found and explain the additional condition that the consumer must fulfill. For example, ''To check if this drug is safe for you, go to *www.XYZCompany.com* and take the self-selection questionnaire. Do not take this drug without completing this step.'' The statement would be followed by the other information required in § 201.66(c)(6). FDA is specifically seeking comment on the content of the statements and the ability of these statements to sufficiently inform consumers that the product is a nonprescription drug product with an ACNU and how consumers would fulfill the ACNU.

The proposed rule would also require that the following statement appear on the immediate container label and, if one exists, the outside container or wrapper of the retail package: ''You must complete an extra step to see if this drug is safe for you before you use it. Do not take this drug without completing this step. See the Drug Facts labeling for more information.'' (See proposed § 201.130(a)(2).) This statement must meet the specific format requirements as specified in proposed § 201.67(d). The statement would remind the original purchaser and alert persons other than the original purchaser that these nonprescription drug products are not suitable for all individuals and should only be used after fulfilling the ACNU. FDA is specifically seeking comment on whether this statement would sufficiently alert consumers that this product is a nonprescription drug product with an ACNU.

The proposed rule would require the ACNU to be implemented by the applicant under the conditions set forth in the approved application for the nonprescription drug product with an ACNU to be exempt from the requirement to be labeled with adequate directions for use (see proposed § 201.130(b)).

K. Misbranding (Proposed § 201.67(e))

As noted immediately above, the proposed rule would exempt a nonprescription drug product with an ACNU from the requirement to be labeled with adequate directions for use under section 502(f)(1) of the FD&C Act, provided that certain conditions are met (see proposed § 201.130). If a nonprescription drug product with an ACNU is made available to consumers without the labeling specified in proposed § 201.130(a) or the ACNU is not implemented by the applicant as approved by FDA in the application, the drug product would be misbranded under section 502(f)(1) of the FD&C Act (see proposed § 201.67(e)).

As discussed in sections V.H and V.I of this document, the proposed rule would include specific labeling requirements for a nonprescription drug product with an ACNU. If the nonprescription drug product with an ACNU is made available to consumers without the specific required labeling, the product would also be misbranded under section 502(a) of the FD&C Act, which provides that a drug's labeling must not be false or misleading in any particular (see proposed § 201.67(e)). Under section 201(n) of the FD&C Act, in determining whether labeling is misleading, there shall be taken into account (among other things), not only representations made or suggested but also the extent to which the labeling fails to reveal facts material in the light of such representations or material with respect to consequences that may result from the use of the drug under the conditions of use prescribed in the labeling or under usual or customary conditions of use. The required labeling statements described in proposed § 201.130(a) are intended to inform consumers that the product is a nonprescription drug product with an ACNU; to instruct consumers on how to fulfill the ACNU; and to remind the original purchaser (and alert persons other than the original purchaser) that

the nonprescription drug product is not suitable for all individuals and should only be used after fulfilling the ACNU. Thus, failure of a nonprescription drug product approved with an ACNU to bear the required labeling statements described in proposed § 201.130(a) would constitute a failure to reveal material facts about the product or with respect to consequences that might result from its use and would misbrand the product.

In addition, a nonprescription drug product with an ACNU could be misbranded under other provisions of section 502 of the FD&C Act. For example, in certain circumstances, such a drug may be misbranded under section 502(j) if the product does not meet the requirements of this proposed rule.

Under the proposed rule, a nonprescription drug product with an ACNU must only be made available to the consumer after the ACNU has been fulfilled by the consumer. It is a prohibited act under section 301(a) of the FD&C Act to introduce or deliver for introduction into interstate commerce any drug that is misbranded (21 U.S.C. 331(a)). It is also a prohibited act under section 301(k) of the FD&C Act to do any act with respect to a drug if such act is done while such drug is held for sale after shipment in interstate commerce and results in the drug being misbranded.

Additionally, a nonprescription drug product approved with an ACNU would be an unapproved new drug if it is made available to consumers without the ACNU. With certain limited exceptions not relevant here, it is a violation of sections 301(d) and 505(a) of the FD&C Act to introduce or deliver for introduction into interstate commerce an unapproved new drug.

VI. Proposed Effective Date

We propose that a final rule based on this proposed rule become effective 60 days after the date the final rule publishes in the **Federal Register**.

