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: Final rule.

SUMMARY: The Food and Drug Administration (FDA, the Agency, or we) is issuing a final rule to establish requirements for a nonprescription drug product with an additional condition for nonprescription use (ACNU). A nonprescription drug product with an ACNU 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 practitioner licensed by law to administer such drug. The final rule is intended to increase options for applicants to develop and market safe and effective nonprescription drug products and increase consumer access to appropriate, safe, and effective drug products, which could improve public health.

DATES: This rule is effective January 27, 2025.

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

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I. Executive Summary

A. Purpose of the Final Rule

FDA is finalizing this rule to establish requirements for a nonprescription drug product with an ACNU. A nonprescription drug product with an ACNU is a drug product that could be legally 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 practitioner licensed by law to administer such drug. Without this rule, nonprescription drug products are limited to drug products that can be labeled with sufficient information for consumers to appropriately self-select and use the drug product without the supervision of a practitioner licensed by law to administer such drug. For certain drug products, labeling alone cannot adequately communicate the information needed for consumers to appropriately self-select or use the drug product without the supervision of a practitioner licensed by law to administer such drug. The final rule is intended to increase options for applicants [1] to develop and market safe and effective nonprescription drug products and increase consumer access to appropriate, safe, and effective drug products, which could improve public health.

B. Summary of the Major Provisions of the Final Rule

This final rule establishes requirements for a nonprescription drug product with an ACNU, including application, labeling, and postmarketing reporting requirements. In addition to applicable existing application requirements, the final rule establishes the specific requirements for a new drug application (NDA) or abbreviated new drug application (ANDA) for a nonprescription drug product with an ACNU. In circumstances where a prescription drug product is already approved, the rule requires an applicant to submit a separate application for the approval of a nonprescription drug product with an ACNU, rather than a supplement to the existing application for the approved prescription drug product. The final rule establishes specific labeling requirements, including the content and format of specific labeling statements. Additionally, the rule requires that an applicant submit a postmarketing report of an ACNU failure.

The final rule clarifies that an ACNU constitutes a meaningful difference [2]

[1] While we recognize that in certain circumstances ''sponsor'' is the correct term for the person who would be developing a nonprescription drug product with an ACNU, we used the term ''applicant'' throughout the final rule for consistency (see the definition for applicant in 21 CFR 314.3(b) and for sponsor in 21 CFR 312.3(b)).

[2] FDA has used the terms ''meaningful difference'' and ''clinically meaningful difference'' interchangeably. Both refer to the same scientific

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 practitioner licensed by law to administer such drug; therefore, a prescription drug product and a nonprescription drug product with an ACNU with the same active ingredient may be simultaneously marketed even if they do not have meaningful differences other than the ACNU, such as different indications or strengths.

The final rule specifies that FDA will refuse to approve an application for a nonprescription drug product with an ACNU if the application fails to meet applicable requirements.

The final rule exempts a nonprescription drug product with an ACNU from the requirement to be labeled with adequate directions for use, provided that certain labeling conditions are met and the ACNU is implemented by the applicant as approved by FDA.

Finally, the final rule explains certain circumstances in which a nonprescription drug product with an ACNU would be misbranded.

FDA received many comments supporting the proposed rule's intent to increase options for applicants to develop and market safe and effective nonprescription drug products and increase consumer access to appropriate, safe, and effective drug products. Additionally, we received comments expressing concerns about certain proposed requirements and the burden of those requirements for applicants. In response to several comments expressing concerns about the proposed postmarketing reporting requirements for nonprescription drug products with an ACNU, we are revising the proposed requirements to provide greater clarity for when a postmarketing report of ACNU failure must be submitted to FDA and to reduce the burden on applicants by decreasing any potential unnecessary reporting and ensuring consistency with existing postmarketing reporting requirements. In response to several comments about the proposed labeling statements on the principal display panel (PDP) and Drug Facts labeling (DFL), we are revising the proposed labeling requirements to allow FDA to approve an applicant's proposed labeling statements that vary somewhat from the labeling statements in the codified text, under certain circumstances. Additionally, we are revising the proposed labeling requirements to allow flexibility for the placement of the labeling statement on the DFL depending on the purpose of the ACNU.

C. Legal Authority

This final rule, which establishes requirements for a nonprescription drug product with an ACNU, is authorized by sections 201(n), 502, 503(b), 505, and 701(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 321(n), 352, 353(b), 355, and 371(a)).

D. Benefits, Costs, and Transfers

The final rule establishes requirements for a nonprescription drug product with an ACNU. Compared to traditional nonprescription drug products, which consumers must be able to self-select and use based on their labeling, this approved ACNU, in addition to the labeling, will ensure the appropriate self-selection, the appropriate use, or both of a nonprescription drug product without the supervision of a practitioner licensed by law to administer such drug. We expect this rule will expand consumer access to certain drug products in a nonprescription setting and increase options for applicants to develop and market safe and effective nonprescription drug products.

We estimate a reduction in access costs to consumers who could transfer from a prescription to a nonprescription drug product with an ACNU. In our analysis, access costs include the time to see a doctor to obtain a prescription, including waiting time and other transportation costs. We also include co-pay and out-of-pocket costs in our estimate of access costs. We compare the baseline access costs to the access costs under potential scenarios with the final rule to estimate the potential benefits for each consumer purchase. In this analysis, we use the costs to obtain candidate prescription-only products as our baseline access cost. Our primary estimate of reduction in access costs is $33.62 per consumer per purchase with a range of $0 to $67.23. We also quantify the value of the potential reduction in the number of meetings with applicants that will occur during the approval process. This estimate includes benefits to FDA and industry. Our primary estimate is $68,773.11 per applicant with a range of $56,332.65 to $81,763.56. 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, and purchases that might occur; and consumer preferences to switch drug products. However, we present estimates in the uncertainty section of this analysis.

Although an applicant will incur the costs to develop and submit an application for a nonprescription drug product with an ACNU, for this analysis, we assume that applicants submit applications only when they believe that the profits from the approval will exceed the costs of the application. We lack information to monetize these potential profits and costs over a 10-year horizon.

Monetized costs include a one-time cost of reading and understanding the rule per interested party in pursuing this path for their drug products. We do not monetize these estimates for more than one interested party because of the high uncertainty about the number of interested parties over this time horizon. The primary estimate equals $1,156.74 with a range of $533.88 to $1,779.60.

Government-sponsored and commercial insurance payers may experience cost savings because the availability of nonprescription drug products with an ACNU may decrease insurance claims and, potentially, future medical costs. For example, access to drug products under this new paradigm will allow consumers to treat some medical conditions using nonprescription drug products with an ACNU without the supervision of a practitioner licensed by law to administer such drug. We do not estimate such cost savings due to lack of data.

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
FTC	Federal Trade Commission
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

determination. See, *e.g.,* 83 FR 13994 (April 2, 2018) and 87 FR 68702 (November 16, 2022).

III. Background

A. Need for the Regulation

Nonprescription drug products are important for the treatment of many conditions and diseases. Unlike prescription drug products, nonprescription drug products may be accessed and used safely and effectively by consumers without the supervision of a practitioner licensed by law to administer such drugs for their intended use. At present, the majority of nonprescription drug products are intended to provide temporary relief of minor symptoms or to treat self-limited conditions and diseases. 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 certain chronic diseases or conditions. This rule will increase options for applicants to develop and market safe and effective nonprescription drug products and increase consumer access to appropriate, safe, and effective drug products. The availability of nonprescription drug products with an ACNU may provide public health benefits by facilitating consumers' ability to care for themselves and access to appropriate medical treatment. For more information on the need for regulation, see 87 FR 38313 (June 28, 2022; 2022 proposed rule).

B. FDA's 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 (21 U.S.C. 355). 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 in the FD&C Act and implementing regulations.

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 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. For more on FDA's regulatory framework for nonprescription drug products, see the 2022 proposed rule entitled ''Nonprescription Drug Product With an Additional Condition for Nonprescription Use'' (87 FR 38313).

C. History of the Rulemaking

In the 2022 proposed rule, FDA proposed requirements for a nonprescription drug product with an ACNU, 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. The proposed rule proposed additional application requirements, labeling requirements, and postmarketing reporting requirements for a nonprescription drug product with an ACNU. For more information on the history of rulemaking for the proposed rule, see 87 FR 38313.

D. Summary of Comments to the Proposed Rule

We received approximately 200 comments. Comments were submitted by different entities and individuals including private citizens, consumer groups, trade organizations, pharmaceutical industry, and public advocacy groups. We received comments on different topics including:

- General support for or opposition to the proposed rule;
- The applicability of the proposed rule and whether certain drug products are appropriate for development as a nonprescription drug product with an ACNU;
- The proposed definition of ACNU;
- The proposed requirements for an application for a nonprescription drug product with an ACNU, including specific application requirements such as the submission of a separate application, labeling, and postmarketing reports;
- The simultaneous marketing of prescription drug products and nonprescription drug products with an ACNU; and
- The role of the pharmacist with a nonprescription drug product with an ACNU.

E. General Overview of the Final Rule

FDA considered all comments received on the proposed rule, and in response, we have made changes for clarity and to reduce the burden on applicants in meeting certain requirements. The following is a summary of certain changes from the proposed rule:

- Revising the postmarketing reporting requirement to further clarify that a report must be submitted when there is an ACNU failure, and further explain the meaning of ACNU failure, to enhance consistency with current processes for the submission of other required postmarketing reports;
- Revising the requirements for required labeling statements on the PDP and DFL to permit applicants to propose revisions to the content of the required statements under certain circumstances;
- Revising the placement for the required labeling statement on the DFL depending on the purpose of the ACNU; and
- Clarifying certain circumstances when a nonprescription drug product with an ACNU would be misbranded by providing more detail about what it means when an ACNU is not implemented by the applicant as approved by FDA in the application.

IV. Legal Authority

We are issuing this final rule under sections 201(n), 502, 503(b), 505, and 701(a) of the FD&C Act. 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 issuing 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.

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 drug. 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 NDA 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 requiring that a drug product be dispensed by prescription when it is not safe for use except under the supervision of a practitioner licensed by law to administer such drug product because of toxicity or other potentiality for harmful effect, or the method of the drug product's use, or the collateral measures necessary to the drug product's use (see section 503(b)(1) of the FD&C Act). If a drug product does not require a prescription under these provisions, it can be marketed as nonprescription. Section 503(b) gives authority for the Secretary, which is delegated to FDA, to make certain decisions regarding a drug's applicable category (see, *e.g.,* section 503(b)(1) and (b)(3); see also the FDA Staff Manual Guide 1410.10 (Delegations of Authority to the Commissioner of Food and Dugs), available at *https://www.fda.gov/about-fda/reports-manuals-forms/staff-manual-guides*.).

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

V. Comments on the Proposed Rule and FDA Response

A. Introduction

We received approximately 200 comment letters on the proposed rule by the close of the comment period, each containing one or more comments on one or more issues. We received comments from entities and individuals including private citizens, consumer groups, trade organizations, pharmaceutical industry, and public advocacy groups. The 120-day comment period was extended by an additional 30 days based on requests from members of the public.

We describe and respond to the comments in sections V.B through V.N of this document. We have numbered each comment to help distinguish between different comments. We have grouped similar comments together under the same number, and in some cases, we have separated different issues discussed in the same comment and designated them as distinct comments for purposes of our responses. The number assigned to each comment or comment topic is purely for organizational purposes and does not signify the comment's value or importance or the order in which comments were received.

B. Description of General Comments and FDA Responses

We received many general comments supporting and opposing the purpose, necessity, and appropriateness of the proposed rule. In the following paragraphs, we discuss and respond to these general comments. We did not make any changes to the final rule based on consideration of these general comments.

(Comment 1) Many comments generally support the proposed rule because it could broaden the types of nonprescription drug products available to consumers. For example, these commenters believe the proposed rule has the potential to improve consumer access, improve consumer autonomy, expand the market for companies, address undertreatment of many common and chronic conditions in the United States, and reduce the number of routine visits to a healthcare practitioner.

(Response 1) We appreciate the general support. The rule is intended to increase options for applicants to develop and market safe and effective nonprescription drug products and increase consumer access to appropriate, safe, and effective drug products, which could improve public health.

(Comment 2) We received a comment recommending that Congress, in conjunction with State boards of pharmacy, State health departments, and State/national pharmacist associations, is better positioned to increase options for the development and marketing of safe and effective nonprescription drug products through legislative changes, as compared to FDA acting through regulatory changes. The same comment sought clarity on whether FDA has the legal authority to approve nonprescription drug products with ACNUs that restrict distribution and sales of the drug product.

(Response 2) As part of the statutory framework for regulation of drug products, Congress recognized the need for specific considerations and requirements for prescription drugs. As explained further in the response to comment 41, Congress amended section 503(b) of the FD&C Act in 1951 to reduce confusion and uncertainty in the market as to when a drug is safe for use without the supervision of a practitioner licensed by law to administer such drug, as well as to remove unnecessary restrictions on dispensing, and to protect public health from abuses in the sale of potent prescription drugs. Several provisions of the FD&C Act, including section 503(b), demonstrate that Congress envisioned that FDA would determine which drugs must be dispensed only upon a prescription and which drugs would not require a prescription. For example, section 503(b)(1) of the FD&C Act states, in relevant part, that a drug intended for human use that, ''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 administer such drug,'' must be limited to prescription use. That section authorizes FDA, in approving an application under section 505 of the FD&C Act, to require the supervision of a practitioner licensed by law to administer such a drug. Conversely, FDA may approve drugs that do not fall within section 503(b)(1) of the FD&C Act for nonprescription use. In addition, section 503(b)(3) of the FD&C Act authorizes FDA to issue regulations to remove the prescription-only dispensing requirements from drugs when such requirements are not necessary for the protection of the public health. Congress explicitly delegated FDA authority to use its scientific judgement to determine which drugs should be prescription or nonprescription, within the statutory criteria.

Further, section 503(b)(1)(A) of the FD&C Act specifies certain identified features of a drug, such as its ''toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary for its use,'' that are relevant to the determination of prescription or nonprescription status. The statute only states these factors in describing the prescription drug category, while leaving the nonprescription drug category described in opposition to the prescription

category. See section 503(b)(4)(A) and (B) (separately prescribing labeling requirements for ''[a] drug that is subject to [section 503(b)(1)]'' and, by contrast, ''[a] drug to which [section 503(b)(1)] does not apply''). However, these factors are not unique to prescription drugs; all drugs have a ''method of . . . use,'' all or nearly all drugs have some level of ''toxicity or other potentiality for harmful effect,'' and many drugs require at least some ''collateral measures'' for safe use. Merriam-Webster defines the adjective ''collateral'' to mean, among other things, ''accompanying as secondary or subordinate. . .[and/or] serving to support or reinforce.'' [3] Thus the key distinction in the statute between prescription and nonprescription drugs is not that certain drugs have these factors while others do not; rather prescription drugs are those that, when considering these factors, are not safe for use except under the supervision of a practitioner licensed by law to administer such a drug.

Features of a drug that qualify as ''collateral measures'' vary from drug to drug, and can include, for example, things which a layperson, because of their lack of education, training, and experience, cannot do to safely manage the disease. These include, but are not limited to, taking a proper history, doing a physical exam, ordering appropriate laboratory tests, having a knowledge of the relevant diseases, integrating the results of the history, exam, and tests with this knowledge, making a diagnosis, designing a treatment plan, and carrying the plan through with proper continuing evaluation. If the collateral measures necessary for safe use of the drug require the supervision of a practitioner licensed by law to administer such drug, section 503(b)(1)(A) requires that it can only be dispensed pursuant to a prescription.

This rule recognizes that drugs approved with certain types of collateral measures do not require supervision of a practitioner licensed by law to administer such drug. Some such measures may be things that used to require a practitioner's direct involvement, but that no longer require such supervision because of the availability of technological advancements. For example, with Drug X (see more information about Drug X, a fictitious nonprescription drug product with an ACNU, in the proposed rule (87 FR 38313 at 38319)), 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. Using a consumer's answers to the questions, the underlying program or other operating information used by the secure website, not the consumer, calculates the risk score for a serious side effect and determines if the consumer has an acceptable disease-specific risk score to use Drug X and therefore purchase Drug X.

This type of collateral measure could also be accomplished through the direct involvement of a practitioner licensed by law to administer such drug, as the practitioner integrates their knowledge of the patient with their knowledge of the disease and the drug—but now, in certain cases, this has the potential to be done without a practitioner's direct involvement because of the availability of technology that can conduct the necessary evaluation. By carefully evaluating whether such advancements in collateral measures mean that the drug ''is *not safe for use except* under the supervision of a practitioner licensed by law to administer such drug . . .'', section 503(b)(1)(A) for the FD&C Act (emphasis added), FDA is implementing the statute's direction to limit the burdens of dispensing drugs by prescription to only those drugs for which they are truly necessary.

More generally, as part of its broad authority to approve and regulate drug products, including to establish specific regulations for drug products, FDA is authorized to determine the conditions under which a drug is safe and effective for use without a prescription, including a determination that an ACNU is needed where labeling alone will not suffice (see, *e.g.,* sections 505, 505G, and 701 of the FD&C Act). Until now, FDA's approval of nonprescription drug products has been limited to those that can be labeled with sufficient information for consumers to appropriately self-select and use the drug product. These nonprescription drug products are generally available ''over-the-counter'' (*e.g.,* on a retail shelf). However, nothing in the FD&C Act compels nonprescription drug products to be limited in this way, nor does the FD&C Act dictate a particular manner in which a nonprescription drug must be made available to consumers.

For certain drug products, labeling alone may not adequately communicate the information needed for consumers to appropriately self-select or use the drug product, but consumers may still be able to use the product safely and effectively without the supervision of a practitioner licensed by law to administer such drug under certain conditions. Nonprescription drug products approved with ACNUs have an additional condition of use, beyond labeling, that allows consumers to appropriately self-select or use the drug product without the supervision of a practitioner licensed by law to administer such drug. Thus, a nonprescription drug product with an ACNU, although not an ''over-the-counter'' drug product, is a nonprescription drug product under section 503(b) of the FD&C Act, because, when approved with an ACNU, it is safe and effective for consumers to use without the supervision of a practitioner licensed by law to administer such drug.

Additionally, FDA disagrees with this comment's suggestion that legislative change is needed to authorize this rule. As explained above, FDA has adequate statutory authority to issue this rule. See also the responses to comments 39 through 43 below. FDA has long determined which drug products are ones that consumers can appropriately self-select or use without the supervision of a practitioner licensed by law to administer such drug, and under what conditions, and these determinations are squarely within FDA's scientific expertise and authority under the FD&C Act. Additionally, FDA has engaged the public in various ways throughout the development of this rule. For example, 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 2022 proposed rule (see 87 FR 38313). FDA also carefully considered public comments in developing the final rule.

(Comment 3) We received many comments on the role of a pharmacist in relation to nonprescription drug products with ACNUs. One comment suggests that nonprescription drug products with ACNUs be available only from State-licensed pharmacies, where there is a licensed pharmacist available to assist consumers. Many of these comments suggest that FDA require nonprescription drug products with ACNUs to be sold only after consultation with a pharmacist. The comments assert that pharmacists should: (1) assist with determining whether a nonprescription drug product with an ACNU is appropriate for the consumer; (2) ensure consumer fulfillment of the ACNU; and (3) provide a stopgap for consumer

[3] *https://www.merriam-webster.com/dictionary/collateral.*

questions or concerns regarding the benefits and risks of the nonprescription drug product with an ACNU.

Additionally, we received many comments about the practice of pharmacy or medicine that are outside the scope for this rulemaking, including comments about reimbursement for pharmacist professional services, increased prescribing authority for pharmacists, pharmacy recordkeeping, documentation of nonprescription drug products in profiles for the consumer or drug history data repositories, State laws about sales of nonprescription drug products, and legal liability for pharmacists.

(Response 3) FDA disagrees that a nonprescription drug product with an ACNU should be available only from State-licensed pharmacies, where there is a licensed pharmacist available to assist consumers, or sold only after consultation with a pharmacist. The purpose of this rule is to increase options for applicants to develop and market safe and effective nonprescription drug products, which in turn may increase consumer access to appropriate, safe, and effective drug products. 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. Nonprescription drug products are generally available for consumers to purchase at such as pharmacies, supermarkets, or other retail locations, and from online retailers. FDA anticipates that nonprescription drug products with an ACNU would be sold similarly. FDA recognizes the potential benefit of providing consumers with appropriate access to nonprescription drug products. As long as consumers can fulfill the ACNU, limiting the locations in which nonprescription drug products with an ACNU can be sold, or requiring consultation with a healthcare professional (*i.e.,* a pharmacist), when not necessary for safe and effective use of the drug product, would limit consumer access to appropriate, safe, and effective drug products, which would unnecessarily undermine these public health benefits of this rule.

Such a system also would be inconsistent with this final rule, which pertains to nonprescription drug products. Section 503(b) of the FD&C Act requires that a drug product be dispensed by prescription when it is not safe for use except under the supervision of a practitioner licensed by law to administer such drug because of toxicity or other potentiality for harmful effect, or the method of the drug product's use, or the collateral measures necessary to the drug product's use (see section 503(b)(1) of the FD&C Act). If an approved drug product does not meet the criteria for prescription-only dispensing, it may be marketed as nonprescription (see 87 FR 38313 at 38316).

C. Comments on Applicability and FDA Responses

We proposed requirements for NDAs and ANDAs for nonprescription drug products with ACNUs (see proposed 21 CFR 201.67, 201.130, 314.56, 314.81, 314.125, and 314.127). In the following paragraphs, we discuss comments on the applicability of the rule. After consideration of public comments received, we are finalizing our proposals without change.

(Comment 4) We received several comments on how the rule will be applied to already marketed drug products. We received a comment asserting that an ACNU cannot be retroactively required for a nonprescription drug product that FDA has already approved without an ACNU. However, the comment requests FDA make clear in the final rule that FDA has the authority to revisit the approval of a nonprescription drug product when information emerges in the postmarketing setting regarding the safety and efficacy of the nonprescription drug product. Further, we received a comment that FDA approval of a nonprescription drug product with an ACNU should not become the ''temporary stopping ground'' for every drug moving from prescription to nonprescription status.

(Response 4) We do not intend, as a result of this rule, to revisit nonprescription drug products marketed under approved applications. The approval of an application for a nonprescription drug product prior to the finalization of this rule was based on FDA's finding, in part, that labeling alone is sufficient for the drug product to be used safely and effectively by consumers. Under this rule, such a finding by FDA would obviate the need for the approved nonprescription drug product to have an ACNU in order for the drug product to be used safely and effectively. In addition, we do not think that FDA approval of a nonprescription drug product with an ACNU will generally become a ''temporary stopping ground'' as a step toward nonprescription approval without an ACNU (*i.e.,* the applicant would regularly propose to remove the ACNU after approval) because the applicant would have demonstrated and FDA would have determined that labeling, alone, was insufficient to ensure appropriate self-selection or appropriate actual use, or both.

We agree that FDA has authority to address safety and efficacy concerns observed for an approved drug product in the postmarketing setting, including existing authority under the FD&C Act and current regulations to withdraw approval of an application in certain circumstances (see section 505(e) of the FD&C Act and 21 CFR 314.150). This includes withdrawal of an approval of an application for a nonprescription drug product with or without an ACNU for safety or efficacy concerns. In certain situations, if FDA withdraws approval of an application for a nonprescription drug product due to the emergence of a safety issue with regard to appropriate self-selection or actual use of the drug product, the applicant could submit a new application for the product as a nonprescription drug product with an ACNU to ensure appropriate self-selection or actual use, as appropriate.

(Comment 5) We received over 100 comments recommending that specific drug products be available as nonprescription (*e.g.,* antibiotics) or that specific drug products not be made available as nonprescription (*e.g.,* albuterol inhaler). The majority of these comments recommend that oral contraceptives should be available as nonprescription. We also received one comment advocating FDA use the rule to increase access to naloxone. These comments did not discuss whether ACNUs would be appropriate for these drug products if available as nonprescription.

Additionally, we received a few comments discussing the appropriateness of approving nonprescription drug products with ACNUs for certain general types of drug products. We received one comment recommending FDA only approve a nonprescription drug product with an ACNU if it has a low risk for misuse. We received a few comments expressing concerns about the appropriateness of nonprescription drug products with ACNUs for the treatment of chronic conditions and asserting that consumers may not be able to appropriately manage chronic health conditions without the communication and supervision by a healthcare practitioner. We also received a comment discussing that FDA may have unintentionally implied that a drug product to treat chronic conditions or intended for long-term use must have an ACNU to be available as nonprescription. We received several comments expressing concern about the approval of a nonprescription drug

product with an ACNU that has potentially harmful interactions and recommending that the ACNU needs to include information on possible interactions (*e.g.,* drug-drug interactions, questions about diet, vitamins, complementary and alternative medicine, and other nonprescription drug products) to avoid potential life-threatening adverse drug experiences.

(Response 5) We disagree that we need to clarify the rule to address comments regarding approval of specific drug products or categories of drug products or restrict the types of drug products that FDA may consider for approval as a nonprescription drug product with an ACNU. FDA considers the specifics of each application during its review, including the potential risk for misuse of the drug product. As long as the application meets the existing evidentiary standards under the FD&C Act and current FDA regulations to demonstrate the safety and effectiveness of the drug product, and the drug product does not meet the criteria for prescription-only dispensing (see section 503(b)(1) of the FD&C Act), FDA may approve the application as nonprescription. FDA has the authority to approve a nonprescription drug product intended for a chronic disease or condition, or for long-term use, that meets the existing evidentiary standards and FDA regulations. In fact, FDA has approved nonprescription drug products for chronic diseases or conditions, or for long-term use, based on FDA's finding, in part, that labeling alone is sufficient for the drug product to be used safely and effectively by consumers. For example, on January 25, 2013, FDA approved NDA 202211 Oxytrol for Women (oxybutynin) extended-release film, 3.9 milligrams (mg), for the treatment of overactive bladder in women. When relevant, the applicant must ensure consumers understand information on potential interactions to safely and effectively use a nonprescription drug product with an ACNU. Further, consistent with the existing requirements for all nonprescription drug products, an applicant of a nonprescription drug product with an ACNU must include specific warnings, including all major drug-drug and drug-food interaction warnings in the DFL (see § 201.66(c)(5)(v) (21 CFR 201.66(c)(5)(v))).

We appreciate the public's interest in advocating for specific drug products or types of drug products to be approved or not be approved for nonprescription use, such as oral contraceptives and naloxone. Of note, on July 13, 2023, FDA approved supplemental NDA 017031 for Opill (norgestrel) tablet, 0.075 mg, as a nonprescription daily oral contraceptive to prevent pregnancy. On March 29, 2023, FDA approved supplemental NDA 208411 for Narcan (naloxone hydrochloride) nasal spray, 4 mg, for nonprescription use to reverse the effects of a life-threatening opioid emergency. Additionally, on July 28, 2023, FDA approved NDA 217722 for RiVive (naloxone hydrochloride) nasal spray, 3 mg, for nonprescription use for emergency treatment of opioid overdose in adults and children. Based on FDA's review under relevant statutory and regulatory standards for approval, FDA determined the labeling for these drug products was sufficient to ensure consumers' appropriate self-selection and use of the products without the supervision of a practitioner licensed by law to administer such drug.

(Comment 6) We received several comments asking FDA to clarify when an applicant should propose an ACNU for a nonprescription drug product. We received a comment that asserts that the definition of an ACNU should be limited to those conditions that are most feasible to implement at the pharmacy-patient level and suggests that FDA provide a finite list of additional conditions that would be applied to real-world situations. We received several comments asking FDA to provide examples when labeling is inherently insufficient for appropriate self-selection or actual use, if these examples exist, or examples of specific drug products that FDA considers as possible candidates for approval.

(Response 6) We decline to establish such inflexible limits on when an ACNU should be proposed. The rule is intended to increase options for an applicant to develop and market safe and effective nonprescription drug products and increase consumer access to appropriate, safe, and effective drug products. The rule is intentionally flexible, mindful that technologies evolve and ACNUs may be developed for many different nonprescription drug products. FDA placing limits on the types of conditions that can be proposed or the creation of a finite list of additional conditions is not warranted and may unnecessarily restrict the type and number of drug products that could be marketed nonprescription, contrary to the intent of this rule.

We expect applicants may submit applications for nonprescription drug products with ACNUs for a wide range of indications, including for drug products intended to treat both acute and chronic diseases. However, FDA cannot predetermine the full range of indications for which nonprescription drug products with ACNUs could be approved, nor can the Agency predetermine that all proposed nonprescription drug products with ACNUs for a given indication would be safe and effective, because FDA considers the specifics of each application during its review. Further, we cannot provide a general list or guideline of when labeling alone is insufficient to ensure appropriate self-selection or appropriate actual use, or both, because the determination of when labeling is insufficient is made for a specific nonprescription drug product based upon the data or other information that the applicant submits to FDA as part of an application.

D. Comments on Definition and FDA Responses

We proposed to establish a definition for additional condition for nonprescription use (ACNU) (see proposed 21 CFR 201.67(b)(1) and 314.56(a)(1)). As proposed, an 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. As an example, an ACNU for appropriate self-selection could be a questionnaire that consumers are required to complete on a secure website or mobile application created by the applicant to determine whether the drug product is appropriate for the consumer. The questionnaire would contain a series of questions that the consumer answers. The underlying program or other operating information used by the secure website or mobile application would determine if the drug is appropriate for the consumer based on these responses. If the drug is indeed appropriate for the consumer, the consumer could then access and purchase the drug product. For a more specific example, see the proposed rule (87 FR 38313 at 38319), in which we discuss Drug X, a fictitious nonprescription drug product with an ACNU.

In the following paragraphs, we discuss comments on the proposed definition. After consideration of public comments received, we are finalizing our proposal with revisions for consistency with the wording in section 503(b) of the FD&C Act. Therefore, we

are revising the phrase ''of a healthcare practitioner'' to ''of a practitioner licensed by law to administer such drug.''

(Comment 7) We received one comment supporting FDA's proposed definition of an ACNU because it provides sufficient flexibility for the applicant to develop and tailor the ACNU to a specific drug product.

(Response 7) We agree that the proposed definition of ACNU is sufficiently broad, as was intended, to give applicants flexibility regarding the types of additional conditions that may be proposed and how those conditions can be implemented (87 FR 38313 at 38318). This flexibility will allow applicants to consider the unique benefit and risk considerations for a particular drug product while developing an ACNU to ensure consumers' appropriate self-selection or appropriate actual use, or both, of the drug product.

(Comment 8) We also received several comments disagreeing with FDA's proposed definition of ACNU. Some comments disagree with the use of the term ''ensure'' in the definition and recommend FDA revise the definition to replace the term ''ensure'' with ''enable.'' The comments assert that the term ''ensure'' implies that any risk to consumers from the nonprescription drug product with an ACNU has been eliminated even though all drug products have residual risk regardless of any mitigation steps taken. We received one comment asserting that the proposed definition is vague and suggesting that FDA provide a definition of ''appropriate actual use'' and ''appropriate self-selection.''

(Response 8) We disagree with replacing the term ''ensure'' with ''enable'' in the definition. The Merriam-Webster dictionary defines ''ensure'' as ''to make sure, certain, or safe.'' The Merriam-Webster dictionary defines ''enable'' as ''to make possible, practical, or easy or to provide with the means or opportunity.'' The term ''ensure'' reflects a greater level of certainty that is consistent with FDA's approval standards. All drug products, including nonprescription drug products, have risks. As part of our regulatory decision-making process, we conduct a structured benefit-risk assessment to facilitate the balanced consideration of benefits and risks (see, *e.g.,* section 505(d) of the FD&C Act and § 314.50 (21 CFR 314.50)). Nothing in the rule affects this benefit-risk assessment for an application for a nonprescription drug product with an ACNU.

FDA disagrees that specifically defining ''appropriate actual use'' and ''appropriate self-selection'' is necessary for nonprescription drug products with an ACNU. The terms ''actual use'' and ''self-selection'' are used in the context of all nonprescription drug products. In general, applicants of nonprescription drug products conduct consumer studies such as label comprehension studies, self-selection studies, actual use studies, and human factors studies to help demonstrate that consumers can correctly self-select and correctly use the drug products (see also 87 FR 38313 at 38316). FDA has defined ''self-selection'' in FDA guidance for industry (Ref. 1 and 87 FR 38313 at 38315).

(Comment 9) Several comments recommend FDA revise the proposed definition to make clear that applicants, not FDA, should determine when an ACNU is necessary. The comments assert that the applicant should have the ability to evaluate the need for an ACNU and propose the use of an ACNU without seeking prior agreement from FDA.

(Response 9) We disagree with revising the definition to permit the applicant, not FDA, to make the final determination on the necessity of the ACNU. To approve a drug product, FDA must determine whether the specific application meets the applicable statutory and regulatory requirements. FDA will not require a nonprescription drug product to have an ACNU if the drug product can be used safely and effectively by consumers, without the supervision of a practitioner licensed by law to administer such drug, based on labeling alone. Requiring unnecessary ACNUs would be inconsistent with the goal of this rulemaking, which is to increase consumer access to safe and effective nonprescription drug products.

While applicants are not required to meet with FDA prior to the submission of an application for a nonprescription drug product with an ACNU, we encourage applicants to meet with FDA to discuss their drug development plans and seek feedback, including whether an ACNU may be necessary. However, it is during FDA's review of an application that FDA must determine whether the application meets the applicable statutory and regulatory requirements, including whether the applicant demonstrates the necessity of the ACNU to ensure appropriate self-selection or appropriate actual use, or both (see, *e.g.,* § 314.56(c)(1)(v)) in order to approve the nonprescription drug product with an ACNU.

E. Comments on Separate Application Required for a Nonprescription Drug Product With an ACNU and FDA Responses

We proposed that an applicant must submit a separate application for a nonprescription drug product with an ACNU (proposed 21 CFR 314.56(b)). For cases where there is an approved prescription drug product, we proposed that initial approval for a nonprescription drug product with an ACNU cannot be obtained through a supplement to the approved application for prescription use of the drug product.

In the following paragraphs, we discuss comments on this proposed requirement. After consideration of public comments received, we are finalizing our proposal with a clarifying revision to explain that this provision supersedes § 310.200(b) (21 CFR 310.200(b)) with regard to nonprescription drug products with an ACNU. To clarify and avoid ambiguity, we are adding the clause ''Notwithstanding § 310.200(b)'' to the beginning of the first sentence in 21 CFR 314.56(b).

(Comment 10) We received a few comments supporting the proposed requirement for the submission of a separate application for a nonprescription drug product with an ACNU because it would improve consumer options. Additionally, a commenter asserted that the proposed requirement increases equity and access to drug products. We also received several comments opposing this proposed requirement and asserting that an applicant should be allowed to submit a supplement to an approved prescription application rather than a separate application. One comment asserts that an applicant should not be required to submit a separate application simply because the ACNU is part of a development program, especially where the formulation is similar to the approved prescription application. We received a comment requesting FDA remove the proposed requirement and, instead, address the issue on a case-by-case basis to determine the circumstances when it would be appropriate for an applicant to seek approval of a nonprescription drug product with an ACNU by submitting a supplement. The comment argues that the proposed requirement for a separate application is inconsistent with the FDA guidance for industry from December 2004 ''Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees'' (available at *https://www.fda.gov/media/72397/download*) and FDA

practices, which, according to the comment, contemplate that labeling changes may be the subject of a supplement. In addition, some comments assert that requiring a separate application would disincentivize innovation and limit utilization of the ACNU pathway because the separate application would allow for the potential continued marketing of generic prescription drugs that would compete with the nonprescription drug with an ACNU. The commenters assert that incorporating an ACNU into a development program for a nonprescription drug product is expected to increase the overall costs and time in developing the nonprescription drug product. The commenters explain that there is typically a limited period of marketing exclusivity when a new nonprescription drug product is approved, a ''long-accepted means of incentivizing'' applicants to undertake such investment. Therefore, the commenters argue that potential continued simultaneous marketing of a generic prescription drug product that could compete with the nonprescription drug product with an ACNU would render any marketing exclusivity moot.

(Response 10) We disagree with removing the requirement for the submission of a separate application. This requirement is essential to achieving the key policy goal of increasing consumer access to appropriate drug products. In cases where there is an approved prescription drug product, this requirement creates a pathway for the simultaneous marketing of the prescription drug product, along with the nonprescription drug product with an ACNU. While many consumers will benefit from the availability of nonprescription drug products with ACNUs, FDA also recognizes that some may not be able to access the nonprescription drug product with an ACNU. For example, a consumer may not be able to access the technology that operationalizes the ACNU. Therefore, continued availability of the prescription drug product along with the nonprescription drug product with an ACNU promotes the greatest access to needed drug products.

We are also clarifying that a separate application must be submitted for a nonprescription drug product with an ACNU notwithstanding § 310.200, which states that an interested person may submit a supplement to an approved new drug application to propose to exempt a drug from the prescription-dispensing requirements of section 503(b)(1)(B) of the FD&C Act. Under § 310.200(b), applicants may continue to submit a supplement to switch a drug from prescription to nonprescription status if the nonprescription drug product would not have an ACNU and the resulting approved application would only address the nonprescription drug product. Nonprescription drug products without ACNUs do not implicate the same issues regarding continued consumer access to appropriate drug products, because they are generally available to consumers and do not have additional conditions of approval that restrict consumer access.

Additionally, we do not agree that the proposed separate application requirement is inconsistent with existing FDA guidance. The guidance entitled ''Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees'' did not contemplate and, therefore, did not address the submission of an application for a nonprescription drug product with an ACNU. Therefore, the guidance is not relevant to the question of whether a separate application or a supplement is appropriate for such a product. Furthermore, the guidance document merely provides FDA's recommendations on submission of certain applications to FDA. The guidance document does not set forth any requirements, and the recommendations therein are not binding on FDA or applicants.

We also do not agree that requiring a separate application would necessarily disincentivize innovation and limit utilization of the ACNU pathway. This assertion is speculative and does not outweigh the potential benefits from requiring a separate application, which would increase consumer access to appropriate drug products. We acknowledge that the cost to develop a nonprescription drug product with an ACNU is higher than a nonprescription drug product without an ACNU. The Appendix of the Regulatory Impact Analysis estimates that the core development cost of a nonprescription drug product is $31.1 million while the estimated cost to develop cost of a nonprescription drug product with an ACNU is $47.3 million, an estimated markup of $16.2 million for ACNU-related development. However, as noted in section I.C. of the Regulatory Impact Analysis, evidence shows that roughly 60 percent of purchases for a nonprescription drug product are from new-to-therapy consumers who had not previously taken the drug before it switched from prescription status, suggesting that the potential to attract new-to-therapy consumers for nonprescription drug products is substantial (Ref. 13). Further, section V.B. of the Regulatory Impact Analysis estimates that every year nonprescription drug manufacturers get $112.02 million of additional revenue from switching a drug to nonprescription status (Ref. 13), which also indicates there will be incentives for drug manufacturers to innovate and use the ACNU pathway. We disagree that simultaneous marketing would reduce or render moot the benefit of any statutory exclusivity that may be associated with a nonprescription drug product. For example, three-year new clinical investigation exclusivity (*e.g.,* section 505(c)(3)(E)(iii) and (j)(5)(F)(iii) of the FD&C Act) rewards an applicant for sponsoring or conducting additional studies on previously approved drug products containing an active moiety that has been previously approved, and an NDA applicant for a nonprescription drug product with an ACNU could be eligible for such exclusivity, provided the relevant statutory requirements are met. We discuss the issue of ''market exclusivity'' or ''statutory exclusivity'' for nonprescription drug products with an ACNU further in our responses to Comments 36 and 72.

(Comment 11) Several comments express concerns that submitting an application is more burdensome than submitting a supplement. Although another comment acknowledges FDA's explanation that applicants can cross-reference information in an approved application, the comment asserts that the applicant would be required to pay a new application user fee, even though the commenter believes that FDA's review would be less resource-intensive compared to other NDAs.

(Response 11) We acknowledge that submitting a separate application may be more burdensome than submitting a supplement to the approved prescription drug application; however, an applicant may cross-reference information from its approved NDA for the prescription drug product and would not need to duplicate studies already conducted for and submitted in its NDA for the prescription drug product (87 FR 38313 at 38318). While we acknowledge that a new application user fee will be required, we disagree that FDA's review of an application for a nonprescription drug product with an ACNU is less resource intensive for the Agency compared to other NDAs. As required for other NDAs, the application must include data and information from studies to support the safety and efficacy of the drug product as nonprescription as well as meet the additional specific requirements for a

nonprescription drug product with an ACNU (see 21 CFR 314.56(c) in this final rule). Generally, these requirements would include the submission of newly generated data and information that FDA would not have previously reviewed, including but not limited to, label comprehension studies, self-selection studies, actual use studies, and human factors studies to demonstrate both the necessity and the effect of the ACNU. In some cases, device information may also be submitted. Additionally, FDA's review of an application for a nonprescription drug product with an ACNU will typically involve many offices in the Center for Drug Evaluation and Research, and in some instances, consults to other Centers within FDA.

(Comment 12) We also received one comment requesting that FDA establish a process for the applicant to revise or remove an approved ACNU for a nonprescription drug product with an ACNU. The comment notes that an ACNU should not be expected to remain unchanged or permanent.

(Response 12) We disagree that we need to establish a new, separate process specific for making post approval changes to an application for a nonprescription drug product with an ACNU. An applicant may propose revisions to an approved application for a nonprescription drug product with an ACNU by submitting a supplement and may describe certain changes in the annual report, consistent with our current regulations for making changes to an FDA-approved application (see §§ 314.70, 314.81, 314.97, and 314.98 (21 CFR 314.70, 314.81, 314.97, and 314.98)). 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 (see §§ 314.60 and 314.96 (21 CFR 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 (see §§ 314.70 and 314.97) (87 FR 38313 at 38319).

F. Comments on Specific Requirements for an Application for a Nonprescription Drug Product With an ACNU and FDA Responses

We proposed to establish specific NDA and ANDA requirements for a nonprescription drug product with an ACNU (proposed 21 CFR 314.56(c)). After consideration of public comments received, we are finalizing these proposals with a few editorial modifications to provide clarity. The changes are described below in sections V.F.1. and V.F.2.

1. NDA

In addition to existing content and format requirements for an NDA (§ 314.50), FDA proposed specific requirements for an NDA for a nonprescription drug product with an ACNU. We discuss the specific requirements in the following paragraphs.

a. Statement regarding the purpose of the ACNU. We proposed to require the applicant to provide 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 practitioner licensed by law to administer such drug (proposed § 314.56(c)(1)(i)). We received no comment specifically regarding this proposed requirement. We are finalizing our proposal with a few editorial modifications to provide greater clarity. We are revising the sentence to add the word ''whether'' after the phrase ''A statement regarding. . . .'' We are also removing the colon after ''ACNU'' and replacing it with the phrase ''is to.''.

b. Statement of necessity of the ACNU. We proposed to require the applicant explain why the ACNU is necessary to ensure appropriate self-selection or appropriate actual use, or both, by consumers of the nonprescription drug product (proposed § 314.56(c)(1)(ii)). We received no comment regarding this proposed requirement, and we are finalizing it without change.

c. Description of how the ACNU ensures appropriate self-selection or appropriate actual use, or both. We proposed to require the applicant describe how the ACNU will ensure appropriate self-selection or appropriate actual use, or both, by consumers (proposed 21 CFR 314.56(c)(1)(iii)). After consideration of public comments received, we are finalizing our proposal without change.

(Comment 13) We received a few comments asserting that the proposed rule lacks clarity on how often an ACNU must be fulfilled by consumers. A few commenters question if the consumer would be required to fulfill an ACNU each time the consumer repurchases the drug product, which would be burdensome, particularly if the drug product is indicated for a chronic condition. One comment recommends that FDA require the application to include information on how the consumer would repurchase a nonprescription drug product with an ACNU.

(Response 13) There is not one standard for the frequency in which an ACNU must be fulfilled by the consumer; this will be determined on a case-by-case basis as we consider the specifics of each application for a nonprescription drug product with an ACNU during our review. As finalized in this final rule, we require that the application include a description of how the ACNU ensures appropriate self-selection or appropriate actual use, or both (21 CFR 314.56(c)(1)(iii) in this final rule), and describe the additional condition(s) implemented and the criteria by which the consumer would successfully fulfill the ACNU, including a description of the specific actions to be taken by a consumer as part of the description of key elements of the ACNU (21 CFR 314.56(c)(1)(iv) in this final rule). Therefore, the application may include information describing how a consumer would make subsequent purchases of the nonprescription drug product with an ACNU, if appropriate. For example, an applicant may explain that a consumer would fulfill an ACNU (*e.g.,* complete a self-selection questionnaire) upon the first time purchasing the nonprescription drug product with an ACNU and at a specific time interval (*e.g.,* every 3 months) in order to repurchase the drug product.

d. Description of the key elements of the ACNU. We proposed to require the applicant to include a description of the key elements of the ACNU, including: the additional condition implemented by the applicant to be fulfilled by the consumer to obtain the nonprescription drug product with an ACNU; the labeling specifically associated with the ACNU; and 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 (see proposed 21 CFR 314.56(c)(1)(iv)). We received no comment regarding this proposed requirement. We are making an editorial modification for clarity. We are adding the introductory clause: ''Key elements of the ACNU'' to better explain the required information and to allow for ease of reference to discuss the requirement.

e. Adequate data or other information that demonstrate the necessity of the ACNU to ensure appropriate self-selection or appropriate actual use, or both. We proposed to require an applicant to include adequate data or other information that demonstrate the necessity of the ACNU to ensure

appropriate self-selection or appropriate actual use, or both (proposed 21 CFR 314.56(c)(1)(v)). After consideration of public comments received, we are finalizing our proposal without change.

FDA believes that the requirement for demonstrating that the ACNU is necessary, as reflected in the ACNU definition and in 21 CFR 314.56(c)(1)(v), and as determined by FDA, is necessary to fulfill the key goals of this rulemaking. The key goals are to: (1) increase options for applicants to develop and market safe and effective nonprescription drug products, which would broaden the types of nonprescription drug products available to consumers and (2) increase consumer access to appropriate, safe, and effective drug products, by providing for the availability of prescription versions of nonprescription drug products approved with ACNUs, both of which in turn could improve public health (see the discussion in this section F.1.*e.*). Allowing a product to be approved as a nonprescription drug product with an ACNU, when the ACNU is not necessary, would not increase options for applicants to develop and market safe and effective nonprescription drug products because they could already be marketed as a nonprescription drug product without an ACNU. Approving a nonprescription drug product with an ACNU that is not necessary also would not necessarily increase consumer access because, although this rule has the potential to provide consumers with access to additional types of nonprescription drug products, FDA recognizes that ACNUs necessarily restrict consumer access, which is appropriate when they are needed to ensure appropriate self-selection or appropriate actual use, or both. However, nonprescription drug products without ACNUs do not necessarily implicate the same issues regarding continued consumer access to drug products because they are generally available to consumers and do not have additional conditions of approval that restrict consumer access. Therefore, if the definition in 21 CFR 201.67(b)(1) and 314.56(a)(1), or the provision at 21 CFR 314.56(c)(1)(v), is stayed or determined to be invalid or unenforceable, the entire rule should be invalidated.

(Comment 14) We received several comments requesting that FDA provide further guidance on the meaning of ''adequate data'' as it pertains to demonstrating the necessity of the ACNU and the effect of the ACNU. FDA received one comment stating the proposed rule does not address the types of consumer studies that would be needed to provide adequate data. A few comments assert that FDA should not limit adequate data to prospective consumer behavior studies if other sources referenced by the applicant are reliable and fit for purpose.

(Response 14) Consistent with our proposal, 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 (87 FR 38313 at 38320 and 21 CFR 314.56(c)(1)(vi) in this final rule). Further, the applicant must submit data that show that consumers appropriately self-select or actually use the drug product, or both, safely and effectively using the ACNU. To clarify, adequate data need to be relevant to the specific application and need to be interpretable for FDA to evaluate the scientific finding. The types of data that can be submitted are not limited. Applicants can submit data from consumer studies such as label comprehension studies, self-selection studies, actual use studies, and human factors studies (87 FR 38313 at 38315) to demonstrate the necessity of the ACNU and the effect of the ACNU. The specific types of consumer studies an applicant would conduct depends on the development program for the particular nonprescription drug product with an ACNU.

FDA has issued guidances on some types of consumer studies (Refs. 1, 2, and 3). We may provide advice (*e.g.,* specific verbal or written feedback) to applicants on adequate data or other information that demonstrate the necessity and effect of the ACNU in the context of a pending or proposed application, as appropriate. Additionally, applicants can request to meet with FDA staff to discuss questions that arise during the development of a nonprescription drug product with an ACNU. FDA may consider issuing guidance in the future to address general considerations that may arise and are applicable to all applicants developing nonprescription drug products with an ACNU.

(Comment 15) We received many comments asserting that FDA should remove the proposed requirement that the applicant must develop or reference adequate data to demonstrate that labeling is insufficient for safe and effective use of a nonprescription drug product. We received many comments expressing concerns that, before developing an ACNU, an applicant must first generate data from a failed labeling study (*i.e.,* fail first) and FDA must then agree with the applicant's assessment that labeling alone is insufficient. Several comments state that the fail-first concept would put the onus on the applicant to prove a negative, rather than developing the key self-selection or use question(s) that trigger the need for an ACNU. One comment asserts that the rigidity of trying to prove a negative is inconsistent with scientific methods in developing a label. A few comments assert that it can become apparent for a variety of reasons that labeling is not adequate throughout the development program. Although the comments note that applicants can utilize meetings with FDA during the development program to obtain alignment, many commenters believe that applicants should have the ability to evaluate the necessity of an ACNU without seeking prior agreement with FDA.

(Response 15) We disagree with removing the requirement that the applicant must provide adequate data or other information to show that labeling alone would not support the safe and effective use of the nonprescription drug product and disagree that the requirement is inconsistent with the methods of developing labeling for nonprescription drug products. An ACNU cannot be proposed merely to provide consumers with additional information when the labeling could be sufficient to ensure appropriate self-selection or actual use or both. In such case, the use of an ACNU can present potential barriers for another applicant developing a nonprescription drug product. We cannot make a determination about whether labeling alone is insufficient without adequate data or other information. While the data or other information will typically come from consumer testing or by reference, it does not necessarily need to come from a failed labeling study. Further, the necessity for adequate data or other information, which typically comes from consumer testing or by reference is consistent with FDA's approval requirements for all nonprescription drug products. For a nonprescription drug product, the applicant develops and optimizes the labeling using an iterative process and conducts consumer studies (*e.g.,* label comprehension studies, self-selection studies, actual use studies, and human factors studies) to demonstrate whether consumers appropriately self-select and use the drug product using labeling alone. In certain circumstances, an ACNU may only be required for appropriate self-selection or appropriate actual use, but not both, of the nonprescription drug product. For example, if the applicant demonstrates that labeling alone is insufficient to ensure appropriate self-selection (but

not appropriate actual use) of the nonprescription drug product and proposes an ACNU for self-selection, the applicant must still conduct consumer studies to demonstrate that consumers will appropriately use the drug product based on labeling, alone. In addition to reflecting the reality of developing a nonprescription drug product, this policy is also intended to help ensure consumers can access nonprescription drug products without barriers or hurdles to access that are unnecessary when that drug product could be approved as nonprescription without an ACNU.

We encourage applicants to meet with FDA to discuss their drug development plans and seek advice. However, these meetings are not required; applicants that view these meetings as unnecessary are not required to have them.

(Comment 16) We received a few comments recommending that FDA clarify when an applicant can submit ''other information'' explaining the necessity of the ACNU. One comment recommends FDA define the criteria for when an applicant can submit ''other information''; for example, situations that require additional tests, lab values, or other ancillary values or measurements as part of self-selection or actual use; literature; and medical practice guidelines. One comment recommends that FDA clarify how FDA will signal to an applicant when labeling alone is insufficient because clear communication with FDA will allow the applicant to proceed in its development program.

(Response 16) FDA disagrees with providing criteria in the rule for when an applicant can submit ''other information'' to demonstrate the necessity of the ACNU. Because this determination is specific to the circumstances surrounding each individual drug development program, FDA does not think specifying such criteria in the rule would be feasible and may instead unnecessarily limit the options available to applicants for development program designs.

An applicant may be able to 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. FDA is available to meet with applicants to discuss drug development plans, which can include discussing questions about when ''other information'' can demonstrate the necessity of the ACNU. FDA encourages applicants to discuss their drug development plans with FDA and seek advice.