VII. Preliminary 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). This proposed rule has been designated by the Office of Information and Regulatory Affairs as 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. This rule would establish the requirements for a nonprescription drug product with an ACNU. We cannot anticipate the number of applicants that would submit applications or the types of drug products that would be covered under such applications. However, we estimate the costs for any applicant to read and understand the rule would likely range between 0.04 percent and 0.14 percent of the gross receipts of very small applicants. Therefore, we propose to certify that the proposed rule, if finalized, would 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 $165 million, using the most current (2021) 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.

B. Summary of Costs and Benefits

The proposed rule, if finalized, would establish the requirements for a nonprescription drug product with an ACNU. Compared to the traditional labeling paradigm of nonprescription drug products, this approved ACNU in addition to the labeling would ensure the appropriate self-selection, appropriate use, or both, of a drug product. We expect this rule could expand consumer access to certain drug products in a nonprescription setting.

Table 1 shows our quantified benefits. We estimate a reduction in access costs to consumers who could transfer from a prescription to a nonprescription drug product with an ACNU. Our primary estimate for this item is $26.70 with a range of $0 to $53.40 per consumer per purchase. We also quantify the value of the potential reduction in the number of repetitive meetings with sponsors that the rule could eliminate, which occur during the approval process. This estimate includes benefits to FDA and industry. Our primary estimate is $55,469 per applicant with a range of $45,260 to $66,174. We do not monetize our estimates of benefits over a 10-year horizon because of the high uncertainty about number of applicants, applications, potential approvals, the number of purchases that might occur, and consumer preferences to switch products but present estimates in the uncertainty section of the full preliminary analysis of economic impacts.

Although an applicant would incur the development and postmarketing, including reporting of failure in the implementation of the ACNU and recordkeeping costs, we assume that applicants submit applications when they believe that their expected profits from the approval will exceed the costs of the application. We present a range of these potential development and postmarketing costs in the appendix of the complete economic analysis. However, we lack information to monetize these costs over a 10-year horizon and request comment or data on these potential costs.

Monetized costs include a one-time cost of reading and understanding the rule. Using a 7-percent discount rate, the primary estimate, annualized over a 10-year horizon, equals $821 with a range of $379 to $1,264. These annualized costs are the same using a 3-percent discount rate.

Government and private insurance payers may experience positive transfers because consumers may decrease future medical costs and the number of submitted insurance claims. Earlier access to drug products would allow consumers to treat medical conditions using nonprescription drug products with an ACNU without the supervision of a healthcare practitioner.

TABLE 1—SUMMARY OF BENEFITS, COSTS AND DISTRIBUTIONAL EFFECTS OF PROPOSED RULE

Category	Primary estimate	Low estimate	High estimate	Units			Notes
				Year dollars	Discount rate (%)	Period covered	
Benefits:							
Annualized Monetized $millions/year.							
Annualized Quantified				2018			Quantified reduction in access costs per consumer purchase range from $0.0 to $53.40, and a primary estimate of $26.70.
				2018			Quantified reduction in meetings between FDA and applicants range from $45,260 to $66,174 per applicant, and a primary estimate of $55,469.
Qualitative.							
Costs:							
Annualized	$0.0	$0.0	$0.0	2018	7	10 years	Reading and understanding one-time costs.
Monetized $millions/year	$0.0	$0.0	$0.0	2018	3	10 years.	
Annualized.							
Quantified.							
Qualitative							Affected firms would incur costs to develop and submit applications.
Transfers:							
Federal					7		
Annualized Monetized $millions/year					3		
From/To	From:			To:			
Other					7		
Annualized Monetized $millions/year					3		
From/To	From:			To:			Potential benefits to government and private payors if access cost of medications decline.

Effects:
State, Local or Tribal Government: No estimated effect.
Small Business: The estimated costs to very small potential applicants in this industry would range from 0.04 percent to 0.14 percent of gross receipts.
Wages: No estimated effect.
Growth: No estimated effect.

We have developed a comprehensive Preliminary Economic Analysis of Impacts that assesses the impacts of the proposed rule. The full preliminary analysis of economic impacts is available in the docket for this proposed rule (Ref. 7) and at *https://www.fda.gov/about-fda/reports/economic-impact-analyses-fda-regulations*.

VIII. Analysis of Environmental Impact

We have determined under 21 CFR 25.30(h) and (k) 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. 3501–3521). A description of these provisions is given in the *Description* section below, with an estimate of the annual reporting, recordkeeping, and third-party disclosure burden. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

FDA invites 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: Premarket applications, postmarketing reports and recordkeeping, and labeling for Nonprescription Drug Products With an Additional Condition for Nonprescription Use.