(Comment 17) We received a few comments suggesting that FDA revise the rule to permit the submission of adequate data or other information that demonstrate ''the rationale for use of an ACNU,'' rather than adequate data or other information that demonstrate ''the necessity of the ACNU.'' Another comment also asserts that the results of the self-selection and label comprehension studies or other adequate data or information should justify, rather than demonstrate, that consumers cannot appropriately self-select the drug product with labeling alone.

(Response 17) While this rule has the potential to provide consumers with access to additional types of nonprescription drug products, FDA recognizes that nonprescription drug products without ACNUs do not necessarily implicate the same issues regarding continued consumer access to appropriate drug products, because they are generally available to consumers and do not have additional conditions of approval that restrict consumer access. Therefore, we disagree with the commenters' assertions because providing adequate data or other information that simply provides a rationale or justification for the use of an ACNU is a lower threshold. A lower threshold may result in an applicant submitting an application for a nonprescription drug product with an ACNU even when an ACNU is not necessary to ensure consumers' appropriate self-selection or appropriate actual use or both (*i.e.,* labeling was sufficient to ensure appropriate self-selection or actual use or both). Consistent with the rigorous scientific data necessary for an application to meet the evidentiary standards under the FD&C Act and current FDA regulations for demonstrating safety and effectiveness, we expect the applicant to provide adequate data or other information that demonstrates the necessity of the ACNU.

(Comment 18) We received a few comments recommending that FDA provide a streamlined process for demonstrating the necessity of an ACNU because, in certain instances, the need for an ACNU may be obvious and requiring data may delay drug product development. One comment requests that FDA clarify—in situations where the need for an ACNU is uncertain—that applicants may streamline the drug development process by running simultaneous trials that test the effectiveness of labeling both with and without an ACNU.

(Response 18) FDA disagrees with providing a streamlined process applicable to all applications. Because each development program is unique, establishing a ''streamlined'' process and standards that applicants must follow as part of the development program may be overly restrictive. FDA acknowledges that applicants may choose to conduct simultaneous trials to demonstrate the necessity of the ACNU and the effect of the ACNU. However, because the results of the studies needed to demonstrate the necessity of the ACNU could affect the studies needed to demonstrate the effect of the ACNU, conducting simultaneous studies may result in the need to conduct additional trials. In general, FDA recommends the development program for a nonprescription drug product with an ACNU proceed in a stepwise approach. The development of labeling for all nonprescription drug products, including a nonprescription drug product with an ACNU, is an iterative process that may depend upon testing and retesting as the label evolves (Ref. 1). The applicant should begin by creating the complete labeling for the drug product that includes consumer-friendly language for all directions, warnings, and precautions, that is consistent with the available prescription labeling, in cases where there is an approved prescription drug product. FDA expects that the applicant will then optimize the labeling using an iterative process and conduct or reference adequate testing (*e.g.,* label comprehension studies, self-selection studies, actual use studies, and human factors studies) to determine if consumer comprehension can be improved to the point where labeling is sufficient for appropriate self-selection or appropriate actual use, or both, without an ACNU. If the conducted or referenced consumer studies demonstrate the necessity for an ACNU, information that is part of the ACNU may need to be aligned with the optimized label. In addition, when it is necessary to conduct pivotal actual use trials, an optimized label is needed before proceeding because consumers will need to refer to the label for use instructions after the point of purchase (*e.g.,* throughout the trial), and the study may be invalid if there are subsequent substantive changes to the labeling. Because each development program is different, we encourage the applicant to discuss its drug development plans with FDA.

(Comment 19) We received one comment questioning whether applicants should assume that the statutory standard for approving an NDA applies to NDAs for nonprescription drug products with ACNUs (*e.g.,* two phase 3 clinical trials to demonstrate safety and effectiveness).

(Response 19) Yes, the statutory standard that an application 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 with an ACNU just as they apply to any other NDAs and ANDAs (see section 505(b)(1) or (2) and (j) of the FD&C Act). For example, an NDA for a nonprescription drug product with an ACNU must demonstrate the proposed drug product's safety and effectiveness. Therefore, the NDA must include 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 (*e.g.,* phase 3 clinical trials or cross reference information in its approved NDA for the prescription product, where applicable (see section 505(d) and (b) of the FD&C Act).

f. Adequate data or other information that demonstrate the effect of the ACNU to ensure appropriate self-selection or appropriate actual use, or both. We proposed to require the applicant to 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 (proposed 21 CFR 314.56(c)(1)(vi)). After consideration of public comments received, we are finalizing our proposal without change.

(Comment 20) A comment recommends that health literacy be a significant factor in determining adequate data or other information that demonstrates the effect of the ACNU.

(Response 20) FDA understands this comment to be suggesting that health literacy be considered when enrolling study participants. An application for a nonprescription drug product with an ACNU must include 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 (21 CFR 314.56(c)(1)(vi)). The data must show that consumers appropriately self-select or use the drug product safely and effectively, or both, with the ACNU. Because a nonprescription drug product with an ACNU, like other nonprescription drug products, would be used by consumers from the general population without the supervision of a practitioner licensed by law to administer such drug, an applicant is expected to include a wide range of subjects in consumer studies. Specifically, in self-selection studies, exclusion criteria should be minimal (*e.g.,* excluding only those who cannot read and understand English) (Ref. 2). While FDA does not have specific recommendations on enrolling subjects with varying levels of health literacy, applicants should include an adequate number of subjects who have limited literacy skills in their consumer studies. The proportion of low-literacy subjects in the study sample should be representative of the proportion of adults in the United States with low-literacy skills based on available national data (Ref. 1) to help ensure that the study population is representative of the population that may use the nonprescription drug product.

g. Description of the specific way the ACNU is operationalized. We proposed to require that the applicant describe the specific way the ACNU is operationalized (proposed 21 CFR 314.56(c)(1)(vii)). We stated that 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 (87 FR 38313 at 38320) (see 21 CFR 314.56(c)(1)(iv) of this final rule regarding key elements of the ACNU). The purpose of the ACNU is to 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 practitioner licensed by law to administer such drug (21 CFR 314.56(c)(1)(i) of this final rule). The ACNU can be operationalized in different ways provided it reliably meets the objective. In the following paragraphs, we discuss and respond to comments on this requirement. After consideration of public comments received, we are finalizing the proposal with editorial modifications for clarity. We are adding the introductory clause: ''Operationalization of the ACNU'' for clarity and to allow for ease of reference to discuss the requirement. We are revising the word ''way'' to ''way(s)'' to add clarity because an application may include more than one way to operationalize the ACNU.

(Comment 21) We received a few comments that support FDA's position that an ACNU can be operationalized in different ways as long as it reliably meets its objective. Specifically, one comment supports the flexibility in how an ACNU may be operationalized given that the technologies used may change over time. One comment requests that FDA clarify its expectation for the description of how the applicant will operationalize the ACNU.

(Response 21) We appreciate commenters' support and firmly believe that the ACNU can be operationalized in different ways provided it reliably meets the objective. The applicant should describe the specific way the ACNU is operationalized so that we can understand how the ACNU is ensuring appropriate self-selection or appropriate actual use, or both. Because each development program is different, we encourage the applicant to discuss its drug development plans with FDA. Additionally, FDA may consider issuing guidance in the future to address general considerations that may arise and are applicable to all applicants developing nonprescription drug products with an ACNU, or to address new technology, if appropriate.

(Comment 22) We received a few comments that request that FDA add language to the rule clarifying that ACNUs must be operationalized in ways that do not restrict the sale of a nonprescription drug product with an ACNU so that the ACNU does not become a barrier to long-term use of a drug product.

(Response 22) We do not think that additional language needs to be added to the rule to address this comment. Because the ACNU is necessary to ensure appropriate self-selection or appropriate actual use, or both, by consumers of the drug product, the nonprescription drug product with an ACNU must only be made available to the consumer after the ACNU has been fulfilled by the consumer. However, in the case of long-term use of a nonprescription drug product with an ACNU where there is the need to repurchase the drug product, there is not one standard for the frequency in which an ACNU must be fulfilled by the consumer; this will be determined on a case-by-case basis as we consider the specifics of each application for a nonprescription drug product with an ACNU during our review. Therefore, the application may include information describing how a consumer would make subsequent purchases of the nonprescription drug product, if appropriate. For example, an applicant may explain that a consumer would fulfill an ACNU (*e.g.,* complete a self-selection questionnaire) upon the first time purchasing the nonprescription drug product with an ACNU and at a

specific time interval (*e.g.,* every 3 months) when repurchasing the drug product.

(Comment 23) Several comments suggest that the operationalization of an ACNU may have potential implications on access, health equity, privacy, and ultimately health outcomes. A few comments state that applicants should consider how to prevent or mitigate potential access issues for older adults, people with disabilities, people in long-term care facilities, incarcerated persons, and for people with limited English proficiency, health literacy, or digital literacy. One comment recommends that FDA require the applicant to describe considerations of ease of use, health equity, access, and privacy in deciding how to operationalize the ACNU. Some comments suggest that applicants should implement more than one way of operationalizing an ACNU to accommodate various health and digital literacy or comfort levels to ensure equitable access. One comment recommends that FDA clarify that applicants and FDA will abide by existing and future Federal, State, and local protections against discrimination in designing, approving, and implementing ACNUs such as the Federal Americans with Disabilities Act and section 1557 of the Affordable Care Act, which prohibits discrimination based on race, color, national origin, sex, age, or disability in any health program administered by the Department of Health and Human Services.

(Response 23) We acknowledge and understand the concerns and emphasize the importance of access to appropriate drug products. FDA recognizes the potential benefit of providing consumers with access to additional types of nonprescription drug products and the rule has the potential to broaden the types of drug products that FDA could approve as nonprescription (87 FR 38313 at 38316). As discussed in Response 20, because a nonprescription drug product with an ACNU, like other nonprescription drug products, would be used by consumers from the general population without the supervision of a practitioner licensed by law to administer such drug, an applicant is expected to include a wide range of subjects in consumer studies. While FDA does not have specific recommendations for enrolling subjects with varying levels of health literacy, applicants should include an adequate number of subjects who have limited literacy skills in their consumer studies (including human factors validation studies of the user interface) to help ensure that the study population is representative of the population that may use ACNU for the nonprescription drug product. As discussed further in our response to Comment 59, FDA acknowledges the benefits of having translated drug information for individuals with limited English proficiency. FDA strongly encourages applicants to work with retailers and other organizations to ensure that a nonprescription drug product with an ACNU is accessible to individuals with limited English proficiency. Additionally, FDA recognizes that in certain situations, an individual may need assistance in fulfilling an ACNU. Therefore, FDA acknowledges the possibility an individual other than the intended user might be the person who fulfills the ACNU and obtains the drug product. For example, a caregiver may fulfill the ACNU on behalf of a child or an older adult.

We disagree with revising the requirement regarding the specific way the ACNU is operationalized because the requirement is intentionally broad to allow applicants significant flexibility regarding how the ACNU can be operationalized, mindful that technologies evolve and ACNUs may be developed for many different nonprescription drug products. The flexibility in this requirement will allow applicants to develop an ACNU appropriate for the specific drug product while taking into consideration a diverse group of consumers who may use the drug product if approved. While FDA will not require an applicant to operationalize an ACNU in more than one way, an applicant may submit and FDA may approve an application that includes more than one way to operationalize an ACNU for a particular nonprescription drug product with an ACNU provided that the ways the ACNU is operationalized reliably meets the objective (*e.g.,* appropriate self-selection). For example, an ACNU that includes the administration of a questionnaire as a key element might operationalize the ACNU by administering the questionnaire using a website and might alternatively operationalize the ACNU by administering the questionnaire using a mobile application or an automated telephone response system (see also 87 FR 38313 at 38320).

Additionally, continued availability of the prescription drug product, if one is approved, along with the availability of the nonprescription drug product with an ACNU, will promote greater access to needed drugs by providing flexibility in how people can obtain them. Patients can continue interacting with their healthcare practitioner and obtain the drug by prescription, or choose to purchase a nonprescription drug product with an ACNU after fulfilling the ACNU, if appropriate (21 CFR 314.56(b) and see also 87 FR 38313 at 38319).

We agree that FDA and applicants must comply with all applicable statutory and regulatory requirements, including Federal, State, and local protections against discrimination. However, FDA does not provide guidance on how to comply with any legal obligations stemming from a source outside of the statutes and regulations that FDA administers. To the extent the comments summarized here also pertain to privacy considerations, those portions of the comments are addressed in our response to Comment 70.

(Comment 24) We received a comment expressing concern that remote, technological access to fulfill an ACNU for a nonprescription drug product may not ensure that the individual fulfilling the ACNU is in fact the consumer.

(Response 24) FDA acknowledges the possibility that an individual other than the intended user might be the person who fulfills the ACNU and obtains the drug product. In some cases, this might be acceptable. For example, a caregiver may fulfill the ACNU on behalf of a child or an older adult. However, in other cases, an individual might attempt to misrepresent themself as the intended user to inappropriately access the nonprescription drug product with an ACNU. FDA expects applicants to mitigate this by incorporating safeguards against such attempts. For example, an applicant may consider bot detection, unique user identification, requirements for affirmation of truthfulness, or other methods.

(Comment 25) We received a few comments requesting guidance on the use of technology. We received a comment recommending that when operationalization of an ACNU is based on software (*e.g.,* via a kiosk or web-based application), the software should be considered a key element of the ACNU. Further, the comment suggests that because the software is being used to direct access, the software should be regulated as a device and the quality assurance system should meet part 4 (21 CFR part 4) for combination products.

(Response 25) We disagree that software should be considered a key element of the ACNU. The applicant must describe the specific way the ACNU is operationalized (see 21 CFR 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 ensure appropriate self-selection, appropriate actual use, or both, of the drug product without the oversight of a healthcare practitioner. The ACNU can be operationalized in different ways provided it reliably meets the objective (87 FR 38313 at 38320). However, any technology, including software, used to operationalize the ACNU must comply with relevant requirements. FDA considers a software function that meets the definition of a device in section 201(h) of the FD&C Act and does not meet the criteria under section 520(o) of the FD&C Act to be a device software function. Software used to operationalize an ACNU that meets the definition of a device and is not otherwise excluded from that definition will generally be regulated as such. Consistent with FDA's approach to other device software functions, we recommend that applicants of such software consult the policies and recommendations set forth in FDA's guidance documents, such as FDA's ''Policy for Device Software Functions and Mobile Medical Applications'' (Ref. 4). FDA acknowledges that certain nonprescription drug products with ACNUs may be considered drug-device combination products as defined in § 3.2(e) (21 CFR 3.2(e)).

(Comment 26) We received one comment asserting that an applicant must ensure that safeguards are in place to deny access to the nonprescription drug product with an ACNU if a technology failure in the operationalization of the ACNU occurs and the ACNU cannot be completed. The comment also suggests that FDA could allow a manufacturer's representative, a pharmacist, or a pharmacy technician to be able to administer a questionnaire to consumers in the event that the technology fails (*e.g.,* kiosks or online portals are not working).

(Response 26) We agree that the applicant must ensure that consumers cannot access the nonprescription drug product with an ACNU without fulfilling the ACNU. ''Additional condition for nonprescription use'' (ACNU) is defined 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 practitioner licensed by law to administer such drug if the applicant demonstrates and FDA determines that labeling alone is insufficient to ensure appropriate self-selection or appropriate actual use, or both (21 CFR 314.56(a) and 201.67(b) of this final rule). The requirement that the applicant describe the specific way the ACNU is operationalized is intentionally broad to allow significant flexibility regarding how the ACNU can be operationalized (21 CFR 314.56(c)(1)(vii) of this final rule). An applicant may submit, and FDA may approve, more than one way to operationalize an ACNU, which could also increase consumers' ability to access the drug product with an ACNU if one way the ACNU is operationalized fails. There is no requirement that an ACNU be operationalized using particular technology.

(Comment 27) We received a few comments recommending that FDA provide clarity about the process and information needed for an applicant to update how an approved ACNU is operationalized. One comment seeks clarity on the process an applicant would use to notify FDA when software upgrades and technology updates are needed for the ACNU. The comment suggests most technical changes and software upgrades should be submitted in the applicant's annual report. However, the comment suggests if the change is expected to result in a substantive change in how a consumer interacts with the ACNU, impacts the drug product's intended use, significantly improves safety and effectiveness of the ACNU, impacts risk controls, or increases risk to consumers, then the applicant would be expected to seek prior approval from FDA before proceeding with the change. The comment further states that the principles outlined in the existing Center for Devices and Radiological Health (CDRH) guidances, including the guidance for industry and FDA staff from October 2017, entitled ''Deciding When to Submit a 510(k) for a Software Change to an Existing Device'' (available at *https://www.fda.gov/media/99785/download*), should apply to applicants that may need to make technical or software changes. The comment requests FDA issue new guidance advising applicants how to inform FDA of the changes needed when the ACNU does not involve software.

(Response 27) An applicant of an approved NDA or ANDA for a nonprescription drug product with an ACNU must follow the same requirements as holders of other approved NDAs and ANDAs to make changes to a drug product. This means that an applicant must propose revisions to an approved application for a nonprescription drug product with an ACNU by submitting a supplement, or, if applicable, by describing changes in an annual report, consistent with our current regulations for making changes to an FDA-approved application (see §§ 314.70, 314.81, 314.97, and 314.98). FDA may consider issuing guidance in the future to address general considerations that may arise applicable to all applicants on changes to the operationalization of, or software or technology associated with, an ACNU, if appropriate.

(Comment 28) FDA sought comment on any unique retail issues that might arise for retailers or consumers based on the way the applicant operationalizes the ACNU. We received two comments asking FDA to clarify whether consumers who satisfy the ACNU for the reference listed drug (RLD) (*i.e.,* branded drug product) could purchase the generic product. These two comments noted that this question may arise, for example, if a retailer does not currently have in stock the specific nonprescription drug product with an ACNU for which the ACNU was fulfilled, or a consumer fulfills the ACNU for the RLD but prefers to purchase the generic version. We received a comment that states FDA should only approve technology-neutral ACNUs and limit the proliferation of excessive proprietary platforms. We received a few comments asserting that if each applicant uses its own mechanism to provide a nonprescription drug product with an ACNU, pharmacies and other retailers may be unable to accommodate the many different mechanisms.

(Response 28) We acknowledge and appreciate the retail concerns expressed in the comments. During the development program of a nonprescription drug product with an ACNU, we encourage applicants to consider the feasibility of the specific way the ACNU is operationalized and the potential impact on retailers so as not to impede consumer access.

As our review is inherently application-specific, we expect a consumer seeking a particular nonprescription drug product with an ACNU will fulfill the ACNU as operationalized for that specific product. Accordingly, in general, consumers could not purchase the generic drug product without fulfilling the ACNU as operationalized for the generic drug product. FDA will review and approve NDAs and ANDAs for nonprescription drug products with an ACNU consistent with applicable requirements, which includes

consideration and review of, the statement of purpose of the ACNU, key elements of the ACNU, and the way(s) the ACNU is operationalized, as finalized in this rule at 21 CFR 314.56(c)(2). FDA must review and understand how the ACNU is operationalized to ensure that the ACNU achieves appropriate self-selection or use. As noted above, 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 ensure appropriate self-selection, appropriate actual use, or both, of the drug product without the supervision of a practitioner licensed by law to administer such drug, and the ACNU can be operationalized in different ways provided it reliably meets the objective (see also 87 FR 38313 at 38320). (See our response to Comment 25 and section V.F.*g.* of this document.) The regulations are intentionally broad and provide applicants significant flexibility in determining the specific way the ACNU may be operationalized, and FDA will not require an ACNU to use any specific technology or be ''technology-neutral.'' Thus, as stated above, since our review is inherently application-specific, and because we are specifically reviewing and approving how the ACNU is operationalized to ensure that the ACNU achieves appropriate self-selection, appropriate actual use, or both, we expect a consumer seeking a particular nonprescription drug product with an ACNU will fulfill the ACNU as operationalized for that specific product. Also, even if a generic applicant operationalizes the ACNU in a different way (*e.g.,* uses a different technology) than its RLD, the purpose and key elements of the ACNU must be the same between RLD and generic drug. As a result, we expect that a consumer who can fulfill the brand drug's ACNU would also be able to fulfill the generic drug's ACNU.

In addition to the content and format requirements under § 314.94, FDA proposed specific requirements for an ANDA for a nonprescription drug product with an ACNU (proposed 21 CFR 314.56(c)(2)). We are making a few editorial modifications to the proposed requirement. The first editorial modification is adding the word ''include'' at the end of the introductory statement for ease of reading, and other changes are described below in section V.F.2. In the following paragraphs, we discuss a general comment on the topic of ANDAs as a whole prior to discussing each of the specific requirements.

h. General comment on ANDAs.

(Comment 29) We received one comment that asserts that when there are significant differences in efficacy or side effect profiles between the RLD nonprescription drug product with an ACNU and an ANDA nonprescription drug product with an ACNU, such discrepancies should be addressed in the ANDA. The comment further asserts that different formulations should require a separate process which might not require a de novo application but would be more rigorous than an ANDA, which could include additional pharmacokinetic data and evidence demonstrating that consumers can safely use the drug product.

(Response 29) We disagree with the comment. To be approved, an ANDA for a nonprescription drug product with an ACNU must meet the standards specified in section 505(j) of the FD&C Act and relevant FDA regulations (see part 314, subpart C (21 CFR part 314, subpart C)) (see also 87 FR 38313 at 38318), as is true for any other ANDA. These standards do not change as a result of this final rule. For example, consistent with all ANDAs (other than ANDAs with differences approved under a petition filed under § 314.93), an ANDA for a nonprescription drug product with an ACNU must contain information to show that the drug product is pharmaceutically equivalent and bioequivalent to its RLD, and thus is expected to have the same clinical effect and safety profile as its RLD when used under the conditions specified in the labeling (see 87 FR 38313 at 38321).

i. Statement regarding the purpose of the ACNU. We proposed to require an ANDA applicant state the purpose of the ACNU (proposed 21 CFR 314.56(c)(2)(i)). We explained that as part of the submission, an ANDA applicant would state the purpose of the ACNU (the same purpose as the ACNU for the RLD) (87 FR 38313 at 38321). The heading in the preamble of the proposed rule was entitled, ''Statement regarding the purpose of the ACNU'' while both the preamble discussion and proposed codified text used the slightly different wording, ''state the purpose of the ACNU'' (see 87 FR 38313 at 38321 and 38330, respectively).

We received no comment regarding this proposed requirement, and we are finalizing it with editorial modifications for clarity and consistency. We are making a modification by revising the wording from ''State the purpose of the ACNU'' to ''A statement regarding whether the purpose of the ACNU is to 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 practitioner licensed by law to administer such drug, which must be the same as the purpose of the ACNU for its reference listed drug (RLD)'' for consistency and to capture the requirement more clearly. This modification clarifies that the ACNU for the ANDA must have the same purpose as the ACNU for the RLD, consistent with the discussion in the proposed rule (87 FR 38313 at 38321). This modification also makes the language consistent with the requirement for NDAs for a nonprescription drug product with an ACNU (see 87 FR 38313 at 38320 and 21 CFR 314.56(c)(1)(i) in this final rule).

j. Information demonstrating that the key elements of the ACNU are the same as the key elements of the ACNU for its RLD.[4] We proposed to require an ANDA applicant 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) (proposed 21 CFR 314.56(c)(2)(ii)). After consideration of public comment received, we are finalizing the proposal with only minor editorial modifications to provide greater clarity. We are revising the heading at 21 CFR 314.56(c)(2)(ii) to remove the word ''include'' since we moved ''include'' to be the last word of the introductory sentence under the broader heading at 21 CFR 314.56(c)(2) for ease of reading as discussed previously. We also shortened ''reference listed drug'' to ''RLD.''

(Comment 30) We received a few comments that specifically support the requirement that an ANDA demonstrate that the key elements of the ACNU are the same as the key elements of the ACNU for its RLD. We also received a comment that suggests FDA reconsider what it defines as the key elements of the ACNU and provide more flexibility than the rule already provides for differences in how an ACNU is implemented by the RLD and ANDA applicants. The commenter further states that it does not believe that if the purpose of the ACNU is to ensure adequate self-selection by screening out consumers with certain conditions, that purpose can only be achieved through a single set of questions and responses that might be proprietary to the RLD.

[4] We note that the heading for this section was ''Description of key elements of the ACNU'' in the proposed rule (87 FR 38313 at 38321). Nonsubstantive edits made here in this final rule for increased clarity.

(Response 30) We appreciate the comments supporting the requirement that an ANDA demonstrate that the key elements of the proposed ACNU are the same as the key elements of the ACNU for its RLD. We disagree that FDA should reconsider what it defines as the key elements of the ACNU and provide more flexibility for differences in how an ACNU is implemented by the RLD and ANDA applicants.

Based on existing statutory and regulatory requirements for ANDAs, applicants may submit an ANDA referencing a listed drug (including 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 (see 87 FR 38313 at 38321). Because FDA is approving the description of the key elements of the ACNU for the NDA (see 21 CFR 314.56(c)(1)(iv)), which includes 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), which are necessary for the safe and effective use of the nonprescription drug product with the ACNU, and because the ANDA is relying upon FDA's previous finding that the RLD is safe and effective, the ANDA must demonstrate that the key elements of the proposed ACNU are the same as the key elements of the ACNU approved for its RLD. 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)(iv) and 314.127(a)(7)). Generally, we anticipate that the ANDA applicant would use the same questions and responses as the RLD in its labeling.

Lastly, consistent with 505(j) of the FD&C Act and our general approach to ANDAs, we are providing flexibility in how an ANDA applicant can operationalize its ACNU in a different way from its RLD (87 FR 38313 at 38321). The ANDA would contain information to support that the way in which the ACNU is operationalized achieves the same purpose as the ACNU for its RLD, and the differences from the RLD are otherwise acceptable in an ANDA (87 FR 38313 at 38321).

(Comment 31) We received a few comments that express concern about the complexities of consumer selection of ANDAs. A comment expresses concerns that allowable differences between the RLD and ANDA(s) for a nonprescription drug product with an ACNU could lead to increased consumer confusion and limit the ability of consumers to transition to a generic drug product, which could undermine the cost-saving potential that accompanies generic drug products. Another comment states that generic drug product applicants may conceivably be able to devise a completely novel ACNU that achieves substantially the same result as the ACNU for the RLD, which could cause consumer confusion. A few comments assert that consumers who have become accustomed to fulfilling an ACNU for a nonprescription drug product may be hesitant to change to a generic drug product if the ACNU varies too drastically from the RLD. One comment requests FDA clarify that all similar drug products that require an ACNU for nonprescription use will be subject to the same ACNU to limit consumer confusion and asserts that such a clarification could aid in retailers' ability to stock multiple nonprescription drug products with an ACNU.

(Response 31) While we agree that the rule permits an ANDA applicant to operationalize its ACNU in a different way from its RLD, we disagree that this rule permits the ANDA applicant to devise a completely novel ACNU. An ANDA for a nonprescription drug product with an ACNU must meet the evidentiary standards under the FD&C Act and FDA regulations for approval of an ANDA (see 87 FR 38313 at 38318). This final rule does not affect the applicability of these standards. As with all ANDAs (other than ANDAs with differences approved under a petition filed under § 314.93), an ANDA for a nonprescription drug product with an ACNU must contain information to show that the drug is pharmaceutically equivalent and bioequivalent to its RLD, and thus is expected to have the same clinical effect and safety profile as its RLD when used under the conditions specified in the labeling. Applicants submitting an ANDA referencing a listed drug that has been approved with an ACNU under section 505(c) of the FD&C Act are relying on FDA's previous finding that the RLD is safe and effective. Therefore, because FDA would have previously approved the description of the key elements of the ACNU for the NDA, which are necessary for the safe and effective use of the nonprescription drug product with the ACNU, and the ANDA is relying upon FDA's previous finding that the RLD is safe and effective, the ANDA must demonstrate that the purpose and key elements of the proposed ACNU are the same as the purpose and key elements of the ACNU approved for its RLD (see 21 CFR 314.56(c)(2)(i) and (ii) of this final rule). As noted, the requirement provides flexibility for ANDAs in how the applicant operationalizes the ACNU. The rule requires that the ANDA contain information to support that the way in which the ACNU is operationalized achieves the same purpose as the ACNU for its RLD, and to show that differences from the RLD are otherwise acceptable in an ANDA. Moreover, 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 section 505(j)(2)(A) and (j)(4) of the FD&C Act and §§ 314.94(a)(8)(iv) and 314.127(a)(7)).

Therefore, while we appreciate concerns that consumers may be hesitant to use a generic drug product with an ACNU that is operationalized differently from the RLD, we disagree that the differences between the RLD and the ANDA would be so great as to impede consumers' consideration of using a generic nonprescription drug product with an ACNU.

(Comment 32) We received a comment that recommends FDA require an ANDA include information demonstrating that the key elements of the ACNU are ''equivalent to'' the key elements of the ACNU for its RLD, rather than ''the same as'' the key elements of the ACNU for its RLD.

(Response 32) We disagree. The use of the term ''same as'' is consistent with current regulations applicable to ANDAs. For example, when determining the appropriateness of an ANDA, the term ''same as'' generally means identical in active ingredient(s), dosage form, strength, route of administration, and conditions of use (see § 314.92(a)(1) (21 CFR 314.92(a)(1))).

k. Information on the way the ACNU would be operationalized.[5] We proposed to require that an ANDA applicant include information on the way the ACNU would be operationalized, as follows. If an

[5] We note that the heading for this section was ''Description of how the applicant will operationalize the ACNU'' in the proposed rule (87 FR 38313 at 38321). Nonsubstantive edits made here in this final rule for increased clarity.

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 (proposed 21 CFR 314.56(c)(2)(iii)). After consideration of public comments received, we are finalizing the proposal with editorial modifications for clarity. We revised the heading at 21 CFR 314.56(c)(2)(iii) to remove the word ''include.'' As previously discussed in section V.F.2., we moved ''include'' to be the last word of the introductory sentence under the broader section, 21 CFR 314.56(c)(2), for ease of reading. We are adding the introductory clause: ''Operationalization of the ACNU:'' to the first sentence of the requirement for clarity and to allow for ease of reference to discuss the requirement. We are revising ''include information on the way the ACNU would be operationalized'' of the first sentence to ''a description of the specific way(s) the ACNU is operationalized'' for consistency with the NDA requirement in 21 CFR 314.56(b)(1)(vii) of this final rule. We are revising the word ''way'' to ''way(s)'' to add clarity because an application may include more than one way to operationalize the ACNU.

(Comment 33) We received a comment asserting that FDA's proposed rule incorrectly suggested that ACNUs are not ''conditions of use'' under section 505(j) of the FD&C Act. The comment states that although the proposed rule contends that ''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,'' the proposed rule does not provide a basis for distinguishing an ACNU from other labeling elements that qualify as ''conditions of use.''

(Response 33) We agree with the comment that an ACNU is a ''condition of use'' under section 505(j) of the FD&C Act, and we appreciate the opportunity to clarify, as relevant to section 505(j), the differences between the ACNU and the way(s) the ACNU is operationalized.

An ANDA for a nonprescription drug product with an ACNU must meet the standards specified under section 505(j) of the FD&C Act and applicable FDA regulations for approval of an ANDA. This final rule does not affect the applicability of these standards, as noted in our responses to Comments 29 and 31. Under section 505(j), an ANDA applicant can rely on FDA's previous finding that the RLD is safe and effective so long as the ANDA applicant demonstrates that the proposed drug product and the RLD are the same with respect to active ingredient(s), conditions of use, dosage form, route of administration, strength, and, with certain exceptions, labeling. (An ANDA must also include sufficient information to demonstrate that the proposed product is bioequivalent to the RLD and that the ANDA meets the approval requirements relating to chemistry, manufacturing, and controls. See sections 505(j)(2)(A) and (4) of the FD&C Act.) This means that for an RLD with an ACNU, FDA would have previously approved the NDA with the description of the key elements of the ACNU (including the additional condition implemented by the applicant to be fulfilled by the consumer, the labeling specifically associated with the ACNU, and the criteria by which the consumer would successfully fulfill the ACNU) as necessary for the safe and effective use of the nonprescription drug product with the ACNU (see 21 CFR 314.56(c)(1)(i) through (vii)). This also means that for an ANDA—which relies upon FDA's previous finding that the RLD is safe and effective—the ANDA must demonstrate that the purpose and key elements of the proposed ACNU are the same as the purpose and key elements of the ACNU approved for its RLD (see 21 CFR 314.56(c)(2)(i) and (ii) of this final rule) as part of meeting section 505(j)'s requirements for sameness (see section 505(j)(2)(A)(ii) of the FD&C Act).

However, an ANDA generally is not required to be the same as the listed drug it references in all respects (see section 505(j)(2)(A)). For example, a generic drug generally can differ from its RLD in certain respects, such as with regard to device configuration or with respect to inactive ingredients. As explained in response to Comment 31, this rule intentionally provides the ANDA applicant flexibility to operationalize its ACNU in a different way from its RLD, as long as the ANDA applicant is able to show that it achieves the same purpose as the ACNU for its RLD and that any differences from the RLD are otherwise acceptable in an ANDA. Moreover, 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 section 505(j)(2)(A) and (j)(4) of the FD&C Act and §§ 314.94(a)(8)(iv) and 314.127(a)(7)). Differences in operationalization between an ANDA and its RLD, and differences in labeling that stem from those differences in operational design, may be permissible; the extent to which such differences affect the approvability of a proposed ANDA will be evaluated on a case-by-case basis. See section 505(j)(2)(A)(v) and (j)(4)(B) of the FD&C Act. We would expect an ANDA that meets the statutory and regulatory sameness requirements for an ANDA, and that operationalizes the ACNU in a different way than the RLD yet achieves the same purpose as the ACNU for its RLD, to be as safe and effective as its RLD.

(Comment 34) We received a comment that recommends that when an ANDA applicant proposes a different way to operationalize the ACNU, the applicant is required to include information to show that this different way to operationalize the proposed ACNU achieves ''an equivalent'' purpose as the ACNU for its RLD, rather than ''the same'' purpose as the ACNU for its RLD.

(Response 34) We disagree. The use of the term ''same as'' is consistent with section 505(j) of the FD&C Act and current regulations applicable to ANDAs. For example, when determining the appropriateness of an ANDA, the term ''same as'' generally means identical in active ingredient(s), dosage form, strength, route of administration, and conditions of use (see § 314.92(a)(1)).

(Comment 35) We received a few comments that encourage FDA to consider the use of shared system ACNUs between the RLD and ANDA applicants. One comment encourages FDA to establish processes to have ANDA applicants use the same ACNU as the RLD to maintain consistency, similar to the use of shared risk evaluation and mitigation strategy (REMS) programs by generic and brand manufacturers. Another comment states that use of shared system ACNUs could facilitate implementation of the systems in pharmacies and other points of sale and provide a simpler ACNU experience for consumers; however, the comment further states that FDA should not require the use of shared system ACNUs because they could be used to block generic competition.

(Response 35) FDA disagrees with the comment that FDA should encourage ANDA applicants to use a shared system to operationalize the ACNU. While ANDA applicants are required to

demonstrate that the purpose and key elements of the ACNU are the same as that of the ACNU for the RLD, we intentionally proposed a broad requirement to allow significant flexibility regarding how the ACNU can be operationalized. An ANDA applicant may operationalize its ACNU in a different way from its RLD so long as it achieves the same purpose as the ACNU for its RLD and that the differences from the RLD are otherwise acceptable in an ANDA (§ 314.56(c)(2)(iii) of this final rule). Requiring a shared system to operationalize the ACNU would limit the ability of the ANDA applicant to operationalize the ACNU in a different manner than the RLD.

(Comment 36) We received a few comments that state that patents claiming aspects of an ACNU for a nonprescription drug product should be eligible for patent listing in FDA's publication ''Approved Drug Products With Therapeutic Equivalence Evaluations'' (commonly known as the Orange Book) if they meet the criteria outlined in the FD&C Act and FDA's patent listing regulations. One comment states that the statute, which was amended by the Orange Book Transparency Act (Pub. L. 116–290, 134 Stat. 4889 (2021)), and existing regulations already identify the factors that govern whether an ACNU-related patent must be listed. Another comment asserts that the ACNU itself should be given the same full purview of patent protection afforded in the ANDA drug review process and require the follow-on applicant to consider and certify as to the NDA holder's patents. The comment further states that this would serve to put the original ACNU applicant on notice and allow them to take any necessary action regarding potential patent infringement before the follow-on nonprescription drug product with an ACNU comes to market. A separate comment discusses patentability of the ACNU and recommends that an ACNU be afforded similar intellectual patent protection as the drug formulation but only as it relates to drug products indicated to treat a specific condition or symptom. The comment further states that such protection is not advisable for the operationalization of the ACNU because it is unlikely that a sufficiently broad array of possibilities exists to operationalize ACNUs to justify any periods of market exclusivity.

FDA also received a comment recommending that patents claiming aspects of an ACNU for the nonprescription drug product should not be submitted for listing because allowing patents claiming aspects of the ACNU to be listed in the Orange Book would allow a patent holder to try to delay FDA approval of an ANDA for a nonprescription drug product with an ACNU.

(Response 36) We appreciate the comments received in response to our request for comments on whether patents claiming aspects of the ACNU for the nonprescription drug product may be submitted consistent with applicable laws and regulations. To the extent the comments opined on whether an ACNU should be subject to patent protection, FDA notes that questions of patentability are overseen by the U.S. Patent and Trademark Office, and not FDA.

As a general matter, any applicant who submits an NDA must submit applicable patent information to FDA. Such submission of patent information must be consistent with section 505(b)(1)(A)(viii) and (c)(2) of the FD&C Act and 21 CFR 314.53, and a patent must not be submitted for listing unless the patent claims the drug that is the subject of the application and is a drug substance (active ingredient) patent or drug product (formulation or composition) patent, or claims a method of using the drug described in the drug's approved labeling. In turn, a 505(b)(2) or ANDA applicant must provide an appropriate patent certification or statement with respect to each such patent. The status of each patent listed for the listed drug(s) relied upon or reference listed drug, and the relevant patent certification or statement, must be considered in determining the timing of the approval of a 505(b)(2) or ANDA application.

Taking into consideration patent certification and other requirements that might serve as potential barriers to ANDA applicants developing nonprescription drug products, we proposed significant flexibility in the rule to allow an ANDA applicant to operationalize its ACNU in a different way from its RLD. As described throughout this rule (*e.g.,* Responses 5, 6, and 7), this rule gives applicants flexibility regarding the types of ACNUs that may be developed, as well as how those ACNUs may be operationalized. Given this flexibility, and without knowing what patents an RLD application holder may ultimately have with respect to a nonprescription drug product with an ACNU (as noted above, the U.S. Patent and Trademark Office oversees determinations of patentability), FDA is unable to predict the patent issues that may be relevant to nonprescription drug products with an ACNU. However, we reiterate that in all cases, submission of patent information must be consistent with section 505(b)(1)(A)(viii) and (c)(2) of the FD&C Act and 21 CFR 314.53, and a patent must not be submitted for listing unless the patent claims the drug that is the subject of the application and is a drug substance (active ingredient) patent or drug product (formulation or composition) patent, or claims a method of using the drug described in the drug's approved labeling.

To the extent the comments summarized here about ''market exclusivity'' also pertain to statutory exclusivity, those portions of the comments are addressed in our response to Comment 72.

G. Comments on Nonprescription and Prescription Approval and Simultaneous Marketing and FDA Response

We proposed to establish that because the ACNU allows the nonprescription drug product to be used safely and effectively without the supervision of a practitioner licensed by law to administer such drug, the ACNU is a meaningful difference between the prescription drug product and the nonprescription drug product with an ACNU. Therefore, 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 (proposed 21 CFR 314.56(d)).

After consideration of public comments received, we are finalizing our proposal with an editorial correction. We are making an editorial correction to the proposed heading in 21 CFR 314.56(d), ''Simultaneous marketing of nonprescription and prescription products,'' by adding the word ''drug'' such that it now more accurately states, ''Simultaneous marketing of nonprescription and prescription drug products''.

FDA believes that the requirement for submission of a separate application (21 CFR 314.56(b)) and the simultaneous marketing provision (21 CFR 314.56(d)) are necessary to fulfill the key goals of this rulemaking, which are to: (1) increase options for applicants to develop and market safe and effective nonprescription drug products, which would broaden the types of nonprescription drug products available to consumers and (2) increase consumer access to appropriate, safe, and effective drug products, by providing for the availability of prescription versions of nonprescription drug products approved with ACNUs, both of which in

turn could improve public health. If either of those requirements in the final rule is stayed or determined to be invalid or unenforceable, the remaining provisions of the rule should no longer continue in effect because the rule would not meet FDA's objectives. Without the requirement to submit a separate application, an applicant could submit a supplemental application to switch the status of an approved prescription drug product to a nonprescription drug product with an ACNU. If such a supplemental ''switch'' application were approved for an RLD, prescription ANDAs that reference the RLD would be required to submit supplemental applications to switch their drug products from prescription to nonprescription with an ACNU. This would potentially remove all the prescription drug products from the market. If a consumer who had been using a prescription drug product is unable to obtain it once it became available only as a nonprescription drug product with an ACNU (*e.g.,* because the person lacks access to the relevant technology), the consumer would lose access to the drug. Similarly, consumers who prefer to interact with their healthcare practitioners and obtain the drug by prescription may be less likely to continue the treatment with a nonprescription drug product with an ACNU. These outcomes would be contrary to FDA's intent for the rule.

Therefore, if 21 CFR 314.56(b) or (d) is stayed or determined to be invalid or unenforceable, the entire rule should be invalidated.

(Comment 37) Many comments support the simultaneous marketing of the same drug as a prescription drug product and a nonprescription drug product with an ACNU. One comment supports simultaneous marketing to increase equitable access to safe and effective drug products and expand consumer choice. Another comment expresses support for FDA clarifying that an ACNU is a meaningful difference and asserts that there has not been clear understanding to date as to what ''meaningful difference'' means. We also received a comment requesting that FDA require the applicant to have a marketed prescription version of the same drug product at the same time as a marketed nonprescription drug product with an ACNU. However, we received a few comments that disagree with simultaneous marketing and assert that it does not improve or otherwise affect opportunities for consumer access. These commenters assert that simultaneous marketing would inadvertently create a less competitive marketplace by failing to incentivize investment in the process of switching prescription drug products to nonprescription status and, consequently, fail to realize the public health benefits associated with the introduction of novel nonprescription drug products. These commenters also assert that simultaneous marketing is not necessary because the applicant could choose to initiate discussions with FDA about possible options for product access for persons who cannot or choose not to fulfill the ACNU or a consumer would be able to speak to their healthcare practitioner about treatment options if they cannot fulfill the ACNU.

(Response 37) As discussed in section V.G. of this document, we agree that simultaneous marketing could increase consumer access. Continued access to the prescription drug product, along with the availability of the nonprescription drug product with an ACNU, allows greater access to needed drugs by providing flexibility in how to obtain them. The consumer may obtain a nonprescription drug product with an ACNU however it is operationalized or continue to interact with their healthcare practitioner and obtain the approved prescription drug product, if appropriate (see also 87 FR 38313 at 38319).

As discussed in our response to Comment 10, we disagree that simultaneous marketing is not necessary to promote greater access to drug products or that simultaneous marketing would disincentivize development of a nonprescription drug product with an ACNU. FDA recognizes that some consumers may not be able to access the nonprescription drug product with an ACNU. While we agree, as discussed in our response to comment 23, that the applicant may operationalize an ACNU in more than one way, there are consumers that the drug product would not be appropriate for in the nonprescription setting, but the drug product would be an appropriate use when under the supervision of a practitioner licensed by law to administer such drug. If there is not simultaneous marketing of the prescription drug product and nonprescription drug product with the ACNU, the prescription drug product would no longer be able to be marketed, which would eliminate the prescription drug product as a treatment option for health care practitioners to prescribe for patients. Therefore, continued availability of the prescription drug product along with the nonprescription drug product with an ACNU promotes the greatest access to needed drug products in both the prescription and nonprescription settings.

We disagree with the recommendations to revise the rule to require that the applicant market both a prescription version of the drug product and a nonprescription with an ACNU version of the drug product. A nonprescription drug product with an ACNU is not required to first be marketed as a prescription drug product. If the application for a nonprescription drug product with an ACNU meets the evidentiary standards under the FD&C Act and current FDA regulations to demonstrate the safety and effectiveness of the drug product in the nonprescription setting, then FDA could approve the application even if there is not a marketed prescription version.

(Comment 38) We received a comment that many stakeholders have misconceptions about a nonprescription drug product with an ACNU, including the view that nonprescription drug products with ACNUs are a third class of drugs or ''an expansion of dual status.'' The commenter states that FDA can address these misconceptions by changing the terminology from ''simultaneous marketing'' to ''simultaneous access.''

(Response 38) We clarify that the rule does not establish a third class of drug products for purposes of section 503(b) of the FD&C Act. FDA approves drugs as either prescription or nonprescription drug products under section 505 of the FD&C Act. The rule is intended to increase options for applicants to develop and market safe and effective nonprescription drug products. Also, we interpret the comment about ''dual status'' to refer to simultaneous marketing of prescription and nonprescription drugs. While we recognize that there may be various misconceptions about what constitutes meaningful differences between prescription and nonprescription drug products, we disagree that changing the terminology in this rule from ''simultaneous marketing'' to ''simultaneous access'' will reduce any confusion that may exist. Based on our experience with industry, the term does not currently cause confusion. FDA has consistently used the term ''simultaneous marketing'' to explain FDA's interpretation of the language in section 503(b) of the FD&C Act to allow the same active ingredient to be simultaneously marketed in both a prescription drug product and nonprescription drug product if a meaningful difference exists between the two that makes the prescription product safe only under the supervision

of a practitioner licensed by law to administer such drug (see 87 FR 38313 at 38321, 83 FR 13994, April 2, 2018, and 70 FR 52050, September 1, 2005). Changing this long-used term may introduce new confusion.

(Comment 39) We received comments that agree that FDA has the legal authority under the FD&C Act to allow the simultaneous marketing of products with the same active ingredient as both a prescription drug product and a nonprescription drug product if there is a meaningful difference between the two drug products.

(Response 39) We agree with the comments that the FD&C Act permits the simultaneous marketing of a prescription drug product and a nonprescription drug product where a meaningful difference exists between the two that makes the prescription product safe only under the supervision of a practitioner licensed by law to administer such drug.

As noted in the proposed rule, under section 503(b) of the FD&C Act, the same active ingredient can be simultaneously marketed in both a prescription drug product and nonprescription drug product if a meaningful difference exists between the two that makes the prescription product safe only under the supervision of a practitioner licensed by law to administer such drug (see 87 FR 68702, 87 FR 38313 at 38321, 83 FR 13994, and 70 FR 52050). Section 503(b)(1)(A) requires a drug to be limited to prescription-only status if, because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, it is not safe for use except under the supervision of a practitioner licensed by law to administer such drug. Conversely, a drug that can be used safely by consumers without the supervision of a practitioner licensed by law to administer such drug does not require a prescription. Under section 503(b)(1), a drug cannot be both prescription and nonprescription at the same time, because it cannot be both safe and unsafe for use without the supervision of a practitioner licensed by law to administer such drug. For the same reason, two drug products with the same active ingredient that don't have meaningful differences also can't be simultaneously marketed as prescription and nonprescription. However, consistent with section 503(b)(1), if there is a meaningful difference (*e.g.* indication, strength, route of administration, dosage form, or patient population) between two drug products with the same active ingredient that makes one drug product safe for use only under the supervision of a practitioner licensed by law to administer such drug, while the other drug product is safe for use without such supervision, then the two products may be simultaneously marketed as prescription and nonprescription drug products, respectively. (See also the discussion on meaningful difference in our response to Comment 40).

In addition, under section 503(b)(4)(B) of the FD&C Act, a drug for which the prescription dispensing provisions of section 503(b)(1) do not apply shall be deemed to be misbranded if at any time prior to 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 them, simultaneous marketing of two drug products with the same active ingredient as both prescription and nonprescription drug products would result in one of the two products being misbranded. However, if there is a meaningful difference between two drug products with the same active ingredient that makes one drug product safe for use only under the supervision of a practitioner licensed by law to administer such drug, then simultaneous marketing of the two products is permitted. See also the responses to Comment 2 and Comments 40 through 43, below.

(Comment 40) Some commenters contend that an ACNU is not a meaningful difference for purposes of simultaneous marketing of prescription and nonprescription drugs under section 503(b) of the FD&C Act (see also Comments 41–43 and FDA responses). Specifically, the comments argue that a meaningful difference between two drug products must exist in indication, strength, route of administration, dosage form, or patient population. The commenters assert that a switch to nonprescription status may be accompanied by one of these meaningful changes in addition to an ACNU, but the ACNU itself does not establish such a difference. The commenters specifically cite FDA's decision to withdraw ANDA drug products that referenced the prescription NDA 020698, MiraLAX Powder (polyethylene glycol (PEG)–3350) powder for occasional constipation because FDA approved a full switch of NDA 02698 from prescription to nonprescription marketing. The commenters assert that FDA found that while there were differences in labeling, FDA looks to differences in indication, strength, route of administration, dosage form, [and] patient population to determine whether there is a meaningful difference between the two products. Therefore, the commenters assert that the mere presence of an ACNU does not implicate any of these factors.

(Response 40) FDA disagrees with these comments. FDA's considered judgment, based on the Agency's scientific and technical expertise, is that an ACNU would in fact constitute a meaningful difference between a prescription drug product and a nonprescription drug product with an ACNU, even if they do not have other meaningful differences, such as different indications or strengths. While we have previously provided some examples of what may constitute a meaningful difference, such as indication, strength, route of administration, dosage form, or patient population (see 83 FR 13994 and 70 FR 52050), we have not created a finite list of what may constitute a meaningful difference and will continue to make determinations of ''meaningful difference'' as appropriate.

In circumstances where the applicant would like to market a previously approved prescription drug product as nonprescription, the applicant must demonstrate that the proposed nonprescription drug product does not meet the criteria in section 503(b)(1) of the FD&C Act. FDA evaluates the data submitted by the applicant and makes a scientific determination about whether consumers can use the drug product safely and effectively without the supervision of a practitioner licensed by law to administer such drug, and therefore the drug product can be approved as nonprescription. When FDA determines that, based on the data, a proposed nonprescription drug product does not meet the criteria in section 503(b)(1) of the FD&C Act, the Agency may also make a scientific determination regarding whether there is a meaningful difference between the nonprescription drug product and a prescription drug product that contains the same active ingredient. If there is no meaningful difference between the products, then the product marketed as a prescription drug product would no longer meet the criteria for prescription drugs in section 503(b)(1) and would need to switch to nonprescription status. For example, with NDA 020698, MiraLAX (PEG–3350) powder for occasional constipation, FDA made a scientific determination that there are no meaningful differences between the prescription and nonprescription drug

products. In that scenario, the following were the same for the prescription and the nonprescription drug product: the active ingredient (PEG–3350), dosage form (powder for solution), strength (17 gram (g) dose in 4 to 8 ounces of liquid), route of administration (oral), indications (constipation), and patient population (17 years of age or older). As discussed in the response to Comment 41, in *Breckenridge Pharm., Inc.* v. *FDA,* 754 Fed. Appx. 1 (D.C. Cir. 2018), the U.S. Court of Appeals for the D.C. Circuit found no error in FDA's determination that differences in the duration of use between the prescription and nonprescription PEG–3350 products were not ''meaningful differences'' such that the prescription and nonprescription products could be marketed simultaneously.

There are also examples in which FDA has determined that, based on the data submitted, a drug meets the criteria in section 503(b)(1) of the FD&C Act for certain conditions of use; however, for other conditions of use, it does not meet the criteria in section 503(b)(1) of the FD&C Act. For example, Nasonex (mometasone furoate) nasal spray, 50 microgram (mcg)/spray (NDA 020762) was approved with two indications. FDA determined that data supported that the indication related to treatment of allergy symptoms did not meet the criteria for a prescription drug in section 503(b)(1) of the FD&C Act and that consumers could self-select and use the drug product for that indication in the nonprescription setting. Therefore, on March 17, 2022, based on data submitted by the applicant, FDA approved nonprescription Nasonex 24HR Allergy (mometasone furoate) nasal spray, 50 mcg/spray (NDA 215712) for the temporary relief of allergy symptoms. However, Nasonex's indication of ''treatment of chronic rhinosinusitis with nasal polyps in adult patients 18 years of age and older'' continues to meet the criteria in section 503(b)(1) of the FD&C Act. Therefore, FDA made a scientific determination that there is a meaningful difference between the prescription and nonprescription drug products because of their different indications, and the prescription and nonprescription drug products may be marketed simultaneously consistent with section 503(b).