Description: We are revising requirements applicable to NDA and ANDA applicants of nonprescription drug products with an ACNU (collectively, respondents). If finalized, the proposed rule will modify information collections applicable to regulations in part 314 governing new and abbreviated new drug application submissions and drug labeling provisions in part 201 pertaining to nonprescription drug products.

Description of Respondents: The respondents are: (1) for NDA and ANDA

submissions, an applicant who submits an NDA (including a 505(b)(2) application) or an ANDA under part 314 to obtain FDA approval of a nonprescription drug with an ACNU; (2) for failure of implementation of an ACNU reporting and recordkeeping, any person who holds an approved NDA (including a 505(b)(2) application) or an approved ANDA that includes an ACNU; and (3) for labeling, any person who holds an approved NDA (including a 505(b)(2) application) or an approved ANDA that includes an ACNU.

We estimate the burden of the information collection as follows:

TABLE 2—ESTIMATED ANNUAL REPORTING BURDEN; OMB CONTROL NO. 0910–0001[1]

Information collection activity; 21 CFR part 314 (application for FDA approval to market a new drug)	Number of respondents	Number of responses per respondent	Total annual responses	Average burden per response (hours)	Total hours
Submission of separate application for nonprescription drug product with an ACNU; § 314.56(b) and (c)	6	1	6	320	1,920
Other postmarketing reports; submission of each individual consumer affected by a failure in implementation of an ACNU; § 314.81	6	25	150	40	6,000
Total			156		7,920

[1] There are no capital, or operating or maintenance costs associated with the information collection.

NDA and ANDA Submissions

Based on our experience with information collection associated with current NDA and ANDA submissions, we estimate six applications for a nonprescription drug product with an ACNU will be submitted annually by six respondents. Based on Broad Agency Announcement proposals that set forth the number of hours anticipated to produce study reports for submission to us, we assume it will take an average of 320 hours per application for both NDA and ANDA applicants to prepare and submit the information required for applications for nonprescription drugs with an ACNU (in addition to meeting the general NDA or ANDA requirements under §§ 314.50 and 314.94, already approved in OMB control number 0910–0001).

Reports of a Failure in Implementation of an ACNU

We estimate six respondents will each submit 25 reports to FDA for an individual failure in implementation of an ACNU under § 314.81(b)(3)(v). We assume an average of 40 hours per response for each applicant, for a total of 6,000 hours annually. As noted in the preamble of the proposed rule, we are also soliciting comments on the alternative reporting mechanism requiring the applicant to submit a single, consolidated report for all consumers affected by the same failure in implementation of an ACNU rather than a report for each individual impacted by the same failure in implementation of an ACNU. If that alternative is implemented in the final rule, we estimate that the number of reports per respondent would be reduced from 25 annual responses per respondent to 1 per year per respondent.

TABLE 3—ESTIMATED ANNUAL RECORDKEEPING BURDEN; OMB CONTROL NO. 0910–0001 [1]

Information collection; 21 CFR part 314 (applications for FDA approval to market a new drug)	Number of respondents	Number of responses per respondent	Total annual responses	Average burden per response (hours)	Total hours
Requirements for failures in implementation of an ACNU; § 314.81	6	25	150	8	1,200

[1] There are no capital, or operating or maintenance costs associated with the information collection.

Based on our experience with postmarket recordkeeping requirements, we assume an average burden of 8 hours of recordkeeping for each report and therefore have calculated 1,200 hours annually.

TABLE 4—ESTIMATED ANNUAL THIRD-PARTY DISCLOSURE BURDEN; OMB CONTROL NO. 0910–0340 [1]

Information collection activity; 21 CFR part 201, subpart C (format and content requirements for over-the-counter drug product labeling)	Number of respondents	Number of responses per respondent	Total annual responses	Average burden per response	Total hours
Disclosure of information on the principal display panel or within Drug Facts Labeling; § 201.66 (including statements specified in § 201.130(a)(1))	6	1	6	15	90
Additional ACNU labeling—§ 201.67	6	1	6	9	54
Total			12		144

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

Labeling for Nonprescription Drugs With an ACNU

Based on our experience with NDA and ANDA submissions, we estimate six respondents will each submit an application for a nonprescription drug product with an ACNU, each becoming subject to all nonprescription labeling regulations in (21 CFR part 201, subpart C). This includes the requirements for statements of identity and net contents (§§ 201.61 and 201.62) which appear on the principal display panel (PDP) (defined by § 201.60); the Drug Facts labeling (DFL) requirements of § 201.66, as part of which the respondents must also include (where applicable) labeling to satisfy sodium, calcium, magnesium, and potassium labeling requirements (§§ 201.64, 201.70, 201.71, and 201.72); and the statements proposed to be required by § 201.130(a)(1). (The proposed requirement in § 201.130(a)(2) to place a specified ACNU statement on the product PDP is not included in the definition of *collection of information* under the PRA and is therefore not subject to review and approval by OMB. See 5 CFR 1320.3(c)(2). These products may also have additional labeling beyond the DFL requirements (§ 201.67(c)(2)).

Estimating six respondents will each have one new, approved drug that must comply with PDP and DFL labeling requirements, including statements specified in § 201.130(a)(1), and assuming compliance with these disclosures will require 15 hours per drug, we calculate a total of 90 hours annually. Additionally, we estimate six respondents will each have one new nonprescription drug product approved with an ACNU that contains additional labeling requirements, for a total of six annual responses. Based on our experience with nonprescription labeling requirements, we assume an average burden per response of 9 hours, for a total of 54 hours annually.

To ensure that comments on this information collection are received, OMB recommends that written comments be submitted through *reginfo.gov* (see **ADDRESSES**). All comments should be identified with the title of the information collection.

In compliance with the Paperwork Reduction Act of 1995 (44 U.S.C. 3407(d)), we have submitted the information collection provisions of this proposed rule to OMB for review. These information collection requirements will not be effective until FDA publishes a final rule, OMB approves the information collection requirements, and the rule goes into effect. FDA will announce OMB approval of these requirements in the **Federal Register**.

X. Federalism

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. We have determined that this proposed rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, we conclude that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

XI. Consultation and Coordination With Indian Tribal Governments

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13175. We have tentatively determined that the rule does not contain policies that would have a substantial direct effect on one or more Indian Tribes, on the relationship between the Federal Government and Indian Tribes, or on the distribution of power and responsibilities between the Federal Government and Indian Tribes. The Agency solicits comments from tribal officials on any potential impact on Indian Tribes from this proposed action.

XII. References

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

1. FDA, Guidance for Industry, ''Self-Selection Studies for Nonprescription Drug Products,'' April 2013 (available at *https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs*).
2. Chang J., A. Lizer, I. Patel, et al., ''Prescription to Over-the-Counter Switches in the United States,'' *Journal of Research in Pharmacy Practice,* vol. 5(3), pp. 149–154, doi:10.4103/2279–042X.185706. Available at: *https://www.jrpp.net/text.asp?2016/5/3/149/185706.*
3. FDA, Guidance for Industry, ''Label Comprehension Studies for Nonprescription Drug Products,'' August 2010 (available at *https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs*).
4. Engelberg Center for Health Care Reform at the Brookings Institution, ''Expert Workshop: Nonprescription Medications With Conditions of Safe Use as a Novel Solution for Undertreated Diseases or Conditions,'' November 8, 2012 (available at *https://www.brookings.edu/events/nonprescription-medications-with-conditions-of-safe-use-as-a-novel-solution-for-undertreated-diseases-or-conditions*), accessed July 30, 2021.
5. Engelberg Center for Health Care Reform at the Brookings Institution, ''Expert Workshop: Innovative Technologies and Nonprescription Medications: Addressing Undertreated Diseases and Conditions through Technology Enabled Self-Care,'' May 9, 2013 (available at *https://www.brookings.edu/events/innovative-technologies-and-nonprescription-medications-addressing-undertreated-diseases-and-conditions-through-technology-enabled-self-care*), accessed July 30, 2021.
6. Engelberg Center for Health Care Reform at the Brookings Institution, ''Expert Workshop: Exploring Implications of the Nonprescription Drug Safe Use Regulatory Expansion (NSURE) Initiative on Reimbursement and Access,'' November 4, 2013 (available at *https://www.brookings.edu/events/exploring-implications-of-the-nonprescription-drug-safe-use-regulatory-expansion-nsure-initiative-on-reimbursement-and-access*), accessed July 30, 2021.
7. FDA, Preliminary Regulatory Impact Analysis; Initial Regulatory Flexibility Analysis; Unfunded Mandates Reform Act Analysis, Nonprescription Drug Product With an Additional Condition for Nonprescription Use; Proposed Rule (available at *http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm*).