Another example involves Xyzal (levocetirizine dihydrochloride) 0.5 mg/milliliter (mL) solution. The prescription product (NDA 022157) was approved in 2008 for the relief of symptoms associated with seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR), and the treatment of uncomplicated skin manifestations of chronic idiopathic urticaria (CIU) for patients 6 years of age and older. In 2009, it was approved for SAR for patients 2 years of age and older, and PAR and CIU in adults and children 6 months of age and older. In 2017, Xyzal Allergy 24HR (NDA 209090) was approved for nonprescription use with the previously prescription indication of SAR in adults and children 2 years of age and older. The nonprescription drug product was also approved with the PAR indication, but only for adults and children 2 years of age and older. The younger age range (6 months of age to under 2 years) remained prescription because the diagnosis of PAR in infants and children under the age of 2 years is more complex and requires the evaluation of a physician. The indication for CIU for all age ranges continues to meet the criteria for prescription use. Thus, the meaningful difference between the prescription and nonprescription versions of Xyzal (levocetirizine dihydrochloride) for the PAR indication is a difference in patient population (*i.e.,* certain age groups).

An ACNU is a condition that must be affirmatively fulfilled by a consumer before they can self-select, use, or both self-select and use, a nonprescription drug product. Therefore, a consumer will generally need to act to fulfill an ACNU, and, as explained further in response to Comment 42 below, this distinguishes it from labeling. Similar to the different indications and patient population in the above examples for Nasonex and Xyzal, an ACNU will be a meaningful difference that exists between two drugs that makes the prescription drug product safe only under the supervision of a practitioner licensed by law to administer the drug and the nonprescription drug product safe for use without the supervision of such a practitioner. If an NDA is submitted for a nonprescription drug with an ACNU, FDA would only approve it if FDA determines that the applicant's studies and other information in the application demonstrate the ACNU would make the nonprescription drug product safe for use without the supervision of a practitioner licensed by law to administer the drug product. However, without the ACNU, the drug product would be safe and effective only under the supervision of a practitioner licensed by law to administer the drug product, and FDA could not approve the drug product as nonprescription.

(Comment 41) Some commenters argue that FDA's position that an ACNU is a meaningful difference ignores the statutory language in section 503(b) of the FD&C Act, legislative history of the Durham-Humphrey Amendments to the FD&C Act, legal precedent, specifically the D.C. Circuit's decision in the MiraLAX case, *Breckenridge Pharm., Inc.* v. *FDA,* 754 Fed. Appx. 1 (D.C. Cir. 2018), and decades of Agency precedent. A commenter explains that the Durham-Humphrey Amendments amended section 503(b) of the FD&C Act to add the definition for prescription drug, which effectively established prescription and nonprescription drugs as two separate categories. The commenter further explains that legislative history shows that Congress amended the FD&C Act to address confusion that arose due to the fact that the same drug could be characterized as a prescription drug by one manufacturer and as nonprescription by another. The commenter further explains that the mutually exclusive nature of the classification of a drug product as either prescription or nonprescription is manifest in the statutory language. The commenter asserts that if FDA were to collapse the two categories for simultaneous marketing of a prescription drug product with a nonprescription drug product with an ACNU, it would not only contradict the plain-language meaning of the FD&C Act but also cause confusion that the Durham-Humphrey Amendments were meant to address. In discussing FDA's decision to withdraw approval of ANDA products that referenced MiraLAX, PEG–3350, the commenters argue that, in reaching its decision that the ANDA products did not have a meaningful difference from the RLD product (NDA 02698, MiraLAX (PEG–3350) powder for occasional constipation), FDA looked to differences in indication, strength, route of administration, dosage form, and patient population, but did not look to whether the product had an ACNU (see also Comment 40).

(Response 41) As discussed in response to Comments 39 through 40 above, and discussed further below in responses to Comments 42 through 43, FDA's position is entirely consistent with, and is in fact the best reading of, the statutory language in section 503(b) of the FD&C Act. Under section 503(b), the same active ingredient can be simultaneously marketed in both a prescription drug product and nonprescription drug product if a meaningful difference exists between the two that makes the prescription product safe only under the supervision of a practitioner licensed by law to administer the drug. FDA disagrees with commenters who argue that a

meaningful difference between two drug products must exist in indication, strength, route of administration, dosage form, or patient population, and that an ACNU is not a meaningful difference because it does not implicate any of these factors.

Recognizing that an ACNU can be a meaningful difference that allows for simultaneous marketing is also consistent with the legislative history of the Durham-Humphrey Amendments of 1951 (Pub. L. 82–215, 65 Stat. 648). Until 1951, the FD&C Act did not contain criteria for determining when to limit a drug's approval to prescription use. As a result, different manufacturers made different decisions about whether to market a drug as prescription or nonprescription. This resulted in confusion and uncertainty for pharmacists and consumers about whether certain drugs were safe for use without the supervision of a physician. To eliminate this confusion and uncertainty, and to protect the public health, Congress amended section 503(b) of the FD&C Act with the Durham-Humphrey Amendments, which had two primary objectives: (1) to protect the public from abuses in the sale of potent prescription drugs; and (2) to relieve retail pharmacists and the public from burdensome and unnecessary restrictions on the dispensing of drugs that are safe for use without the supervision of a physician (see S. Rep. No. 946, at 1 (1951), reprinted in 1951 U.S.C.C.A.N. 2454). By recognizing that there are circumstances under which an ACNU (*e.g.,* restricting access to the drug unless a consumer demonstrates an appropriate medical history through a questionnaire) can help ensure that a patient can self-select and use a drug safely and effectively without the supervision of a practitioner licensed by law to administer such drug, this rulemaking advances the second primary objective of these amendments. Simultaneous marketing of a prescription drug product and a nonprescription drug product with an ACNU that do not have other meaningful differences can reduce burdens on access for patients for whom a drug is safe and effective for use without supervision of a practitioner licensed by law to administer such drug, without causing confusion. The ACNU would be a meaningful difference that consumers and pharmacists would recognize, along with its associated labeling including the ACNU Instructions and Statement, as differentiating the product from a potential prescription version of the product.

FDA's decision to withdraw approval of ANDA products that referenced NDA 020698 MiraLAX (PEG–3350) powder for occasional constipation, and the D.C. Circuit's decision in *Breckenridge Pharm., Inc.* v. *FDA* upholding the Agency's position, have no bearing on whether an ACNU is a meaningful difference between prescription and nonprescription drug products. As a threshold matter, MiraLAX is not a nonprescription drug product with an ACNU. Additionally, when FDA made its decision, and when *Breckenridge Pharm., Inc.* v. *FDA* was decided, this regulation had not yet been promulgated. Instead, the court focused on whether labeling regarding duration of use could constitute a meaningful difference; the court upheld FDA's conclusion that it did not in that case, while expressly leaving open the possibility that it might in another case (see 754 Fed. Appx. at 4). Accordingly, whether an ACNU is an example of a meaningful difference with regard to the PEG–3350 products was not relevant to FDA's withdrawal decision for MiraLAX and, likewise, was not at issue in *Breckenridge Pharm., Inc.* v. *FDA.* As discussed further in response to Comment 42 below, as defined in this rule, an ACNU cannot consist merely of labeling, even if one aspect of it includes labeling, nor is an ACNU ''functionally equivalent to labeling.''

Furthermore, FDA's determination here that an ACNU would constitute a meaningful difference is consistent with FDA's approach to the MiraLAX proceedings. There, FDA stated: ''In determining whether an Rx drug product and an OTC drug product are the same, FDA considers whether there are any meaningful differences between the OTC and Rx products that would justify the different marketing status of the products'' (see 73 FR 63491 at 63492, October 24, 2008). As explained in our response to Comment 40, FDA's considered judgment is that an ACNU, as defined in this rule, would be such a meaningful difference because it would allow a drug product that would otherwise require a prescription to be marketed as a nonprescription drug product.

(Comment 42) One comment argues that an ACNU is labeling or ''functionally equivalent to labeling'' because it is intended to enable an individualized consumer response for the purpose of self-selection and/or actual use, the same role played by traditional drug labeling, and therefore it does not constitute a meaningful difference between a prescription drug product and a nonprescription drug product.

(Response 42) FDA does not agree that an ACNU is labeling or ''functionally equivalent to labeling,'' or that legal precedent is being ignored. Prescription drug labeling is designed to inform healthcare practitioners and thus contains more detailed information than nonprescription drug labeling. Nonprescription drug labeling is designed for consumers. As illustrated in the MiraLAX proceedings in *Breckenridge Pharm., Inc.* v. *FDA,* we determined that the differences in the labeling between the nonprescription drug product and the generic prescription drug products that were ''simply . . . due to the different audiences (*i.e.,* learned intermediary versus lay consumer) and the difference in setting (*i.e.,* use with a physician's supervision versus consumer self-directed use)'' were not meaningful differences for purposes of section 503(b) of the FD&C Act (see 83 FR 14007). However, certain meaningful differences between drugs may be reflected in their labeling (*e.g.,* indication or patient population).

This is consistent with FDA's determination than an ACNU is a meaningful difference because an ACNU (as defined in this regulation) cannot consist merely of labeling, even if one aspect of it includes labeling. A label is the written, printed, or graphic matter on the immediate container of the drug product (see section 201(k) of the FD&C Act). Labeling is all labels or other written, printed, or graphic matter on the drug product or any of its containers or wrappers, or accompanying the drug product (see section 201(m) of the FD&C Act). Labeling for nonprescription drugs provides information to consumers to self-select and use the drug product, and the consumer reads this information to self-select and use the drug product.

In contrast to labeling, an ACNU is a condition that must be affirmatively fulfilled by a consumer before they can self-select, use, or both self-select and use, a nonprescription drug product. Therefore, a consumer will generally need to act to fulfill an ACNU. For example, with Drug X (see more information about Drug X, a fictitious nonprescription drug product with an ACNU, in the proposed rule (87 FR 38313 at 38319)), 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. Using a consumer's answers to the questions, the underlying program or other operating information used by the secure website, not the consumer,

calculates the risk score for a serious side effect and determines if the consumer has an acceptable disease-specific risk score to use Drug X and therefore purchase Drug X. As shown in this example, an ACNU may include labeling, but the ACNU is not in itself labeling. It is a condition that a consumer must affirmatively satisfy, which ensures that a drug product can be appropriately selected and used safely and effectively without the supervision of a practitioner licensed by law to administer such drug.

FDA disagrees that an ACNU is ''functionally equivalent to labeling.'' With previous prescription-to-nonprescription switches that have been approved by FDA, including the one at issue in the MiraLAX proceedings in *Breckenridge Pharm., Inc.* v. *FDA,* the drug product was safe for use without the supervision of a practitioner licensed by law to administer such drug under section 503(b) of the FD&C Act; it simply needed to be labeled to satisfy the requirement for adequate directions for use and other labeling requirements for nonprescription marketing under the FD&C Act and FDA regulations. On the other hand, for a nonprescription drug product approved with an ACNU, FDA has determined that labeling alone is insufficient to ensure appropriate self-selection or appropriate actual use, or both (see generally 21 CFR 314.56 of this final rule). Therefore, a drug product approved with an ACNU could not satisfy the requirement for adequate directions for use for a layperson under the FD&C Act and FDA regulations, and would not be safe for use without the supervision of a practitioner licensed by law to administer such drug. We have provided in this rule an exemption from the requirement for adequate directions for use on the condition that, among other conditions, the approved ACNU is implemented as approved under the application, so that the drug would then become safe for use in the nonprescription setting (see 21 CFR 201.130 in this final rule).

With regard to the comment's argument that an ACNU is functionally equivalent to labeling because they both ''ensure appropriate self-selection and use of the OTC product,'' the comment does not explain why this is different from other characteristics of a drug that it concedes are meaningful differences. In particular, the comment ''request[s] that the final rule acknowledge and maintain FDA's prior position that it will look to indication, strength, route of administration, dosage form, and patient population to determine whether there are meaningful differences between two products with the same active ingredient . . . .'' The comment therefore concedes that the indication and patient population can be meaningful differences for purposes of simultaneous marketing under section 503(b) of the FD&C Act, but does not acknowledge that these conditions, which are only reflected in the labeling, also serve to ''ensure appropriate self-selection and use of the OTC product.'' Such conditions are, in fact, critical to appropriate self-selection and use. Because the ACNU would similarly provide a difference for the drug that is meaningful, the nonprescription drug with an ACNU would be a different drug product from a prescription version, even if it does not have other meaningful differences for purposes of simultaneous marketing under section 503(b) of the FD&C Act.

(Comment 43) We received a comment that argues that this rule, by allowing the simultaneous marketing of the prescription version of the drug product and a nonprescription with an ACNU version of the drug product, ''indisputably triggers the major questions doctrine because it would radically overhaul the OTC drug market and limit consumer access to OTC drugs . . . which is undeniably an issue of 'vast economic and political significance.' '' (quoting *West Virginia* v. *EPA,* 142 S. Ct. 2587, 2605).

(Response 43) We do not agree that this rule implicates the ''major questions doctrine'' because of the provision providing for simultaneous marketing. In *West Virginia* v. *EPA,* the Supreme Court found that, ''to substantially restructure the American energy market,'' the '' 'claim[ed] to discover in a long-extant statute an unheralded power' representing a 'transformative expansion in [its] regulatory authority,' '' and that the Agency ''located this newfound power in the vague language of an 'ancillary provision[ ]' of the Act.'' 597 U.S. 697, 724 (2022) (citations omitted). The Court further found that this ancillary provision ''had rarely been used in the preceding decades,'' but was then used ''to adopt a regulatory program that Congress had conspicuously and repeatedly declined to enact itself.'' *Id.* Consequently, the Court stated that ''there is every reason to 'hesitate before concluding that Congress' meant to confer . . . the authority'' in question to the EPA and that the case was a ''major questions case.'' *Id.* at 724–725. To overcome its hesitation and ''skepticism toward EPA's claim,'' the Court stated that ''the Government must—under the major questions doctrine—point to 'clear congressional authorization' to regulate in that manner.'' *Id.* at 732.

None of the findings described above in *West Virginia* v. *EPA* applies to the provision in this rule providing for simultaneous marketing of prescription drugs and nonprescription drugs with ACNUs. As discussed in the response to Comment 2, Congress has given FDA the authority to make scientific determinations about which drugs may be marketed as prescription or nonprescription drugs. In addition, section 503(b)(3) gives FDA the authority to issue regulations to remove the prescription-only dispensing requirements from drugs when such requirements are not necessary for the protection of the public health. FDA's finding that an ACNU would constitute a meaningful difference is simply the latest determination in a series of determinations under section 503(b) of the FD&C Act regarding whether some difference constitutes a meaningful difference for purposes of prescription and nonprescription marketing. For example, in 1984, the Agency approved a nonprescription ibuprofen product because it had meaningful differences from the prescription versions of ibuprofen (see 67 FR 54139 for general background related to this regulatory history).

Likewise, for decades other drug products have been approved as nonprescription drug products even though prescription drug products contained the same active ingredient (see 70 FR 52051 for some examples, including loperamide in a prescription drug product for chronic diarrhea and in an OTC drug product for acute diarrhea). In 2005, FDA noted that such meaningful differences had, up to that time, included a difference in indication, strength, route of administration, and dosage form. FDA also indicated that it was considering whether a difference in patient population could also constitute a meaningful difference for purposes of simultaneous marketing (see 70 FR 52050, September 1, 2005). Later, in the **Federal Register** of October 24, 2008 (73 FR 63491; see also 83 FR 13994), related to the MiraLAX proceeding, and in 2013 related to an approval decision for NDA 202211 Oxytrol for Women (oxybutynin) extended-release film, 3.9 mg, for the treatment of overactive bladder in women, FDA made clear that patient population could also be a meaningful difference between a prescription drug product and a nonprescription drug product.

In addition, in 2018, the D.C. Circuit Court of Appeals in *Breckenridge Pharm, Inc.* v. *FDA* upheld FDA's determination that the labeled duration of use for the nonprescription MiraLAX

product did not constitute a meaningful difference from the generic prescription drugs, and recognized that ''the agency left open the possibility that differences in duration of use—in other circumstances—could add up to a 'meaningful difference.' '' 754 Fed. Appx. 1, 4 (citing FDA's publications in the **Federal Register** related to the MiraLAX proceeding, at 83 FR 13994 at 13999 and 73 FR 63491 at 634913). Thus, whether a difference between a prescription drug product and a nonprescription drug product constitutes a meaningful difference that permits simultaneous marketing in accordance with section 503(b) of the FD&C Act is something FDA has considered and acted upon in numerous instances for decades. FDA's determination in this rule that an ACNU would constitute the same kind of meaningful difference is hardly a ''sweeping assertion of 'unprecedented power over American industry,' '' as the commenter claims.

The simultaneous marketing provision in this rule is also unlike the Agency actions in ''major questions'' cases because, among other things, it does not represent an attempt to ''substantially restructure'' a market. All that this provision of the rule will do is provide an additional consideration for applicants seeking authorization for a product to enter the market. With regard to simultaneous marketing of prescription drug products and nonprescription drug products, as noted above, there are currently, and there have long been, marketed prescription drug products and nonprescription drug products that contain the same active ingredient because there is some meaningful difference that supports the simultaneous marketing of the drug products, and FDA has made determinations regarding what constitutes a meaningful difference under section 503(b) of the FD&C Act for decades. For this same reason, the simultaneous marketing provision in this rule, which simply clarifies another difference that the Agency has determined would constitute a meaningful difference between prescription and nonprescription drug products under section 503(b), does not represent a ''transformative expansion in . . . regulatory authority'' that is derived from ''vague language of an 'ancillary provision[ ]' of the Act.'' In addition, inclusion of the simultaneous marketing provision does not create a ''regulatory program that Congress [has] conspicuously and repeatedly declined to enact itself.'' FDA is not aware of any Congressional consideration of legislation regarding the marketing of nonprescription drugs with ACNUs alongside prescription versions of such drugs.

The comment also appears to be arguing that the simultaneous marketing provision implicates the major questions doctrine because it would ''limit consumer access to OTC drugs.'' But any prediction that the simultaneous marketing provision would limit consumer access is highly speculative. To support this assertion, the comment claims that ''prescription drug companies may decide not to pursue OTC switch opportunities that use an ACNU'' if prescription versions of the drug continue to be marketed. Similarly, by way of analogy, one might argue that the benefit of statutory exclusivity, such as that provided at section 505(j)(5)(F)(iii) of the FD&C Act, would be undermined by FDA's rule. However, FDA would disagree with this because as noted below in response to Comment 72, an application—including an application for a nonprescription drug product with an ACNU—is eligible for exclusivity if applicable statutory requirements are met. Further, as noted above, the assertion that the ACNU pathway or the benefit of exclusivity would be undermined by the rule is speculative, particularly considering the evidence showing that roughly 60 percent of purchases for a nonprescription drug product are from new consumers who had not previously taken the drug before it switched from prescription status, suggesting that the potential to attract new-to-therapy consumers for nonprescription drug products is substantial (Ref. 13). Moreover, this critique is not specific to nonprescription drug products with ACNUs; it would also apply to other drug products for which there is a meaningful difference that allows simultaneous marketing. Furthermore, although we do not anticipate this scenario, even if no applicant pursues the development and eventual marketing of a nonprescription drug product with an ACNU, ACNU products do not currently exist in the marketplace. So, it is not clear how this rule would ''limit consumer access to OTC drugs,'' or how that would implicate the major questions doctrine. Rather, the final rule is intended to increase options for applicants to develop and market safe and effective nonprescription drug products and increase consumer access to appropriate, safe, and effective drug products, which could improve public health.

Ultimately, the simultaneous marketing provision in this rule does not present one of the ''extraordinary cases that call for a different approach'' in statutory interpretation, because it is not one of the ''cases in which the 'history and the breadth of the authority that [the agency] has asserted,' and the 'economic and political significance' of that assertion, provide a 'reason to hesitate before concluding that Congress' meant to confer such authority.'' 597 U.S. at 721.

We also note that in the context of arguing that the major questions doctrine applies, this comment further argued that *Chevron* deference would consequently not apply. Since this comment was submitted, the Supreme Court decided *Loper Bright Enterprises* v. *Raimondo,* which overruled *Chevron* (*see* 144 S. Ct. 2244 (2024)). Therefore, we acknowledge *Chevron* deference would not apply when analyzing the statutory authority for this rule, including the simultaneous marketing provision. However, *Loper Bright* itself recognized that ''Congress has often enacted . . . statutes'' that by their terms delegate authority to ''exercise a degree of discretion'' in ''giv[ing] meaning to a particular statutory term'' or ''fill[ing] up the details of a statutory scheme.'' *Loper Bright,* 144 S. Ct. at 2263 (cleaned up). Section 503(b)(3) of the FD&C Act, which empowers the Secretary to adopt regulations ''remov[ing] drugs subject to section 505 from the requirements of paragraph (1) of this subsection when such requirements are not necessary for the public health,'' delegates just such an authority. As explained in the response to comment 2, throughout section 503(b), Congress also more broadly delegated FDA the explicit authority to use its scientific judgment to determine which drugs should be prescription or nonprescription, within the statutory criteria. And as part of its broad authority to approve and regulate drug products, including to establish specific regulations for drug products, FDA is authorized to determine the conditions under which a drug is safe and effective for use without a prescription. See, *e.g.,* sections 505, 505G, and 701 of the FD&C Act.

In any case, we believe this rule represents the best reading of the FD&C Act. As explained in the response to comment 39 and in the proposed rule, section 503(b) of the FD&C Act allows the same active ingredient to be simultaneously marketed in both a prescription drug product and nonprescription drug product if a meaningful difference exists between the two that makes the prescription product safe only under the supervision of a practitioner licensed by law to

administer the drug (see 87 FR 68702, 87 FR 38313 at 38321, 83 FR 13994, and 70 FR 52050). Section 503(b)(1)(A) requires a drug to be limited to prescription-only status if, because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, it is not safe for use except under the supervision of a practitioner licensed by law to administer such drug. Conversely, a drug that can be used safely by consumers without the supervision of a practitioner licensed by law to administer such drug does not require a prescription. Under section 503(b)(1), a drug cannot be both prescription and nonprescription at the same time, because it cannot be both safe and unsafe for use without the supervision of a practitioner licensed by law to administer such drug. For the same reason, two drug products with the same active ingredient that don't have meaningful differences also can't be simultaneously marketed as prescription and nonprescription. However, consistent with section 503(b)(1), if there is a meaningful difference between two drug products with the same active ingredient that makes one drug product safe for use only under the supervision of a practitioner licensed by law to administer such drug, while the other drug product is safe for use without such supervision, then the two products may be simultaneously marketed as prescription and nonprescription drug products, respectively.

In addition, under section 503(b)(4)(B) of the FD&C Act, a drug, for which the prescription dispensing provisions of section 503(b)(1) do not apply, shall be deemed to be misbranded if at any time prior to 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. The juxtaposition of these two provisions dictates 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. However, if there is a meaningful difference between two drug products with the same active ingredient that makes one drug product safe for use only under the supervision of a practitioner licensed by law to administer such drug, then simultaneous marketing of the two products is permitted.

We believe that FDA's longstanding interpretation of section 503(b), in which a meaningful difference allows prescription and nonprescription drug products with the same active ingredient to be simultaneously marketed, represents the best reading of that provision. A contrary reading would require all ibuprofen products, for example, to be restricted to prescription status because some products containing ibuprofen meet the prescription drug definition in section 503(b)(1) of the FD&C Act. Under the Agency's longstanding interpretation of section 503(b), however, because the nonprescription versions of ibuprofen have meaningful differences from the prescription versions, such as different indications and strengths, they are different drugs that no longer meet the prescription drug definition for purposes of section 503(b). Likewise, a drug that no longer meets the prescription drug definition in section 503(b)(1) of the FD&C Act because it is approved with an ACNU is a different drug for purposes of simultaneous marketing of prescription drugs containing the same active ingredient consistent with section 503(b).

We have already explained in this response how the simultaneous marketing provision of this rule simply reflects another determination by the Agency regarding whether a particular difference constitutes a meaningful difference for purposes of simultaneous marketing of prescription and nonprescription drugs with the same active ingredient under section 503(b) of the FD&C Act. In our responses to Comments 2 and 39 through 42, we also explained how this is consistent with FDA's statutory authority to make scientific determinations about which drugs should be prescription or nonprescription drugs, the legislative history of the Durham-Humphrey Amendments, which added section 503(b) to the FD&C Act, as well as legal precedent and Agency practice.

(Comment 44) We received a few comments asserting that simultaneous marketing of a prescription drug product and the nonprescription drug product with an ACNU could lead to inaccurate case reporting of adverse events for the nonprescription drug product with an ACNU. The comments describe concerns that reports of adverse events for the prescription drug product and the nonprescription drug product with an ACNU could be conflated and identification of a true safety signal for a drug product may not be detected accurately or could be delayed due to background noise.

(Response 44) We disagree that simultaneous marketing of a prescription drug product and a nonprescription drug product with an ACNU, where the only meaningful difference between the two drug products is the ACNU, could lead to inaccurate case reporting of adverse events or delayed identification of a safety signal arising for either drug product. An applicant must report adverse drug experience information to FDA in compliance with applicable postmarketing reporting requirements (§ 314.80). Among other information, an individual case safety report contains certain identifiable information that would be unique to either the prescription drug product or the nonprescription drug product with an ACNU, such as application number and type, drug product name, national drug code, and lot number (§ 314.80(f)). Therefore, FDA would have information to investigate whether the safety signal was associated with a prescription drug product, nonprescription drug product with an ACNU, or both.