List of Subjects

21 CFR Part 201

Drugs, Labeling, Reporting and recordkeeping requirements.

21 CFR Part 314

Administrative practice and procedure, Confidential business information, Drugs, Reporting and recordkeeping requirements.

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 parts 201 and 314 be amended as follows:

PART 201—LABELING

■ 1. The authority citation for part 201 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 343, 351, 352, 353, 355, 358, 360, 360b, 360ccc, 360ccc–1, 360ee, 360gg–360ss, 371, 374, 379e; 42 U.S.C. 216, 241, 262, 264.

■ 2. Add § 201.67 to subpart C to read as follows:

§ 201.67 Labeling requirements for a nonprescription drug product with an additional condition for nonprescription use (ACNU).

(a) *Scope.* This section sets forth labeling requirements for a nonprescription drug product with an ACNU.

(b) *Definition.* The following definition applies to this section:

(1) *Additional condition for nonprescription use* (ACNU) means one or more FDA-approved conditions that an applicant of a nonprescription drug product must implement to ensure consumers' appropriate self-selection or appropriate actual use, or both, of the nonprescription drug product without the supervision of a healthcare practitioner if the applicant demonstrates and FDA determines that labeling alone is insufficient to ensure appropriate self-selection or appropriate actual use, or both.

(2) [Reserved]

(c) *General labeling requirements.* (1) A nonprescription drug product with an ACNU must comply with applicable labeling requirements for nonprescription drug products under this part, including the format and content requirements for nonprescription drug product labeling under § 201.66 and the statements specified in § 201.130(a).

(2) A nonprescription drug product with an ACNU may also be approved with additional labeling that supplements the format and content requirements for nonprescription drug product labeling under § 201.66.

(d) *Format requirements for required ACNU statement.* The statement specified in § 201.130(a)(2) must meet all format requirements as follows:

(1) The statement must appear on the principal display panel (see § 201.60) and the immediate container surface that the consumer is most likely to view when seeking information about the drug product. If the immediate container is a bottle, the statement must appear on the surface that the consumer is most likely to consider the front of the bottle. If the immediate container is a blister card (including a card that contains more than one blister unit), the statement must appear on the blister card surface that the consumer would most likely view when removing the drug product from the blister card. If the blister card contains more than one blister unit (*e.g.,* perforated blister card where individual blister units can be separated from one another), the statement does not need to be included on each blister unit of a blister card. However, the statement must remain intact and be readable on the blister card when the drug product is removed from each blister unit.

(2) The statement must appear in boldface and black type.

(3) The statement must appear in a yellow background banner. No other information or statements may be included within the yellow background banner.

(4) The statement must be in one of the following font sizes, whichever is greater:

(i) At least 25 percent as large as the font size of the largest printed words on the principal display panel and immediate container; or

(ii) At least 12 point font (1 point = 0.0138 inches).

(5) An applicant may request an exception to the minimum font size requirement specified in paragraph (d)(4) of this section for containers where its size would render compliance with this requirement impractical. FDA may allow such an exception upon request by an applicant if FDA determines an exception is warranted.

(e) *Misbranding.* A nonprescription drug product with an ACNU is misbranded under section 502 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 352) if—

(1) It is made available without the labeling specified in § 201.130(a); or

(2) The ACNU is not implemented by the applicant as approved by FDA in the application.

■ 3. Add § 201.130 to subpart D to read as follows:

§ 201.130 Exemption from adequate directions for use for a nonprescription drug product with an additional condition for nonprescription use.

A nonprescription drug product approved under section 505(c) or 505(j) of the Federal Food, Drug, and Cosmetic Act with an ACNU as defined in § 201.67(b) is exempt from section 502(f)(1) if all the following conditions in paragraphs (a) and (b) of this section are met:

(a) The label of the drug:

(1) Bears, as the first direction under the ''Directions'' heading required in § 201.66(c)(6), the statement ''To check if this drug is safe for you, go to [insert where or how consumers can find information about the ACNU; for example, applicant's website, applicant's phone number, or specific retail location] and [insert action to be taken by consumer]. Do not take this drug without completing this step.'' The statement must be followed by the other information required in § 201.66(c)(6).