Additionally, FDA has robust reporting systems for consumers to report adverse drug experiences, complaints, or other issues with FDA-regulated products, including nonprescription drug products. MedWatch is FDA's program for reporting serious adverse drug experiences, product quality problems, therapeutic inequivalence/failure, and product use errors with human medical products (Ref. 5). Additionally, consumers can contact the FDA Consumer Complaint Coordinator for the State in which they reside to report adverse drug experiences or other problems with FDA-regulated products. FDA's Consumer Complaint Coordinators, located in FDA offices, will listen, document a complaint about an FDA-regulated product, and follow up as necessary (Ref. 6). As with other FDA-regulated products, FDA has experience investigating if there is a safety signal with a particular product.

(Comment 45) We received a few comments opposing simultaneous marketing stating that marketing of a prescription drug product and a nonprescription drug product with an ACNU may lead to consumer confusion because the labeling information for the prescription drug product and nonprescription drug product with an ACNU would not be identical in content or format.

(Response 45) We disagree that simultaneous marketing of a prescription drug product and a

nonprescription drug product with an ACNU, where the only meaningful difference between the two drug products is the ACNU, would cause consumer confusion because of labeling differences between the prescription drug product and the nonprescription drug product with an ACNU. The commenter did not support its assertion with any evidence. There are numerous drug products with the same active ingredient that are currently simultaneously marketed as a prescription drug product and a nonprescription drug product where there is a meaningful difference between the two products. FDA does not have any data to show that there is consumer confusion and industry has not previously conveyed concerns with these products that are currently simultaneously marketed. Generally, labeling for nonprescription drug products and prescription drug products are not identical in content and format because they are directed to different audiences (primarily consumers for nonprescription drug products and healthcare practitioners for prescription drug products) to provide the information necessary for the safe and effective use of the drug product. Therefore, different content and format regulations apply to prescription and nonprescription labeling (see generally §§ 201.57 and 201.66 (21 CFR 201.57 and 201.66), respectively). Labeling for nonprescription drug products is directed to consumers (see § 201.66). Although patient labeling is required for certain prescription drug products (see, *e.g.,* 21 CFR part 208), generally, labeling for prescription drug products, including the prescribing information (see § 201.57), is directed to the healthcare practitioner—not the patient—and a patient uses the prescription drug product under the supervision of a practitioner licensed by law to administer such drug.

H. Comments on Refusal To Approve an Application With an ACNU and FDA Response

FDA specified in the proposed rule that we would refuse to approve an application for a nonprescription drug product with an ACNU if FDA has determined the application failed to meet the requirements specified in proposed 21 CFR 314.56 applicable to NDAs (proposed 21 CFR 314.125(b)(20)) or ANDAs (proposed 21 CFR 314.127(a)(15)). In the following paragraphs, we discuss the comments on this proposal. After consideration of public comments received, we are finalizing our proposals without change.

(Comment 46) We received a few comments supporting the provision. One comment explains that this provision is important because it alerts applicants to the requirements for a nonprescription drug product with an ACNU and explains FDA's action if the application does not comply with the requirements. We received one comment requesting that FDA include language in the rule to explain that FDA would not approve a nonprescription drug product with an ACNU if it has not been shown that the ACNU is necessary because the commenter believes this specific reason for rejecting an application is somewhat unusual.

(Response 46) An application for a nonprescription drug product with an ACNU must meet all applicable requirements for an application in addition to the specific requirements for a nonprescription drug product with an ACNU in § 314.56 in this final rule. FDA is including in the rule when FDA would refuse to approve an application for a nonprescription drug product with an ACNU. In addition to the other reasons for refusing to approve an application previously established at 21 CFR 314.125 and 314.127, we are establishing at 21 CFR 314.125(b)(20) and 314.127(a)(15) in this final rule, that we would refuse to approve an application for a nonprescription drug product with an ACNU if FDA determined the application failed to meet the applicable requirements in 21 CFR 314.56. For example, if an application for a nonprescription drug product with an ACNU fails to include a statement regarding the necessity of the ACNU (21 CFR 314.56(b)(1)(ii) in this final rule) or include adequate data or other information that demonstrates the necessity of the ACNU to ensure appropriate self-selection or appropriate actual use, or both (21 CFR 314.56(b)(1)(v) in this final rule), FDA would not approve the application.

I. Comments on Other Postmarketing Reports and FDA Responses

We proposed to require a new postmarketing report for nonprescription drug products with ACNUs. We proposed that applicants must report to FDA information concerning any incident of failure in the implementation of an ACNU using the FDA Adverse Event Reporting System (FAERS) (proposed 21 CFR 314.81(b)(3)(v)). In the following paragraphs, we discuss comments on this proposed requirement.

After considering the comments, which we discuss below, we are making clarifying changes to the requirement because of significant commenter confusion as to when a postmarketing report should be submitted to FDA and concerns about duplicative reporting requirements. We are replacing the title ''Report of failure in the implementation of an additional condition for nonprescription use'' with ''Report of additional condition of nonprescription use (ACNU) failure for a nonprescription drug product with an ACNU'' in the heading. We are replacing the phrases ''when a failure in the implementation of an additional condition for nonprescription use (ACNU) for a nonprescription drug product occurs'' and ''report of a failure in implementation of an ACNU'' with ''report of an ACNU failure'' throughout 21 CFR 314.81(b)(3)(v) of the final rule. We are designating 21 CFR 314.81(b)(3)(v)(A) and adding the subtitle ''ACNU failure'' followed by the explanation that an ACNU failure occurs upon either of the following events: (1) a failure associated with the implementation of the key elements of the ACNU under 21 CFR 314.56(c)(1)(iv) or (c)(2)(ii)) or (2) a failure associated with the operationalization of an ACNU under 21 CFR 314.56(c)(1)(vii) or (c)(2)(iii), as approved by FDA in the application (21 CFR 314.81(b)(3)(v)(A) in this final rule). To address confusion about applicant responsibilities in connection with ACNU failure reporting requirements and to be consistent with certain existing postmarketing reporting requirements for adverse drug experiences (see § 314.80), we are adding 21 CFR 314.81(b)(3)(v)(B), stating that the applicant must develop written procedures for the surveillance, receipt, evaluation, and reporting of ACNU failures to FDA. We note that FDA has described its intention to issue a proposed rule that, among other things, would modernize postmarketing safety reporting requirements for human drug and biological products and require application holders for drug products and certain biological products to establish and maintain a pharmacovigilance quality system (see Regulation Identifier Number 0910–AI61 on Fall 2023 Unified Agenda of Regulatory and Deregulatory Actions). In that proposed rule, FDA intends to provide notice and an opportunity for comment on any proposed changes that, if finalized, may affect the requirements in § 314.81(b)(3)(v) of this final rule.

We are designating § 314.81(b)(3)(v)(C) and adding the subtitle ''Report of ACNU failure'' followed by information about the report of ACNU failure. To address commenter confusion that a report of an ACNU failure is duplicative of existing

postmarketing reporting requirements for adverse drug experiences (see § 314.80), we are removing the clause ''that may cause or lead to inappropriate medication use or consumer harm'' from the explanation of an event that triggers the submission of a report of an ACNU failure because an ACNU failure may still occur even if such failure does not cause or lead to inappropriate medication use or consumer harm. In addition, we are removing the clause stating that a report must be submitted, ''whether or not the failure is associated with an adverse event,'' to avoid confusion between a report of an ACNU failure submitted under § 314.81(b)(3)(v) of this final rule and a postmarketing report of an adverse drug experience, which would be submitted under § 314.80. To reduce burden and further address commenter confusion, we are clarifying that if an applicant receives or otherwise obtains information regarding an adverse drug experience associated with an ACNU failure before the submission of a report of an ACNU failure, a single individual case safety report must be submitted to FDA that describes both the adverse drug experience and the associated ACNU failure. To clarify the term ''supplement,'' and not to confuse with a supplement to an approved application, we are revising the phrase ''must supplement the report'' to ''submit a follow-up report to the previously submitted report,'' and ''the supplement must include'' to ''the follow-up report must include.''

We are designating the content of the report of ACNU failure to § 314.81(b)(3)(v)(D) in this final rule and adding the subheading ''Content of Report of ACNU failure.'' We are revising the subheading in § 314.81(b)(3)(v)(A)(*2*) from ''Additional information, if known.'' to ''Additional Information if available to the applicant.'' for clarity. In order to reduce burden on industry by having consistency with current processes for ICSR submissions, we are also revising the requirement for the content of an ACNU report to include the additional information, if available to the applicant, as a dataset in a structured manner instead of a narrative summary (see proposed § 314.81(b)(3)(v)(A)(*2*)(*iv*) and (*v*)). Therefore, while the additional information is consistent with the proposed rule, we are separating the additional information into separate provisions consistent with current practices for reporting structure beginning at § 314.84(b)(3)(v)(D)(*2*)(*iv*) in this final rule (21 CFR 314.81(b)(3)(v)(D)(*2*)(*iv*) through (*x*) in this final rule). Among other requirements, § 314.84(b)(3)(v)(D)(2)(*iv*) in this final rule requires the use of ACNU failure terms. The applicant may use, for example, a MedDRA (Medical Dictionary for Regulatory Activities) term or the verbatim phrasing used by the reporter as the ACNU failure term. Additionally, new MedDRA terms have been added to describe certain ACNU failures.

We are also making nonsubstantive changes to align with existing postmarketing reporting requirements. We are replacing ''adverse event'' with ''adverse drug experience'' throughout § 314.81(b)(3)(v) in this final rule to align with the terminology used for postmarketing reporting requirements for adverse drug experiences in § 314.80. Although reports of an ACNU failure will be submitted to FAERS, we have removed specific mention of FAERS from the rule to align with existing postmarketing reporting requirements which do not specifically refer to an FDA database for submissions (see, *e.g.,* § 314.80). Therefore, in addition to the reasons stated in the previous paragraphs, we are omitting the following sentence from the regulation: ''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.'' (as stated in proposed § 314.81(b)(3)(v)). We are also removing the phrase ''to FAERS'' throughout the section.

We are also making the following clarifying revisions on our own initiative in § 314.81(b)(3)(v): (1) replacing the word ''submitter'' with ''applicant,'' (2) replacing ''obtains'' with ''receives or otherwise obtains,'' (3) removing the word ''as'' before the clause ''required in § 314.80(f),'' and making corresponding grammatical changes in sentences (*e.g.,* revising an ''a'' to ''an'' due to sentence revisions).

(Comment 47) We received many comments that support FDA's proposal to require postmarketing reports for an ACNU failure. We received many comments that support robust postmarketing surveillance for nonprescription drug products with ACNUs for FDA to monitor the drug products. One comment recommends that if an applicant does not comply with the reporting requirement, the applicant must market its drug product as a prescription drug product and cannot market its drug product as a nonprescription drug product with an ACNU.

(Response 47) FDA agrees that postmarketing reports of an ACNU failure are an important part of FDA surveillance to ensure that consumers are appropriately accessing the nonprescription drug product with the ACNU as approved by FDA. If an applicant does not comply with the requirements for postmarketing reports, the applicant may be subject to an FDA enforcement action for failure to submit required postmarketing reports (see section 301(e) of the FD&C Act (21 U.S.C. 331(e)); see also section 505(e) of the FD&C Act).

(Comment 48) We received a few comments asserting that the requirement for a report of an ACNU failure exceeds FDA's statutory authority, particularly where no adverse event occurred.

(Response 48) We disagree that FDA lacks authority to require postmarketing reports of ACNU failures, including when they are not associated with particular adverse drug experiences.[6] Section 505(k)(1) of the FD&C Act authorizes FDA to require such reporting. Specifically, section 505(k)(1) requires reports ''of data relating to clinical experience and other data or information'' as FDA prescribes by regulation, ''on the basis of a finding that such . . . reports are necessary in order to enable [FDA] to determine, or facilitate a determination, whether there is or may be ground'' for withdrawing approval of an application.

When describing the kinds of data or information that FDA may require to be reported, section 505(k)(1) of the FD&C Act does not expressly refer to adverse drug experiences, and instead refers to a broader category of ''data relating to clinical experience and other data or information.'' In contrast, in other parts of the FD&C Act, the statute does expressly use the term ''adverse drug experience,'' see, *e.g.,* sections 505(k)(3) and 505–1, underscoring that ''data relating to clinical experience and other data or information'' means something distinct from data or information relating to ''adverse drug experiences.'' Indeed, consistent with the statutory text, FDA has long interpreted ''data relating to clinical experience and other data or information,'' as described in section 505(k)(1) of the FD&C Act, as

[6] See 21 CFR 314.80(a), (defining *adverse drug experience* as ''any adverse event associated with the use of a drug in humans, whether or not considered drug related'' including the following:, An adverse event occurring in the course of the use of the drug in professional practice; an adverse event occurring from drug overdose whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action).

covering a broader set of information than solely adverse drug experiences. For example, under 21 CFR 314.81(b), implementing section 505(k)(1) of the FD&C Act, applicants are required to report other kinds of information, regardless of whether the information is associated with adverse drug experiences, such as ''information concerning any incident that causes the drug product or its labeling to be mistaken for, or applied to, another article,'' ''a summary of new information from the previous year that might affect safety, effectiveness, or labeling of the drug product,'' and ''distribution data.''

Additionally, like these other kinds of information, even when there is no adverse drug experience that is clearly associated with an ACNU failure, ACNU failures generally would have a bearing on whether the Agency may consider withdrawal proceedings pursuant to section 505(e) of the FD&C Act. For example, under section 505(e), the Agency may withdraw approval of an application if certain new information shows that a drug is not safe for use under the conditions of use upon the basis of which the application was approved. If the applicant does not ensure that the ACNU is implemented and operationalized as approved by FDA in the application, then the drug may no longer be considered safe and effective for use in the nonprescription setting. In such a case, FDA may consider withdrawing an application, if, for example, an applicant fails to take appropriate corrective action to prevent reoccurrence of an ACNU failure of the same nature.

More specifically, because a nonprescription drug product with an ACNU must only be made available to consumers who fulfill the ACNU for whom it is appropriate, ACNU failures are relevant to understanding the safety and effectiveness of the drug. With an ACNU failure, an adverse drug experience may very well occur even if there are no reported adverse drug experiences associated with a particular ACNU failure. The ACNU failure could be an indication that the method of implementing or operationalizing the ACNU is flawed, which may result in the drug product not being made available to consumers for whom it is appropriate and, in other instances, may result in the drug product being made available to consumers for whom it is not appropriate. For example, with Drug X (see more information about Drug X, a fictitious nonprescription drug product with an ACNU, in the proposed rule (87 FR 38313 at 38319)), 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 consumer answers the series of questions in the questionnaire and the underlying program or other operating information used by the secure website calculates the risk score for a serious side effect and determines if the consumer has an acceptable disease-specific risk score to use Drug X and therefore purchase Drug X. A software failure that results in a miscalculation of the risk score would be an ACNU failure even if the failure did not provide the consumer with access to drug product because such failure in calculating the risk score could similarly provide consumers access to the drug product for whom it is not appropriate. FDA and applicants have an interest in understanding the ACNU failures and mitigating the risk of reoccurrence of an ACNU failure because ACNU failures could result in adverse drug experiences or lead to the drug product being made available to consumers that should not be taking the drug product for various reasons.

(Comment 49) We also received several comments that oppose the proposed postmarketing reporting requirement for a nonprescription drug product with an ACNU as ''overly broad,'' ''unnecessary'', or ''excessive burdensome.'' Those comments request that FDA revise or remove the requirement to report an ACNU failure. The comments contend that a nonprescription drug product with an ACNU would already be subject to the same postmarketing reporting requirements for adverse drug experiences in § 314.80 and, if applicable, 21 CFR part 803 for medical devices. The comments assert that the postmarketing reporting requirement for ACNU failures could require the submission of a very large number of postmarketing reports and will place undue resource demands on both applicants and FDA. Several comments suggest revisions in how FDA defines a failure in implementation of an ACNU to narrow the scope of the reporting requirement. A few of these comments suggest that the submission of a report should be limited to an ACNU failure that results in an adverse event or that is likely to result in an adverse event. A few comments suggest that what they consider nonsignificant failures (*e.g.,* ACNU failures with no adverse events) should be captured and investigated under an applicant's existing complaint handling processing instead of under a postmarketing reporting requirement.

(Response 49) After consideration of comments received, FDA is revising the requirement to report ACNU failures for clarity and to decrease any potential duplicative reporting. We are clarifying the events that would result in the submission of a report of an ACNU failure to make clear that these reports are not duplicative of the applicable regulatory requirement for the submission of postmarketing reports of adverse drug experiences under § 314.80. In order to clarify that only reports of ACNU failures are required to be submitted in a postmarketing report under § 314.81 and because postmarketing reports of adverse experiences are currently required under § 314.80, we are removing language that: (1) a report of an ACNU failure should be submitted if the failure may cause or lead to inappropriate medication use or consumer harm and (2) a report must be submitted to FAERS whether or not the failure in implementation of the ACNU is associated with an adverse event. We clarify that a report of an ACNU failure must be submitted to FDA when an event occurs that differs from the following, as approved by FDA in the application including: (1) a failure associated with the implementation of one or more of the key elements of an ACNU under § 314.56(c)(1)(iv) or (c)(2)(ii) or (2) a failure associated with operationalization of the ACNU under 21 CFR 314.56(c)(1)(vii) or (c)(2)(iii) (§ 314.81(b)(3)(v) in this final rule). A nonprescription drug product with an ACNU that includes a device constituent part is also subject to combination product reporting requirements, including malfunction reporting (see 21 CFR 803.50 and part 4) for an event involving the device constituent part.

For the reasons explained in response to Comment 48, we disagree that reports of ACNU failure should only be submitted for ACNU failures that result in an adverse event or that is likely to result in an adverse event.

(Comment 50) We received a comment suggesting that the proposed postmarketing reporting provision would require reports about a wide range of technological failures, including routine and quickly resolved technological failures (*e.g.,* broken kiosks or credit card readers, disruptions at a retailer, or temporarily inaccessible websites or mobile applications).

(Response 50) Reports of ACNU failures may need to be submitted for various types of technological failures. However, the specific circumstances of the technological failure would

determine whether it constitutes an ACNU failure. We are revising the rule to clarify the events that would be considered ACNU failures. We further clarify that a report of an ACNU failure must be submitted to FDA when there is an event that occurs that differs from how FDA approved the nonprescription drug product with an ACNU: (1) a failure associated with the implementation of the key elements of an ACNU under § 314.56(c)(1)(iv) or (c)(2)(ii), as approved by FDA in the application or (2) a failure associated with operationalization of an ACNU under 21 CFR 314.56(c)(1)(vii) or (c)(2)(iii), as approved by FDA in the application (§ 314.81(b)(3)(v) in this final rule).

(Comment 51) One comment states that frequent reporting of ''problems'' to FDA also might stigmatize nonprescription drug products with ACNUs, as some observers may incorrectly equate any reported problem with a threat to someone's health.

(Response 51) We interpret the comment about ''frequent reporting of problems'' to mean frequent reporting of ACNU failures and disagree. FDA has a public health interest in receiving reports of ACNU failures because the FDA-approved ACNU ensures consumers' appropriate self-selection or appropriate actual use, or both, of the nonprescription drug product without the supervision of a practitioner licensed by law to administer such drug. FDA and applicants have an interest in understanding the ACNU failures and mitigating the risk of reoccurrence of an ACNU failure because ACNU failures could result in adverse drug experiences or lead to the drug product being made available to consumers that should not be taking the drug product for various reasons, even if the initial failure did not.

(Comment 52) We received a comment expressing concerns that the proposed rule requires immediate reporting regardless of the nature of the failure and will require a significant change to pharmacovigilance programs with limited benefit.

(Response 52) As explained in our responses to Comments 49–50, FDA clarified the events that would result in the submission of a report of an ACNU failure. The applicant must submit the report of an ACNU failure as soon as possible but no later than 15 calendar days from the date when the applicant has acquired the minimum dataset for an ACNU failure (§ 314.81(b)(3)(v)(E) of this final rule). We disagree that applicants will need to make significant changes to pharmacovigilance programs in order to comply with the timeframe for submitting a report of an ACNU failure under § 314.81 because the requirement is consistent with the timeframe for the submission of certain postmarketing reports of adverse drug experiences under § 314.80. Therefore, applicants will generally already have systems in place that could be adapted to facilitate the reporting of ACNU failures. FDA has a public health interest in receiving reports of ACNU failures expeditiously because the FDA-approved ACNU ensures consumers' appropriate self-selection or appropriate actual use, or both, of the nonprescription drug product without the supervision of a practitioner licensed by law to administer such drug. Further, as explained previously, FDA and applicants have an interest in understanding the ACNU failures and working to mitigate the risk of recurrence of an ACNU failure.

(Comment 53) We received several comments on the burden and benefits of submitting individual reports to FDA for each individual ACNU failure encountered by a consumer resulting from the same cause of failure, as opposed to a single, consolidated report for all such failures. We received several comments supporting a single, consolidated report to reduce the reporting burden on applicants. We received a few comments that recommend FDA consider the nature of the failure or clinical outcome of the failure (*i.e.,* a risk-based approach) to determine whether individual or consolidated reporting is appropriate. We received one comment recommending consolidated reporting whereby reports would be submitted at intervals less than 5 days apart or when the particular error occurs after a certain number of times because applicants may not have the capacity to submit individual reports for every occurrence of a particular technical malfunction or error. Another comment urges FDA to consider consolidated reporting for ACNU failures that the comment characterized as unrelated to safety and effectiveness (such as a computer system failure). Finally, we received a comment that requests FDA consider implementing a more streamlined reporting procedure for nonprescription drug products with ACNUs similar to CDRH's Voluntary Malfunction Summary Reporting (VMSR) program for medical devices.

(Response 53) As explained in our responses to Comments 49–50, FDA clarified the events that would result in the submission of a report of an ACNU failure as not all issues related to an ACNU are ACNU failures. FDA specifically sought comment on the burden and benefits of submitting an individual report to FDA for each ACNU failure encountered by a consumer resulting from the same cause of failure, as opposed to a single, consolidated report for such failures. Given the possibility for numerous reasons for an ACNU failure depending on the particular circumstances, FDA believes that individual reporting for ACNU failures would provide more specific information to facilitate an understanding of ACNU failures, their causes, and their outcomes. Therefore, we disagree with submitting a single, consolidated report of an ACNU failure resulting from the same cause of failure.

The VMSR program (see 83 FR 40973, August 17, 2018) is a voluntary program intended to streamline reporting of device malfunctions in certain situations based on FDA experience with summary reporting programs, key findings from CDRH's pilot program for the submission of Medical Device Reports (MDRs) in summary format on a quarterly basis, and other information summarized in the 2017 proposal for the VMSR program (see 82 FR 60922, December 26, 2017). Therefore, we disagree with implementing a reporting procedure for nonprescription drug products with ACNUs similar to the VMSR program because we do not have findings on which to base a streamlined approach. To decrease any potential duplicative reporting burden by applicants, we clarified the events that would result in the submission of a report of an ACNU failure to FDA.

(Comment 54) We received a few comments questioning whether FAERS is an appropriate database for collecting reports of ACNU failures. One comment specifically raises a concern about whether FAERS is appropriate to collect reports of technological failures, considering that FAERS currently focuses on adverse events and product defects and quality. The comment further asks FDA to clarify any changes that would be required to the reporting forms to accommodate ACNU failures. A few comments also question whether the clinical reviewers of FAERS reports have the expertise to evaluate reports of technological problems and the attempted remedies.

(Response 54) FAERS is the database currently designed to support FDA's postmarketing safety surveillance program for drugs and certain biological products and can currently accommodate reports of ACNU failures. Although reports of an ACNU failure will currently be submitted to FAERS, we have removed specific mention of FAERS from the rule to align with other postmarketing reporting regulations,

which do not specifically refer to a current FDA database for submissions (see, *e.g.,* § 314.80).

The informatic structure of the FAERS database aligns with the International Council for Harmonisation guidance for industry entitled ''E2B(R3) Electronic Transmission of Individual Case Safety Reports (ICSRs) Implementation Guide—Data Elements and Message Specification'' (available at *https://www.fda.gov/media/81904/download*).

FDA reviewers are trained to evaluate reports of technological problems and the attempted remedies. Center for Drug Evaluation and Research (CDER) reviewers may consult CDRH reviewers, when appropriate, to address any issues regarding technology related to an ACNU.

(Comment 55) We received one comment suggesting that pharmacies or sellers would be required to report and record ACNU failures thereby placing a tremendous burden on the pharmacies or sellers.

(Response 55) We disagree. While a pharmacist or other individual may voluntarily submit a report of an ACNU failure to FDA's reporting systems such as Medwatch (Ref. 5), the rule requires the applicant of the nonprescription drug product with an ACNU to submit reports of an ACNU failure (see § 314.81(b)(3)(v) in this final rule). Therefore, unless they are applicants for the relevant drug product, pharmacies and sellers are not required under the rule to report ACNU failures.

(Comment 56) We received a comment seeking clarification on whether FDA expects an applicant to implement remediation for every ACNU failure. The comment further states that an applicant should determine when remediation should be implemented based on its safety assessment and that the remedial action taken to address the ACNU failure depends on the type of failure and the consequence of the failure.

(Response 56) If there is an ACNU failure, an event has occurred that is not consistent with FDA's approval of the nonprescription drug product with an ACNU in one or both of two ways: (1) a failure associated with the implementation of the key elements of an ACNU under 21 CFR 314.56(c)(1)(iv) or (c)(2)(ii) or (2) a failure associated with operationalization of the ACNU under 21 CFR 314.56(c)(1)(vii) or (c)(2)(iii), as approved by FDA in the application (§ 314.81(b)(3)(v) in this final rule). The applicant must explain the remedial action initiated or completed and the corrective action to prevent ACNU failures of the same nature in the future (§ 314.81(b)(3)(v)(A)(*2*)(*v*) in this final rule).

(Comment 57) We received a comment requesting that FDA provide guidance on how often applicants should monitor a nonprescription drug product with an ACNU.

(Response 57) We understand the need for additional clarity here. In the proposed rule, we stated that, ''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'' (87 FR 38313 at 38322). The proposed rule also proposed that the report must 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 (87 FR 38313 at 38323 and proposed § 314.81). As mentioned earlier, to address confusion and be consistent with the existing postmarketing reporting requirements for adverse drug experiences (see § 314.80) and cognizant of minimizing burden we are adding § 314.81(b)(3)(v)(B), stating that the applicant must develop written procedures for the surveillance, receipt, evaluation, and reporting of ACNU failures to FDA. This gives applicants flexibility to develop procedures specific to the drug product and potentially align with any written procedures already established with respect to § 314.80 to help minimize burden. We anticipate that applicants could adapt any written procedures for surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences as already required under § 314.80 to also include instances of an ACNU failure.

(Comment 58) We received a comment that recommends FDA create a consumer-friendly website and telephone number for consumers to report issues with a nonprescription drug product with an ACNU.

(Response 58) FDA already has reporting systems for consumers to report adverse drug experiences, complaints, or other issues with FDA-regulated products, including nonprescription drug products. MedWatch is the FDA's program for reporting serious adverse drug experiences, product quality problems, therapeutic inequivalence/failure, and product use errors with human medical products (Ref. 5). Additionally, consumers can contact the FDA Consumer Complaint Coordinator for the State in which they reside to report adverse drug experiences or other problems with FDA-regulated products. FDA's Consumer Complaint Coordinators, located in FDA offices, will listen, document a complaint about an FDA-regulated product, and follow up as necessary (Ref. 6). Therefore, we disagree that FDA needs to create an additional consumer-friendly website and telephone number for consumers to report issues specific for a nonprescription drug product with an ACNU.

J. Comments on General Labeling Requirements and FDA Responses

We proposed to require that a nonprescription drug product with an ACNU must comply with all applicable regulatory requirements for nonprescription drug products under part 201 (21 CFR part 201), including the format and content of nonprescription drug product labeling under § 201.66 and the statements specified in proposed 21 CFR 201.130(a) (proposed 21 CFR 201.67(c)). In the following paragraphs, we discuss the comments on these requirements. After consideration of public comments received, we are finalizing our proposals with modifications for clarity and consistency with revisions made to § 201.130 in this final rule. Specifically, we are revising the citation in 21 CFR 201.67(c) of the final rule from ''§ 201.130(a)'' to ''§ 201.130(a) and (b).''

(Comment 59) We received several comments supporting the proposed labeling requirements because the labeling will help consumers use nonprescription drug products with ACNUs safely and effectively. However, a few comments express concerns about whether consumers possess the capacity to obtain, process, and understand the basic health information needed to make an appropriate health decision using the labeling for nonprescription drug products with ACNUs. A few comments discuss accessibility of labeling for nonprescription drug products with an ACNU, and one comment recommends that labeling should be made available to consumers in multiple languages using a quick-response code (commonly referred to as a QR code) on the labeling. Another comment requests that FDA develop criteria to ensure accessibility of labeling for nonprescription drug products with ACNUs.

(Response 59) We understand commenters' concerns that some consumers may have difficulty using the labeling for a nonprescription drug product with an ACNU. However, consistent with the development of nonprescription drug products,

applicants of nonprescription drug products with ACNUs may be required to conduct consumer studies which can help demonstrate that the requirement for adequate directions for use is met (87 FR 38313 at 38316). These studies may include label comprehension studies, self-selection studies, actual use studies, and other human factors studies (87 FR 38313 at 38316). FDA has issued guidances on certain types of consumer studies (Refs. 1 to 3). Because nonprescription drug products with an ACNU, like other nonprescription drug products, will be used by consumers from the general population without supervision of a practitioner licensed by law to administer such drug, applicants are expected to include a wide range of subjects in consumer studies. Specifically, in self-selection studies, exclusion criteria should be minimal (*e.g.,* inability to read and understand English) (Ref. 2). In label comprehension studies, applicants should include an adequate number of subjects in self-selection studies who have limited literacy skills. The proportion of low-literacy subjects in the study sample should be representative of the proportion of adults in the United States with low literacy skills based on available national data (Ref. 1).

FDA acknowledges the benefits of having translated drug information for individuals with limited English proficiency. FDA's current regulations require that all words, statements, and other information required by or under authority of the FD&C Act appear on the label or labeling in the English language, with limited exceptions (see § 201.15(c)). In the case of articles distributed solely in the Commonwealth of Puerto Rico or in a Territory where the predominant language is one other than English, the predominant language may be substituted for English. In addition to English, an applicant may provide consumers with labeling in other languages; however, applicants (and not FDA) must ensure the translation of the labeling is accurate and complete. FDA strongly encourages applicants to work with retailers and other organizations to ensure that a nonprescription drug product with an ACNU is accessible to individuals with limited English proficiency. To the extent an applicant, retailer, or other organization receives Federal financial assistance from the U.S. Department of Health and Human Services (HHS), they are required to take reasonable steps to provide meaningful access to their programs and activities by individuals with limited English proficiency under Title VI of the Civil Rights Act of 1964 and its implementing regulations (42 U.S.C. 2000d, *et seq.;* 45 CFR part 80; see also section 1557 of the Affordable Care Act, 42 U.S.C. 18116, which provides similar protections as those under Title VI in health programs and activities receiving Federal financial assistance).

We note that we considered requiring that the label include additional information for consumers such as information that the drug may also be available as a prescription drug product. We ultimately rejected that idea, however; the purpose of applicable labeling requirements for nonprescription drug products and the specific labeling requirements for nonprescription drug products with an ACNU is to provide consumers with the information that they need to self-select and use the drug product in the nonprescription setting, not to inform them of other treatment options. However, while FDA would not require this information on the labeling of the nonprescription drug product, the applicant may choose to engage in promotional communications for both the approved prescription and nonprescription drug products.

(Comment 60) We received one comment that requests FDA clarify the standards for permissible labeling differences between an RLD and an ANDA nonprescription drug product with an ACNU that is operationalized differently from the RLD to increase the viability of the ACNU pathway for generic drug products.

(Response 60) We disagree with the need to clarify permissible labeling differences specific to an RLD and an ANDA nonprescription drug product with an ACNU because the rule does not change the standards for permissible labeling differences between an RLD and an ANDA. 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 section 505(j)(2)(A) and (j)(4) of the FD&C Act and §§ 314.94(a)(8)(iv) and 314.127(a)(7)). Any permissible labeling difference would be determined on a case-by-case basis as we consider the specifics of each application for a nonprescription drug product with an ACNU during our review.

(Comment 61) We received a comment that the proposed labeling requirements of 21 CFR 201.67(c) do not impose any incentive or requirement for consumers to read the information provided by the applicant before accessing and fulfilling the ACNU. The comment suggests that consumers could access the information on the provided website, disregard the information, and fulfill the ACNU without having the requisite knowledge to make an informed decision.

(Response 61) While FDA acknowledges that we cannot require a consumer to read labeling, the applicant must describe how the ACNU will ensure appropriate self-selection or appropriate actual use, or both, by consumers (21 CFR 314.56(c)(1)(iii) in this final rule) and submit adequate data or other 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 (21 CFR 314.56(c)(1)(vi) in this final rule).

K. Comments on Format Requirements for Required ACNU Statement and FDA Responses

We proposed to require that the ACNU Statement specified in proposed 21 CFR 201.130(a)(2) meet specific format requirements (proposed 21 CFR 201.67(d)). In the following paragraphs, we discuss the comments on this proposed requirement. After consideration of public comments received, we are finalizing our proposal with modifications for consistency with changes made to 21 CFR 201.130 and elsewhere in this final rule. We are finalizing the proposed title of the requirement, ''Format requirements for required ACNU statement'' with minor revision to read as follows: ''Format requirements for the required statement about the ACNU.'' We are replacing the word ''statement'' with the phrase ''statement about the ACNU'' in all instances throughout § 201.67(d) for clarity. We proposed that the statement specified in § 201.130(a)(2) must meet all format requirements that are specified in § 201.67(d). However, due to revisions in the regulation's text, we are revising the citation of 21 CFR 201.130(a)(2) to 21 CFR 201.130(b)(1).

(Comment 62) We received one comment in support of the proposed format requirement that the ACNU Statement specified in proposed 21 CFR 201.130(a)(2) appear in a yellow background banner. However, several comments oppose the proposed format requirement that the statement about the ACNU appear in boldface and black type in a yellow background banner. Several comments state that the proposed format requirements: (1) are overly prescriptive, (2) may not achieve

the desired visibility in all cases, and (3) do not appropriately consider a drug product's unique trade dress. One comment argued that while there are benefits of highlighting the statement to increase attention to it, too much highlighted information could reduce attention to other important elements on the PDP. Many comments state that the format of the statement about the ACNU should be determined on a product-by-product basis. A few comments recommend that FDA allow flexibility in the font type, color of the font, and highlight color that fits the requirement of prominence and the proposed trade dress consistent with the format requirements in 21 CFR 201.66(d)(3).

(Response 62) We disagree with revising the format requirements for the statement about the ACNU. While we understand concerns from some commenters that the formatting of the statement may visually conflict with trade dress, the distinctive formatting (*e.g.,* boldface and black type in a yellow background banner) of the statement is necessary for consistency across all nonprescription drug products with ACNUs. Having standardized format and content on labeling is consistent with FDA practice and regulations, where possible (see generally 21 CFR part 201). Consistency in the format and content of the statement about the ACNU is important so that consumers become familiar with the statement and can easily identify the drug product as a nonprescription drug product with an ACNU, not a traditional nonprescription drug product that can be purchased without fulfilling an ACNU. We want consumers to know that there is something different about an ACNU drug product and for consumers and other persons to understand that these drug products are not suitable for all individuals and should only be used after fulfilling the ACNU. This statement is to provide immediate notice to consumers and for other people who may have access to the drug product purchased by the consumer (*e.g.,* household members, visitors to the consumer's house) but did not fulfill the ACNU. This drug may not be right for that person and using the drug product without fulfilling the ACNU could put the person at risk for side effects and medication errors. Thus, the format requirements for the statement are intended to help ensure the safe and effective use of nonprescription drug products with ACNUs.

(Comment 63) A few comments oppose the proposed font size requirement asserting the font size is exceptionally large given the variability of package sizes. One comment suggests that the proposed font size requirements result in the statement consuming a significant portion of the PDP, from one-quarter to one-third of the PDP, at a minimum. One comment recommends permitting the use of a smaller font size when the required minimum font size is not feasible due to the package size (*e.g.,* convenience or small size packaging).

(Response 63) FDA disagrees that the required font size is exceptionally large. Published references recommend a larger font size, such as 12-point sans serif to improve readability (Refs. 7 and 8). A larger font size will help ensure consumers can identify a nonprescription drug product with an ACNU and read the statement that alerts consumers that the drug product is not suitable for all individuals and should only be used after fulfilling the ACNU. As required in existing regulations for nonprescription drug product labeling, the PDP must be large enough to accommodate all the mandatory label information required to be placed on the PDP with clarity and conspicuousness and without obscuring designs, vignettes, or crowding (see § 201.60). Applicants can reduce the font size of the trade or proprietary name of the nonprescription drug product with an ACNU, if one exists, and promotional material to allow room for the statement about the ACNU. We believe an applicant should generally be able to include the statement on the PDP as specified in the rule without having to increase the package size. However, we also proposed an exception—an applicant may request an exception to the minimum font size requirement for containers where its size would render compliance with the requirement impractical (§ 201.67(d)(5) in this final rule).

L. Comments on Exemption From Adequate Directions for Use and FDA Responses

We proposed to 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, we proposed 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 21 CFR 201.130(a) and the ACNU is implemented by the applicant as approved by FDA in the application (proposed 21 CFR 201.130). We proposed to require that the following statement appear as the first direction under the heading ''Directions'' in the labeling, as required in 21 CFR 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.'' (Proposed 21 CFR 201.130(a)(1)) We also proposed to 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.'' (Proposed 21 CFR 201.130(a)(2)) We proposed that this statement must meet the specific format requirements as specified in proposed 21 CFR 201.67(d). We also proposed that the labeling of the drug must comply with other applicable labeling requirements for nonprescription drug products under part 201, including the format and content requirements for nonprescription drug product labeling under 21 CFR 201.66 (proposed 21 CFR 201.130(a)(3)). Lastly, we proposed to 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 87 FR 38313 at 38324 and proposed 21 CFR 201.130(b)).

In the following paragraphs, we discuss the comments on this requirement. After consideration of public comments received, we are finalizing our proposals with modifications as discussed. After considering comments, as discussed below, we are adding flexibility to the labeling requirements regarding instructions for the ACNU and the statement about the ACNU (21 CFR 201.130(a) and (b) in this final rule). These requirements, as revised based on comments we received, provide flexibility for applicants to better convey information to consumers for a particular nonprescription drug product with an ACNU. FDA feels strongly that the content of required labeling in 21 CFR 201.130(a)(1) and (b)(1) in this final rule should generally be consistent across all nonprescription drug products with ACNUs. Consistency in the content of the labeling is important to help consumers understand (including the original purchaser and persons other than the original purchaser) that these nonprescription drug products are not

suitable for all individuals and should be only used after fulfilling the ACNU. Consistency assists consumers in understanding the ACNU that the consumer must fulfill and where to find additional information. Consistency in the labeling can reduce consumer confusion about nonprescription drug products with an ACNU because the labeling will become familiar to consumers and promote recognition that a nonprescription drug product has an ACNU. However, we recognize that in certain situations, revisions to the required labeling may be appropriate for a drug product due to the specifics of the drug product or the ANCU. Therefore, we are revising the requirement to allow FDA to approve an NDA applicant's revisions to the labeling specified in 21 CFR 201.130(a)(1) and (b)(1) in this final rule when the revisions are appropriate for a specific drug product and the applicant supports the revisions with adequate data or other information that demonstrates sufficient consumer understanding of the revised labeling. Because FDA believes that consistency in the content of the required labeling is important FDA does not intend to approve revisions to the labeling that are minor in nature, do not address a specific aspect of the particular drug product or ACNU, or are inconsistent with the labeling for similar nonprescription drug products with ACNUs in the same therapeutic category. For example, if FDA has approved an NDA for Drug X as a nonprescription drug product with an ACNU for condition A and in therapeutic category B with the ACNU Statement in 21 CFR 201.130(b)(1)(i), FDA would generally expect to approve an NDA for a nonprescription drug product with an ACNU for Drug Y also for condition A and in therapeutic category B with the same ACNU Statement as Drug X (*i.e.,* the ACNU Statement in 21 CFR 201.130(b)(1)(i) in this final rule).

FDA is also adding flexibility by requiring the location of the instructions for the ACNU specified in 21 CFR 201.130(a)(1) in this final rule to either appear under the ''Use'' or ''Uses'' heading or the ''Directions'' heading, depending on the purpose of the ACNU, to better inform consumers of the reason that the ACNU needs to be fulfilled (21 CFR 201.130(a)(2) in this final rule).

To accommodate the revisions, we had to make changes to the structure of the regulatory text. We are adding ''(ACNU)'' to the header in 21 CFR 201.130 in this final rule. We are deleting the clause ''in paragraphs (a) and (b) of this section are met'' in the introductory text. We are revising 21 CFR 201.130(a) completely in this final rule to explain the required instructions for the ACNU. The introductory text at 21 CFR 201.130(a) in this final rule now states: ''The label of the drug must include instructions for the ACNU as follows:''. We are also completely revising 21 CFR 201.130(a)(1) introductory text in this final rule to read ''Content of instructions for the ACNU must either be:'' in order to accommodate revisions that the applicant may propose to the instructions for the ACNU. We are also moving the language of the instructions for the ACNU from 21 CFR 201.130(a)(1) as proposed to 21 CFR 201.130(a)(1)(i). Therefore, the ACNU instructions in 21 CFR 201.130(a)(1)(i) will read as follows: ''[T]o 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''. Additionally, we are adding alternative ACNU instructions in 21 CFR 201.130(a)(1)(ii) to read ''FDA may approve an NDA applicant's revisions to the ACNU Instructions when the revisions are appropriate for a specific drug product and the applicant supports the revisions with adequate data or other information that demonstrate sufficient consumer understanding of the revised statement.'' We are deleting the clause in proposed 21 CFR 201.130(a)(1) ''The statement must be followed by the other information required in 21 CFR 201.66(c)(6)'' as it was redundant after the revisions to the final rule. We are adding 21 CFR 201.130(a)(2) introductory text for clarity and to provide the location of the instructions, which will read ''The locations of instructions for the ACNU are as follows:''. We are adding flexibility to the placement of the statement by adding 21 CFR 201.130(a)(2)(i) through (iii) in this final rule (previously proposed in 21 CFR 201.130(a)(1)). We are adding 21 CFR 201.130(a)(2)(i), stating that if the purpose of the ACNU is for self-selection, the instructions for the ACNU must appear under the ''Use'' or ''Uses'' heading required in 21 CFR 201.66(c)(4) as the first statement, followed by the other information required in 21 CFR 201.66(c)(4). We are also adding 21 CFR 201.130(a)(2)(ii) in the final rule, stating that if the purpose of the ACNU is for actual use, the instructions for the ACNU must appear under the ''Directions'' heading required in 21 CFR 201.66(c)(6) as the first direction, followed by the other information required in 21 CFR 201.66(c)(6), which is consistent with the location of the statement on the labeling as proposed. We are adding 21 CFR 201.130(a)(2)(iii) in the final rule, stating that if the purpose of the ACNU is for both self-selection and actual use, the instructions for the ACNU must appear under the ''Use'' or ''Uses'' heading as the first statement, followed by the other information required in 21 CFR 201.66(c)(4) and may also appear under the ''Directions'' heading as the first direction, followed by the other information required in 21 CFR 201.66(c)(6).

Additionally to further accommodate the added flexibility, we are revising 21 CFR 201.130(b) introductory text in this final rule to state that the label of the drug must include a statement about the ACNU. We are also adding 21 CFR 201.130(b)(1) to read ''Content of the statement about the ACNU must either be:'' We are adding 21 CFR 201.130(b)(1)(i) to include the language of the statement in proposed 21 CFR 201.130(a)(2) as follows: ''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''. We are also adding 21 CFR 201.130(b)(1)(ii), stating that FDA may approve an NDA applicant's revisions to the ACNU Statement when revisions are appropriate for a specific drug product and the applicant supports the revisions with adequate data or other information that demonstrate sufficient consumer understanding of the revised statement. We are adding 21 CFR 201.130(b)(2) in this final rule to include information consistent with the format information proposed in § 201.130(a)(2) to read as follows: ''The statement about the ACNU must be in the form and manner required by § 201.67(c).'' We are redesignating proposed 21 CFR 201.130(a)(3) to § 201.130(c) of this final rule with minor editorial changes to revise ''Complies'' to ''The labeling of the drug must comply'' for clarity. We are redesignating proposed § 201.130(b) to § 201.130(d) in this final rule with minor editorial revisions to revise ''The additional condition for nonprescription use'' to ''ACNU.'' Furthermore, we are also making revisions for consistency with revisions to 21 CFR 201.67(e) and 314.81(b)(3)(v) in this final rule to provide clarity on implementation of an ACNU by revising ''under the conditions set forth in the approved application.'' to state that the ACNU

must be implemented by the applicant in accordance with: (1) key elements of the ACNU under § 314.56(c)(1)(iv) or (c)(2)(ii) and (2) the operationalization of the ACNU under § 314.56(c)(1)(vii) or (c)(2)(iii), as approved by FDA in the application.

(Comment 64) A few comments oppose the placement of the proposed statement of instructions for the ACNU specified in proposed 21 CFR 201.130(a)(1) in the DFL under the ''Directions'' heading because the placement of the statement should distinguish between an ACNU that is necessary for appropriate self-selection, appropriate actual use, or both. For example, one comment recommends that the labeling statement should appear under the ''Use'' heading in the DFL to alert consumers that they will need to fulfill an ACNU for the listed use(s) rather than under the ''Directions'' heading because information under the ''Directions'' heading is more closely associated with how consumers should take a product after the consumer determines whether the nonprescription drug product with an ACNU is appropriate for the consumer to use.

(Response 64) We agree with the concerns about the standardized placement of the statement in the DFL under the heading ''Directions.'' Therefore, FDA is revising the rule to require the labeling statement to either appear under the ''Use'' or ''Uses'' heading or the ''Directions'' heading, depending on the purpose of the ACNU, to better inform consumers of the reason that the ACNU needs to be fulfilled. Therefore, we are revising the requirement at 21 CFR 201.130(a)(2) in this final rule to require that if the purpose of the ACNU is to ensure appropriate self-selection, the labeling statement must appear under the ''Use'' or ''Uses'' heading as the first statement, followed by the other information required in 21 CFR 201.66(c)(4) (21 CFR 201.130(a)(2)(i) in this final rule); if the purpose of the ACNU is to ensure appropriate actual use, the labeling statement must appear under the ''Directions'' heading as the first direction, followed by the other information required in 21 CFR 201.66(c)(6) (21 CFR 201.130(a)(2)(ii) in this final rule); or if the ACNU is for both self-selection and actual use, the statement must appear under the ''Use'' or ''Uses'' heading as the first statement, followed by the other information required in 21 CFR 201.66(c)(4) and may also appear under the ''Directions'' heading as the first direction, followed by the other information required in 21 CFR 201.66(c)(6) (21 CFR 201.130(a)(2)(iii) in this final rule).

(Comment 65) Several comments support the use of standardized statements in proposed 21 CFR 201.130(a)(1) and (2) to communicate the presence of an ACNU clearly and prominently for a nonprescription drug product to consumers, especially because fulfillment of an ACNU will be a completely new behavior for consumers. However, many comments oppose the standardized wording of the proposed labeling statement specified in proposed 21 CFR 201.130(a)(1) and (2) for being unnecessarily specific and restrictive. Many comments suggest the proposed labeling statements are too lengthy, not consumer-friendly and should be significantly streamlined. Many comments recommend that FDA's proposed language should be an example or template to help guide applicants during their development programs to allow for flexibility to convey specific information about a particular ACNU. A few comments state that the proposed wording for the required labeling statement in proposed 21 CFR 201.130(a)(2) is only appropriate for an ACNU necessary to ensure appropriate self-selection, but not an ACNU necessary to ensure appropriate actual use. We received one comment providing results of a small qualitative research study assessing consumer understanding of the proposed labeling statement specified in proposed 21 CFR 201.130(a)(2); the study suggested poor understanding of the statement's intended purpose. A few comments suggest FDA consider requiring a validated symbol or simple, universal flag in lieu of the proposed ACNU Statement. Several comments recommend that the content of the proposed required labeling statement be determined on a product-by-product basis. For example, a comment recommends that a stronger labeling statement be used on nonprescription drug products with ACNUs that have the potential for more adverse events.

(Response 65) FDA believes that consistency in the content of the required labeling is important to alert consumers and decrease confusion (see discussion above). However, we recognize that in certain situations, revisions to the required labeling may be appropriate for a drug product to convey specific information for a particular nonprescription drug product with an ACNU. Therefore, we are revising the requirements at 21 CFR 201.130(a)(1)(ii) and (b)(1)(ii) in this final rule to permit FDA to approve an NDA applicant's revisions to the required labeling when the revisions are appropriate for a specific drug product and the applicant supports the revisions with adequate data or other information that demonstrate sufficient consumer understanding of the revised statement. For example, the NDA applicant would submit adequate data from robust label comprehension studies that demonstrate consumers understand the revised labeling statement(s). Additionally, while we reviewed the qualitative research study that was submitted, the study was small and did not provide usable data with which to assess or revise the required labeling.

(Comment 66) One comment supports the proposed exemption from adequate directions for use for nonprescription drug products with an ACNU provided the following information is adequately described and provided to consumers at the point of purchase: (1) name and description of the drug product, (2) dosage form, dosage, route of administration, and duration of drug therapy, (3) special directions and precautions for preparation, administration, and use by the consumer, (4) common severe side effects or adverse effects or interactions and therapeutic contraindications that may be encountered, (5) techniques for self-monitoring of drug therapy, (6) proper storage, and (7) action to be taken in the event of an erroneous dose (*e.g.,* a missed dose or a double dose).

(Response 66) Existing statutory and regulatory requirements ensure that the information discussed in the comment would be included on the labeling of the nonprescription drug product with an ACNU, if relevant for the drug product. Consistent with section 502(c) of the FD&C Act, approved labeling for a nonprescription drug product with an ACNU would need to be available to consumers under the customary conditions of purchase and use of the product. Nonprescription drug products, including nonprescription drug products with ACNUs, must comply with applicable labeling requirements under part 201, including the format and content requirements for the DFL (see 21 CFR 201.66).

(Comment 67) A few comments discuss the need for exemption from the labeling requirements in part 201. One comment recommends that FDA amend proposed 21 CFR 201.130(a)(3) by adding the following sentence at the end of the paragraph: ''This requirement would not apply when an exemption has been granted or approved.'' One comment states that because nonprescription drug products may be sold in convenience or small pack sizes, there may be limited space for the required statement provided at

proposed 21 CFR 201.130(a)(1). The comment recommends that the rule include an exemption for nonprescription drug products with an ACNU when the container is too small to bear all of the required information, similar to the exemption in 21 CFR 201.10(h)(2)(i) through (iv).

(Response 67) We disagree with revising the rule to provide a waiver or an exemption for nonprescription drug products with an ACNU from the applicable labeling requirements in part 201. The required labeling in 21 CFR 201.130(a)(1) and (b)(1) of this final rule are important for consumers to appropriately self-select or appropriately use the nonprescription drug product with an ACNU because it informs consumers where the additional condition would be found and explains the additional condition that the consumer must fulfill. The statement about the ACNU also alerts consumers that the drug product is not suitable for all individuals and should only be used after fulfilling the ACNU. Further, a nonprescription drug product with an ACNU must comply with all applicable labeling requirements for nonprescription drug products, including the DFL requirements under 21 CFR 201.66.

M. Comment on Misbranding and FDA Response

We proposed an exemption for a nonprescription drug product with an ACNU from the requirement for adequate directions for use in section 502(f)(1) of the FD&C Act, if the product contains the labeling specified in proposed 21 CFR 201.130(a) and the ACNU is implemented by the applicant as approved by FDA in the application (see proposed 21 CFR 201.67(e)). In the following paragraphs, we discuss a comment on this proposal. After consideration of the public comment received, as discussed below, we are finalizing our proposal with modifications for consistency with revisions made elsewhere to the rule. We are revising 21 CFR 201.67(e)(1) from ''It is made available without the labeling'' to ''It does not comply with the labeling requirements'' for clarity. We are revising the citation in 21 CFR 201.67(e)(1) from ''§ 201.130(a)'' to ''paragraphs (c) and (d) of this section and § 201.130(a) through (c)'' for clarity and completeness. We are also making revisions to 21 CFR 201.67(e)(2) for clarity and consistency with revisions to 21 CFR 201.130(d) and 314.81(b)(3)(v) in this final rule by revising ''as approved by FDA in the application'' to state that the ACNU is not implemented by the applicant in accordance with the following, as approved by FDA in the application: (1) the key elements of the ACNU under 21 CFR 314.56(c)(1)(iv) for NDAs or 21 CFR 314.56(c)(2)(ii) for ANDAs or (2) the operationalization of the ACNU under 21 CFR 314.56(c)(1)(vii) for NDAs or 21 CFR 314.56(c)(2)(iii) for ANDAs.