(2) Bears, in the form and manner required by § 201.67(d), the statement ''You must complete an extra step to see if this drug is safe for you before you use it. Do not take this drug without completing this step. See the Drug Facts labeling for more information.''

(3) Complies with other applicable labeling requirements for nonprescription drug products under this part, including the format and content requirements for nonprescription drug product labeling under § 201.66.

(b) The additional condition for nonprescription use is implemented by the applicant under the conditions set forth in the approved application.

PART 314—APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG

■ 4. The authority citation for part 314 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 355a, 355f, 356, 356a, 356b, 356c, 356e, 360cc, 371, 374, 379e, 379k–1.

■ 5. Add § 314.56 to subpart B to read as follows:

§ 314.56 Nonprescription drug product with an additional condition for nonprescription use (ACNU).

(a) *Definition.* The following definition applies to this section:

(1) *Additional condition for nonprescription use* (ACNU) means one or more FDA-approved conditions that an applicant of a nonprescription drug product must implement to ensure consumers' appropriate self-selection or appropriate actual use, or both, of the nonprescription drug product without the supervision of a healthcare practitioner if an applicant demonstrates and FDA determines that labeling alone is insufficient to ensure appropriate self-selection or appropriate actual use, or both.

(2) [Reserved]

(b) *Separate application required for a nonprescription drug product with an ACNU.* An applicant must submit a separate application for a nonprescription drug product with an ACNU. Initial approval for a nonprescription drug product with an ACNU cannot be obtained through a supplement to an approved application.

(c) *Specific requirements for an application for a nonprescription drug product with an ACNU.* The applicant must submit an application that complies with the following requirements:

(1) *New drug application (NDA).* When fulfilling the content and format requirements under § 314.50, an NDA for a nonprescription drug product with an ACNU must include—

(i) A statement regarding the purpose of the ACNU: ensure appropriate self-selection or appropriate actual use, or both, by consumers of the nonprescription drug product with an ACNU without the supervision of a healthcare practitioner;

(ii) A statement regarding the necessity of the ACNU;

(iii) A description of how the ACNU ensures appropriate self-selection or appropriate actual use, or both;

(iv) A description of the key elements of the ACNU, including:

(A) The additional condition implemented by the applicant to be fulfilled by the consumer to obtain the nonprescription drug product with an ACNU;

(B) The labeling specifically associated with the ACNU; and

(C) The criteria by which the consumer would successfully fulfill the ACNU, including a description of the specific actions to be taken by a consumer or required responses to be provided by a consumer;

(v) Adequate data or other information that demonstrates the necessity of the ACNU to ensure appropriate self-selection or appropriate actual use, or both;

(vi) Adequate data or other information that demonstrates the effect of the ACNU on the appropriate self-selection or appropriate actual use, or both; and

(vii) A description of the specific way the ACNU is operationalized.

(2) *Abbreviated new drug application (ANDA).* When fulfilling the content and format requirements under § 314.94, an ANDA for a nonprescription drug product with an ACNU must—

(i) State the purpose of the ACNU;

(ii) Include information demonstrating that the key elements of the proposed ACNU are the same as the key elements of the ACNU for its reference listed drug (RLD); and

(iii) Include information on the way the ACNU would be operationalized. If an applicant believes the ACNU is operationalized in the same way as the RLD, include information demonstrating that the ACNU is operationalized in the same way as the RLD. If a different way to operationalize the proposed ACNU is used, include information to show that this different way to operationalize the proposed ACNU achieves the same purpose as the ACNU for its RLD and that the differences from the RLD are otherwise acceptable in an ANDA.

(d) *Simultaneous marketing of nonprescription and prescription products.* An ACNU constitutes a meaningful difference between a nonprescription drug product and a prescription drug product, such that a prescription drug product and a nonprescription drug product with an ACNU may be simultaneously marketed even if there is not another meaningful difference between the two products that makes the nonprescription drug product safe and effective for use without the supervision of a healthcare practitioner licensed by law to administer the drug (*e.g.,* a different active ingredient, indication, strength, route of administration, dosage form, or patient population).

■ 6. Amend § 314.81 by adding paragraph (b)(3)(v) to read as follows:

§ 314.81 Other postmarketing reports.

* * * * *

(b) * * *

(3) * * *

(v) *Report of failure in the implementation of an additional condition for nonprescription use.* The applicant must submit a report when a failure in the implementation of an additional condition for nonprescription use (ACNU) for a nonprescription drug product occurs. A report of a failure in implementation of an ACNU includes any event that results from a deviation in an applicant's implementation of the ACNU that may cause or lead to inappropriate medication use or consumer harm. All failures in implementation of an ACNU must be reported to the FDA Adverse Event Reporting System (FAERS), whether or not the failure in implementation of an ACNU is associated with an adverse event. If an applicant becomes aware of both a failure in implementation of an ACNU and an associated adverse event before the submission to FAERS, a single individual case safety report (ICSR) that describes both the failure in implementation of an ACNU and the associated adverse event must be submitted and must contain the information as required in § 314.80(f) and paragraph (b)(3)(v)(A) of this section. If a previously submitted report to FAERS describes only a failure in implementation of an ACNU or a previously submitted ICSR reports only an adverse event, and the submitter subsequently becomes aware of an associated adverse event or associated failure in implementation of an ACNU, the submitter must supplement the original report to FAERS with the new information. The supplement must include the information required in § 314.80(f) or paragraph (b)(3)(v)(A) of this section, as applicable.

(A) *Content.* The report must include the following for a failure in implementation of an ACNU:

(*1*) *Required information.* The name, address, email, and telephone number of the applicant; an identifiable reporter; the drug product name; and the description of the failure in implementation of the ACNU.

(*2*) *Additional information, if known.* In addition, the report must include the following information, if known:

(*i*) Drug product strength; National Drug Code (NDC); lot number; and NDA or ANDA number.

(*ii*) Initial reporter information including name, address, and telephone number of the initial reporter.

(*iii*) Unique case identification number, which must be the same in the initial report and any subsequent followup report(s).

(*iv*) Narrative summary of failure in implementation of an ACNU, including the date of failure in implementation of an ACNU (or best estimate); the date the failure in implementation of an ACNU was reported to applicant; the location of failure in implementation of an ACNU, including business name and contact information; and whether any of the following circumstances occurred: The consumer accessed or used the drug product without successfully fulfilling the ACNU; the consumer successfully fulfilled the ACNU but could not access or use the drug product; or the consumer was unable to make an attempt to fulfill the ACNU; and

(*v*) The remedial action taken or completed to address the failure in implementation of an ACNU, including the type of remedial action initiated or completed (for example, repair, replace, recall, inspection, modification, or adjustment) and a description of how the applicant will prevent failures of the same nature in the future.

(B) *Submission.* (*1*) The applicant must submit the report for each failure in implementation of an ACNU as soon as possible but no later than 15 calendar days from the date when the applicant has acquired the minimum dataset for a failure in implementation of an ACNU.

(*2*) The applicant must also investigate any new information it obtains or otherwise receives about previously submitted reports and assess the relationship or impact of the new information on the initial report. The applicant must submit followup reports as soon as possible but no later than 15 calendar days after obtaining the new information.

(C) *Electronic format for submissions.* (*1*) The report must be submitted to FDA in accordance with § 314.80(g).

(*2*) An applicant may request, in writing, a waiver of the requirements in paragraph (b)(3)(v)(C)(*1*) of this section in accordance with § 314.90 or § 314.99.

(D) *Recordkeeping.* The applicant must maintain for a period of 10 years, the records of all reports of failures in implementation of an ACNU and associated adverse events known to the applicant, including raw data and any correspondence relating to a report of a failure in implementation of an ACNU.

* * * * *

■ 7. Amend § 314.125 by adding paragraph (b)(20) to read as follows:

§ 314.125 Refusal to approve an NDA.

* * * * *

(b) * * *

(20) For an NDA for a nonprescription drug product with an additional condition for nonprescription use under § 314.56, if FDA has determined the application failed to meet the requirements in § 314.56 applicable to NDAs.

* * * * *

■ 8. Amend § 314.127 by adding paragraph (a)(15) to read as follows:

§ 314.127 Refusal to approve an ANDA.

(a) * * *

(15) For an ANDA for a nonprescription drug product with an additional condition for nonprescription use under § 314.56, if FDA has determined the application failed to meet the requirements in § 314.56 applicable to ANDAs.

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Dated: June 15, 2022.

Robert M. Califf,

Commissioner of Food and Drugs.

[FR Doc. 2022–13309 Filed 6–27–22; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF THE TREASURY

Internal Revenue Service

26 CFR Part 20

[REG–130975–08]

RIN 1545–BI11

Guidance Under Section 2053 Regarding Deduction for Interest Expense and Amounts Paid Under a Personal Guarantee, Certain Substantiation Requirements, and Applicability of Present Value Concepts

AGENCY: Internal Revenue Service (IRS), Treasury.

ACTION: Notice of proposed rulemaking and notice of public hearing.

SUMMARY: This document proposes to amend existing regulations issued under section 2053 of the Internal Revenue Code (Code). The proposed regulations provide guidance on the proper use of present-value principles in determining the amount deductible by an estate for funeral expenses, administration expenses, and certain claims against the estate. In addition, the proposed regulations provide guidance on the deductibility of interest expense accruing on tax and penalties owed by an estate, and interest expense accruing on certain loan obligations incurred by an estate. The proposed regulations also amend and clarify the requirements for substantiating the value of a claim against an estate that is deductible in certain cases. Finally, the proposed regulations provide guidance on the deductibility of amounts paid under a decedent's personal guarantee. The proposed regulations will affect estates of decedents seeking to deduct funeral expenses, administration expenses, and/or certain claims against the estate under section 2053. This document also provides a notice of a public hearing on these proposed regulations.

DATES: Electronic or written comments must be received by September 26, 2022. The public hearing is being held by teleconference on October 12, 2022, at 10 a.m. EST. Requests to speak and outlines of topics to be discussed at the public hearing must be received by September 26, 2022. If no outlines are received by September 26, 2022, the public hearing will be cancelled. Requests to attend the public hearing must be received by 5:00 p.m. EST on October 7, 2022. The telephonic hearing will be made accessible to people with disabilities. Requests for special assistance during the telephonic hearing must be received by October 6, 2022.

ADDRESSES: Commenters are strongly encouraged to submit public comments electronically. Submit electronic submissions via the Federal eRulemaking Portal at *www.regulations.gov* (indicate IRS and REG–130975–08). Once submitted to the Federal eRulemaking Portal, comments cannot be edited or withdrawn. The IRS expects to have limited personnel available to process comments that are submitted on paper through the mail. The IRS will publish any comments submitted electronically, and to the extent practicable, comments submitted on paper to the public docket. Send paper submissions to CC:PA:LPD:PR (REG–130975–08), Room 5205, Internal Revenue Service, P.O. Box 7604, Ben Franklin Station, Washington, DC 20044.

For those requesting to speak during the hearing, send an outline of topic submissions electronically via the Federal eRulemaking Portal at *www.regulations.gov* (indicate IRS and REG–130975–08).

Individuals who want to testify (by telephone) at the public hearing must send an email to *publichearings@irs.gov* to receive the telephone number and access code for the hearing. The subject line of the email must contain the regulation number REG–130975–08 and the word TESTIFY. For example, the subject line may say: Request to TESTIFY at Hearing for REG–130975–08. The email should include a copy of the speaker's public comments and outline of topics. Individuals who want to attend (by telephone) the public hearing must also send an email to *publichearings@irs.gov* to receive the telephone number and access code for the hearing. The subject line of the email must contain the regulation number REG–130975–08 and the word ATTEND. For example, the subject line may say: Request to ATTEND Hearing for REG–130975–08. To request special assistance during the telephonic hearing, contact the Publications and Regulations Branch of the Office of Associate Chief Counsel (Procedure and Administration) by sending an email to *publichearings@irs.gov* (preferred) or by telephone at (202) 317–5177 (not a toll-free number).

FOR FURTHER INFORMATION CONTACT: Concerning the proposed regulations, Karlene Lesho or Melissa Liquerman at (202) 317–6859; concerning the submission of comments, the hearing, or to be placed on the building access list to attend the hearing, Regina Johnson at (202) 317–6901 (not toll-free numbers) or by sending an email to *publichearings@irs.gov.*

SUPPLEMENTARY INFORMATION:

Background and Explanation of Provisions

I. Overview

This document contains proposed amendments to the Estate Tax Regulations (26 CFR part 20) under section 2053.

Section 2001(a) imposes a tax on the transfer of the taxable estate of every decedent who was at death a citizen or resident of the United States. Section 2051 defines the taxable estate as the value of the gross estate less the deductions provided for in sections 2053 through 2058. Section 2031(a) describes the value of the gross estate of the decedent as including the value at the time of the decedent's death of all property, real or personal, tangible or intangible, wherever situated.

Under section 2053(a), for Federal estate tax purposes, the value of the