(Comment 68) We received one comment seeking clarity on what it means when an ACNU is not implemented by the applicant as approved by FDA in the application. The comment questions whether implementation of the ACNU means to make the ACNU available, or whether implementation includes the steps the pharmacy/seller must take to ensure the ACNU was fulfilled.

(Response 68) We understand the commenter's need for clarity and are revising the misbranding provision accordingly. Specifically, we are revising 21 CFR 201.67(e)(2) in this final rule, consistent with the revisions in 21 CFR 201.130(d) in this final rule, to state that a nonprescription drug product with an ACNU is misbranded when the ACNU is not implemented by the applicant in accordance with: (1) the key elements of the ACNU under 21 CFR 314.56(c)(1)(iv) or (c)(2)(ii) or (2) the operationalization of the ACNU under in 21 CFR 314.56(c)(1)(vii) or (c)(2)(iii), as approved by FDA in the application.

N. Miscellaneous Comments and FDA Responses

We received other relevant comments on the proposed rule, but not specific to a requirement. In the following paragraphs, we discuss and respond to these comments. After considering these comments, we are not making any changes as a result of these comments.

(Comment 69) We received several comments requesting that FDA advise applicants on where the specific NDA and ANDA requirements for a nonprescription drug product with an ACNU should be included in the existing structure of an application (*e.g.,* in which module(s) should information be placed).

(Response 69) Consistent with applications for nonprescription drug products, an application for a nonprescription drug product with an ACNU must be submitted electronically (see section 745A(a) of the FD&C Act) in electronic common technical document (eCTD) format. eCTD is the standard format for submitting applications, amendments, supplements, and certain reports to FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research. Generally, the eCTD format consists of five modules. FDA issues guidances related to eCTD, which are applicable to nonprescription drug products with ACNUs (Ref. 9). We may provide guidance specific for applications for nonprescription drug products with ACNUs in the future as appropriate. Additionally, an applicant can request to meet with FDA staff to discuss questions that arise during the development of a nonprescription drug product with an ACNU, including in which module(s) specific information should be placed.

(Comment 70) We received a comment that requests FDA require applicants to protect any consumer data that may have been collected via an ACNU.

(Response 70) It is unclear what kinds of data are the focus of the comment. Although FDA does not provide guidance on how to comply with any legal obligations stemming from a source outside of the statutes and regulations that FDA administers, FDA generally expects that applicants will comply with applicable statutory and regulatory requirements related to protecting consumer information, including health information and consumer data (*e.g.,* purchasing history). Additionally, FDA has resources on a web page entitled ''Digital Health Policy Navigator,'' which includes information on privacy and is available on FDA's website at *https://www.fda.gov/,* which based on our understanding of the comment, addresses the commenter's concerns.

(Comment 71) We received a few comments stating that the proposed rule lacks clarity on the criteria that FDA will use to determine when a nonprescription drug product with an ACNU is a combination product because of the inclusion of a component that is deemed to be a medical device. The comments request that FDA issue a companion guidance to explain the criteria that will be used to determine whether a nonprescription drug product with an ACNU is a combination product. The comments also request that FDA confirm that when a nonprescription drug product with an ACNU is considered a combination product, CDER will continue to be the lead review center if the primary mode of action is attributed to the drug component, which aligns with current practices.

(Response 71) In some cases, a nonprescription drug product with an ACNU may be comprised of a drug constituent part and a device constituent part (see § 3.2(e)) and, therefore, be subject to regulatory requirements applicable to combination

products (see, *e.g.,* part 4). FDA would continue to follow existing regulatory requirements to determine whether a nonprescription drug product with an ACNU is a drug or a combination product. Under 21 CFR 3.4, the center that leads the premarket review and regulation of a combination product is determined by the product's primary mode of action (*i.e.,* the single mode of action of a combination product that provides the most important therapeutic action). Because FDA expects that nonprescription drug products with an ACNU that are combination products generally will have a drug primary mode of action, FDA expects CDER would be the lead center for the review. We encourage applicants to utilize FDA resources on combination products (Ref. 10). We also encourage applicants to engage with FDA during the drug development process for a nonprescription drug product with an ACNU, including regarding questions about how their product is classified.

(Comment 72) FDA received a comment that the proposed rule does not discuss whether an NDA for a nonprescription drug product with an ACNU would be eligible for 3-year, new clinical investigation exclusivity, or whether an ANDA for a nonprescription drug product with an ACNU and containing a paragraph IV certification could give rise to 180-day exclusivity even if the RLD was originally approved as a prescription drug product. The comment requests that FDA address these issues in the final rule.

(Response 72) FDA declines to address these exclusivity comments in the final rule, as this rulemaking does not propose any changes or considerations regarding exclusivity. An NDA or ANDA holder, including an NDA or ANDA holder for a nonprescription drug product with an ACNU, is eligible for exclusivity if applicable statutory requirements are met (see, *e.g.,* section 505(c)(3)(E)(iii), (j)(5)(B)(iv), and (j)(5)(F)(iii) of the FD&C Act) (see also 21 CFR 314.108). As explained in our response to Comment 36, FDA proposed significant flexibility in the types of ACNUs that may be developed, as well as how those ACNUs may be operationalized. Given this flexibility, and that eligibility for statutory exclusivity (such as, 3-year new clinical investigation exclusivity for an NDA) depends on the facts of each application, FDA is unable to predict potential eligibility for statutory exclusivity for nonprescription drug products with an ACNU across the board.

(Comment 73) We received a comment stating that the proposed rule does not mention whether FDA or the Federal Trade Commission (FTC) will oversee the advertisement of nonprescription drug products with ACNUs.

(Response 73) Consistent with the memorandum of understanding between FTC and FDA, FTC has primary responsibility with respect to the regulation of the truth or falsity of all advertising of nonprescription drug products, which would include nonprescription drug products with ACNUs (Ref. 11). FDA has primary responsibility with respect to regulating the labeling of nonprescription drug products.

(Comment 74) We received a comment that strongly encourages FDA to implement educational campaigns geared toward consumers, retailers, and healthcare professionals to explain the differences between prescription drug products, nonprescription drug products, and nonprescription drug products with ACNUs. The comment further states that members of the Nonprescription Drugs Advisory Committee will also need training about how they should evaluate applications that propose an ACNU.

(Response 74) We will provide robust communication to inform the public about the final rule. We will have specific communications tailored to interested parties, including consumers, retailer, and healthcare providers. We will also have specific communication and educational information for members of FDA advisory committees, should an advisory committee be necessary for a specific application for a nonprescription drug product with an ACNU. FDA will especially focus communication and education for consumers both about the final rule and in the future should FDA approve a nonprescription drug product with an ACNU.

(Comment 75) We received a comment requesting that FDA create a public registry of all approved nonprescription drug products with ACNUs, including all data and information about the ACNU and the purpose of the ACNU.

(Response 75) FDA agrees with including approved nonprescription drug products with an ACNU, including relevant information about the approval, in a database. FDA has an existing public database of approved drug products entitled ''Drugs@FDA'' available at *https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm.* FDA issues approval letters that are publicly available for all drug product approvals. Consistent with FDA approval for all drug products, upon approval of a nonprescription drug product with an ACNU, FDA will issue an approval letter for a nonprescription drug product with an ACNU that includes, among other things, a statement that the drug product requires an ACNU and the key elements of the ACNU. Information about the approved nonprescription drug product with an ACNU will also be available in FDA's database of approved drug products at *https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm.* Additionally, FDA communicates certain nonprescription drug product approvals on our website (see Ref. 12), and we intend to consider a similar process to communicate approvals of nonprescription drug products with an ACNU.

(Comment 76) We received a comment requesting that FDA either clarify how it will enforce the requirement that a nonprescription drug product with an ACNU not be made available to consumers unless the ACNU is fulfilled, or require the applicant to submit procedures to ensure that requirement is met.

(Response 76) The burden is on the applicant to implement the ACNU as approved by FDA in the application and to ensure that the drug product is not made available to consumers unless the ACNU is fulfilled. A nonprescription drug product with an ACNU that is made available to a consumer without the ACNU being fulfilled by the consumer would be misbranded (21 CFR 201.67(e) in this final rule). 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 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 with an ACNU would be an unapproved new drug product if it is made available to consumers without an 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 into interstate commerce an unapproved new drug (87 FR 38313 at 38325). FDA may pursue enforcement action against applicants who violate the FD&C Act.

(Comment 77) We received a few comments requesting further clarification of certain topics (*e.g.,* submission requirements and labeling) through guidance documents. We also received a comment requesting that FDA provide clear and timely input on

the development program for a nonprescription drug product with an ACNU throughout the development process.

(Response 77) We encourage applicants to read existing applicable FDA guidance documents by searching for relevant topics on our website available at *https://www.fda.gov/regulatory-information/search-fda-guidance-documents.* For example, search ''nonprescription'' to find relevant guidances on labeling specific for nonprescription drug products. Additionally, FDA may consider issuing guidance in the future to address general considerations that may arise and are applicable to all applicants developing nonprescription drug products with an ACNU. We encourage applicants to meet with FDA to discuss their drug development plans and seek advice.

(Comment 78) We received a comment encouraging FDA to explain how it intends to address any application proposing an ACNU for a nonprescription drug product that was submitted for approval before the proposed rule is finalized.

(Response 78) Once the rule is in effect, FDA may approve applications for nonprescription drug products that meet the relevant standard, regardless of whether such applications were submitted before or after the rule was in effect.

VI. Effective Date

This rule is effective January 27, 2025.

VII. Economic Analysis of Impacts

A. Introduction

We have examined the impacts of the final rule under Executive Order 12866, Executive Order 13563, Executive Order 14094, the Regulatory Flexibility Act (5 U.S.C. 601–612), the Congressional Review Act/Small Business Regulatory Enforcement Fairness Act (5 U.S.C. 801, Pub. L. 104–121), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4).

Executive Orders 12866, 13563, and 14094 direct us to assess all benefits, costs, and transfers 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). Rules are ''significant'' under Executive Order 12866, section 3(f)(1) (as amended by Executive Order 14094) if they ''have an annual effect on the economy of $200 million or more (adjusted every 3 years by the Administrator of [the Office of Information and Regulatory Affairs (OIRA)] for changes in gross domestic product); or adversely affect in a material way the economy, a sector of the economy, productivity, competition, jobs, the environment, public health or safety, or State, local, territorial, or tribal governments or communities.'' OIRA has determined that this final rule is not a significant regulatory action under Executive Order 12866, section 3(f)(1).

Because this rule is not likely to result in an annual effect on the economy of $100 million or more or meets other criteria specified in the Congressional Review Act/Small Business Regulatory Enforcement Fairness Act, OIRA has determined that this rule does not fall within the scope of 5 U.S.C. 804(2).

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 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 0.12 percent of the gross receipts of very small applicants. Therefore, we certify that the final rule will not have a significant economic impact on a substantial number of small entities.

The Unfunded Mandates Reform Act of 1995 (section 202(a)) requires us to prepare a written statement, which includes estimates of anticipated impacts, before issuing ''any rule that includes any Federal mandate that may result in the expenditure by State, local, and Tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year.'' The current threshold after adjustment for inflation is $183 million, using the most current (2023) Implicit Price Deflator for the Gross Domestic Product. This final rule will not result in an expenditure in any year that meets or exceeds this amount.

B. Summary of Benefits, Costs, and Transfers

The final rule will establish requirements for a nonprescription drug product with an ACNU. Compared to traditional nonprescription drug products, which consumers must be able to self-select and use based on labeling, alone, an approved ACNU, in addition to the labeling, will ensure the appropriate self-selection, the appropriate use, or both of a nonprescription drug product without the supervision of a practitioner licensed by law to administer such drug. We expect this rule will expand consumer access to certain drug products in a nonprescription setting and increase options for applicants to develop and market safe and effective nonprescription drug products.

Table 1 shows our quantified benefits. We estimate a reduction in access costs to consumers who could transfer from a prescription drug product to a nonprescription drug product with an ACNU. Our primary estimate for this item is $33.62 per consumer per purchase with a range of $0 to $67.23. We also quantify the value of the potential reduction in the number of repetitive meetings with applicants that will occur during the approval process. For example, potential applicants have requested additional meetings with us for each development program to discuss this topic; these types of individual meetings are time-consuming and use Agency resources. Multiple potential applicants have been asking the same types of questions, creating repetitiveness and inefficiencies. Because the rule addresses these and other questions, we anticipate that the rule will reduce or eliminate this burden for potential applicants and us. Our primary estimate is $68,773.11 per applicant with a range of $56,332.65 to $81,763.56. 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, and purchases that might occur; and consumer preferences to switch products. However, we present estimates in the uncertainty section of this analysis.

Although an applicant will incur the costs to develop and apply for a nonprescription drug product with an ACNU, for this analysis, we assume that applicants submit applications only when they believe that the profits from the approval will exceed the costs of the application. We lack information to monetize these potential profits and costs over a 10-year horizon.

Monetized costs include a one-time cost of reading and understanding the rule for those potentially interested in pursuing this path for their drug products. We do not monetize these estimates for more than one interested party because of the high uncertainty about the number of interested parties over this time horizon. The primary estimate equals $1,156.74 with a range of $533.88 to $1,779.60.

Government-sponsored and commercial insurance payers may experience cost savings because the availability of nonprescription drug products with an ACNU may decrease insurance claims and, potentially, future medical costs. For example, access to drug products under this new paradigm will allow consumers to treat medical conditions using nonprescription drug products with ACNUs without the supervision of a practitioner licensed by law to administer such drug. We do not estimate such cost savings due to lack of data.

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

[Millions 2023 dollars]

Category	Primary estimate	Low estimate	High estimate	Units			Notes
				Year dollars	Discount rate (%)	Period covered	
Benefits:							
Annualized Monetized ($millions/year)							
Annualized Quantified				2023			Quantified reduction in access costs per consumer purchase range from $0.0 to $67.23, and a primary estimate of $33.62.
				2023			Quantified reduction in meetings between FDA and applicants range from $56,332.65 to $81,763.56 per applicant, and a primary estimate of $68,773.11.
Qualitative							
Costs:							
Annualized	$0.0	$0.0	$0.0	2023	7	10 years	The reading and understanding one-time costs primary estimate is $1,156.74 and ranges from $533.88 to $1,779.60 per interested party.
Monetized ($millions/year)	$0.0	$0.0	$0.0	2023	3	10 years	
Annualized							
Quantified							
Qualitative	Interested firms will incur costs to develop and submit applications						
Transfers:							
Federal					7		
Annualized Monetized ($millions/year)					3		
From/To	From:			To:			
Other					7		
Annualized Monetized ($millions/year)					3		
From/To	From:			To:			Potential cost savings to government and commercial insurers if coverage 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 range from 0.04 percent to 0.12 percent of gross receipts.

Wages: No estimated effect.

Growth: No estimated effect.

We have developed a Final Economic Analysis of Impacts that assesses the impacts of the final rule. The full analysis of economic impacts is available in the docket for this final rule (Ref. 13) and at *https://www.fda.gov/about-fda/economics-staff/regulatory-impact-analyses-ria.*

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 final rule contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3521). The title, description, and respondent description of the information collection provisions are shown in the following paragraphs with an estimate of the annual reporting and recordkeeping burden. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

Title: Premarket applications, postmarketing reports and

recordkeeping, and labeling for Nonprescription Drug Products With an Additional Condition for Nonprescription Use—OMB Control Numbers 0910–0001 and 0910–0340—Revision.

Description: The final 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 product with an ACNU; (2) for ACNU failure 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.

In the proposed rule, we sought comments on this analysis. We did not receive any comments that were specific to our numeric hour burden estimates. However, we received numerous comments on the provisions of the proposed rule having to do with proposed requirements for applications, postmarketing reports, and labeling. This final rule contains comment summaries and responses for these comments in section V. E and F, and I through M. Additionally, we received comments that the preliminary regulatory impact analysis does not adequately account for the costs of quality assurance systems or implementing the reporting requirements. We understand concerns about the potential costs of establishing and maintaining quality assurance systems. However, due to the uncertainty about the nature of ACNU failures that could occur, the likelihood, the number, and the cost, any estimate would be characterized by a substantial degree of uncertainty.

FDA estimates the burden of existing information collection 0910–0001 will be increased by the information collections in this rule this information collection as follows:

NDA and ANDA Submissions

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

Activity; 21 CFR part 314	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 an ACNU failure; § 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.

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. 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 drug products 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). The 320 hours would include scientific studies and experimentation such as developing new technology to aid consumers in self-selection, advancing statistical methods for analyzing complex data, developing innovative clinical trial designs, or research on new drug delivery systems for both NDA and ANDA applications.

Reports of ACNU Failure

We estimate six respondents will submit 25 reports each to FDA for an individual ACNU failure 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.

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

Activity; 21 CFR part 314	Number of respondents	Number of responses per respondent	Total annual responses	Average burden per response (hours)	Total hours
Requirements for reports of ACNU failure for a non-prescription drug product with an ACNU (§ 314.81(b)(3)(v)(D))	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.

FDA estimates the burden of existing information collection 0910–0340 will be increased by the information collections in this rule, as follows:

Labeling for Nonprescription Drugs with an ACNU

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

Activity; 21 CFR part 201, subpart C	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) and (2)	6	1	6	15	90
ACNU Statement; (§ 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.

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, including 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), and 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 required by § 201.130(a)(1) and (2). These products may also have additional labeling beyond the DFL requirements (§ 201.67(c)(2)).

Estimating six respondents will expend 1 hour annually to comply with PDP and DFL labeling requirements under § 201.67(c)(1), and assuming each disclosure will require 15 hours, we calculate a total of 90 hours annually. Additionally, we estimate six respondents will each submit one application for a nonprescription drug product 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.

The information collection provisions in this final rule have been submitted to OMB for review as required by section 3507(d) of the Paperwork Reduction Act of 1995.

Before the effective date of this final rule, FDA will publish a notice in the **Federal Register** announcing OMB's decision to approve, modify, or disapprove the information collection provisions in this final rule. An Agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

X. Federalism

We have analyzed this final rule in accordance with the principles set forth in Executive Order 13132. We have determined that the 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 rule in accordance with the principles set forth in Executive Order 13175. We have determined that the rule does not contain policies that have substantial direct effects 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. Accordingly, we conclude that the rule does not contain policies that have Tribal implications as defined in the Executive order and, consequently, a Tribal summary impact statement is not required.

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 are also available electronically at *https://www.regulations.gov/*. Although FDA verified the website addresses in this document, please note that websites are subject to change over time.

1. FDA, Guidance for Industry, ''Label Comprehension Studies for Nonprescription Drug Products,'' August 2010 (available at *https://www.fda.gov/media/75626/download*).

2. FDA, Guidance for Industry, ''Self-Selection Studies for Nonprescription Drug Products,'' April 2013 (available at *https://www.fda.gov/media/81141/download*).

3. FDA, Guidance for Industry, ''Application of Human Factors Engineering Principles for Combination Products: Questions and Answers,'' September 2023 (available at *https://www.fda.gov/media/171855/download*).

4. FDA, Guidance for Industry and FDA Staff, ''Policy for Device Software Functions and Mobile Medical Applications,'' September 2013 (updated September 2019 and September 2022) (available at *https://www.fda.gov/media/80958/download*).

5. FDA, Medwatch: The FDA Safety Information and Adverse Event Reporting Program, (available at *https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program*). Accessed November 27, 2023.

6. FDA, Consumer Complaint Coordinators, web page, (available at *https://www.fda.gov/safety/report-problem-fda/consumer-complaint-coordinators*). Accessed November 27, 2023.

7. National Patient Safety Agency, ''Information Design for Patient Safety: A Guide to the Graphic Design of Medication Packaging,'' 2nd edition, 2007 (available at *https://webarchive.nationalarchives.gov.uk/ukgwa/20080727044055mp_/http://www.npsa.nhs.uk/EasySiteWeb/GatewayLink.aspx?alId=5599*); National Patient Safety Agency, ''Design for Patient Safety: A Guide to Labelling and Packaging of Injectable Medicines,'' 1st edition, 2008 (available at *https://www.intmedsafe.net/wp-content/uploads/2014/01/0592_InjectablesBookV9_Web1.pdf*).

8. United States Pharmacopeia, Recommendations to the Safe Medication Use Expert Committee by the Health Literacy and Prescription Container Labeling Advisory Panel, May and November 2009, posted April 2010 (available at *https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/recommendContainerLabeling.pdf*).

9. FDA, eCTD Resources, web page (available at *https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/ectd-resources*). Accessed November 27, 2023.

10. FDA, Combination Products, web page (available at *https://www.fda.gov/combination-products*). November 27, 2023.

11. Memorandum of Understanding Between the Federal Trade Commission and the Food and Drug Administration Concerning the Exchange of Information (FDA–225–71–8003), April 1971 (available at *https://www.fda.gov/about-fda/domestic-mous/mou-225-71-8003*). Accessed November 27, 2023.

12. FDA, Prescription to Over-the-Counter (OTC) Switch List, web page (available at *https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/prescription-over-counter-otc-switch-list*). Accessed November 27, 2023.

13. FDA, Final Regulatory Impact Analysis; Final Regulatory Flexibility Analysis; Unfunded Mandates Reform Act Analysis, Nonprescription Drug Product With an Additional Condition for Nonprescription Use; Final Rule (available at *https://www.fda.gov/about-fda/economics-staff/regulatory-impact-analyses-ria*).

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, 21 CFR parts 201 and 314 are 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 practitioner licensed by law to administer such drug, 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) and (b).

(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 the required statement about the ACNU.* The statement about the ACNU specified in § 201.130(b)(1) must meet all format requirements as follows:

(1) The statement about the ACNU 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 about the ACNU 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 about the ACNU 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 about the ACNU does not need to be included on each blister unit of a blister card. However, the statement about the ACNU must remain intact and be readable on the blister card when the drug product is removed from each blister unit.

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

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

(4) The statement about the ACNU 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 does not comply with the labeling requirements specified in paragraphs (c) and (d) of this section and § 201.130(a) through (c); or

(2) The ACNU is not implemented by the applicant in accordance with the following, as approved by FDA in the application:

(i) The key elements of the ACNU under § 314.56(c)(1)(iv) of this chapter for NDAs or § 314.56(c)(2)(ii) of this chapter for ANDAs; or

(ii) The operationalization of the ACNU under § 314.56(c)(1)(vii) of this chapter for NDAs or § 314.56(c)(2)(iii) of this chapter for ANDAs.

■ 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 (ACNU).

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)(1) is exempt from section 502(f)(1) only if all the following conditions are met:

(a) The label of the drug must include instructions for the ACNU as follows:

(1) Content of instructions for the ACNU must either be:

(i) ACNU Instructions, which read as follows: ''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''; or

(ii) Alternative ACNU Instructions: FDA may approve an NDA applicant's revisions to the ACNU Instructions when the revisions are appropriate for a specific drug product and the applicant supports the revisions with adequate data or other information that

demonstrate sufficient consumer understanding of the revised statement.

(2) The locations of instructions for the ACNU are as follows:

(i) If the purpose of the ACNU is for self-selection, the instructions for the ACNU must appear under the ''Use'' or ''Uses'' heading required in § 201.66(c)(4) as the first statement, followed by the other information required in § 201.66(c)(4);

(ii) If the purpose of the ACNU is for actual use, the instructions for the ACNU must appear under the ''Directions'' heading required in § 201.66(c)(6) as the first direction, followed by the other information required in § 201.66(c)(6); or

(iii) If the purpose of the ACNU is for both self-selection and actual use, the instructions for the ACNU must appear under the ''Use'' or ''Uses'' heading as the first statement, followed by the other information required in § 201.66(c)(4) and may also appear under the ''Directions'' heading as the first direction, followed by the other information required in § 201.66(c)(6).

(b) The label of the drug must include a statement about the ACNU as follows:

(1) The content of the statement about the ACNU must either be:

(i) The ACNU Statement, which reads as follows: ''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''; or

(ii) An Alternative ACNU Statement: FDA may approve an NDA applicant's revisions to the ACNU Statement when the revisions are appropriate for a specific drug product and the applicant supports the revisions with adequate data or other information that demonstrate sufficient consumer understanding of the revised statement.

(2) The statement about the ACNU must be in the form and manner required by § 201.67(c).

(c) The labeling of the drug must comply 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.

(d) The ACNU must be implemented by the applicant in accordance with the following, as approved by FDA in the application:

(1) The key elements of the ACNU under § 314.56(c)(1)(iv) of this chapter for NDAs or § 314.56(c)(2)(ii) of this chapter for ANDAs; and

(2) The operationalization of the ACNU under § 314.56(c)(1)(vii) of this chapter for NDAs or § 314.56(c)(2)(iii) of this chapter for ANDAs.

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 practitioner licensed by law to administer such drug 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.* Notwithstanding § 310.200(b) of this chapter, 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 whether the purpose of the ACNU is to 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 practitioner licensed by law to administer such drug;

(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(s) 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 include:

(i) A statement regarding whether the purpose of the ACNU is to 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 practitioner licensed by law to administer such drug, which must be the same as the purpose of the ACNU for its reference listed drug (RLD);

(ii) Information demonstrating that the key elements of the ACNU are the same as the key elements of the ACNU for its RLD; and

(iii) A description of the specific way(s) the ACNU is 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 drug 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 such 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 an additional condition for nonprescription use (ACNU) failure for a nonprescription drug product with an ACNU*—(A) *ACNU failure.* An ACNU failure occurs upon either of the following events:

(*1*) A failure associated with the implementation of a key element of an ACNU under § 314.56(c)(1)(iv) or (c)(2)(ii); or

(*2*) A failure associated with the operationalization of an ACNU under § 314.56(c)(1)(vii) or (c)(2)(iii).

(B) *Review of ACNU failure.* The applicant must develop written procedures for the surveillance, receipt, evaluation, and reporting of ACNU failures to FDA.

(C) *Report of ACNU failure.* If an applicant receives or otherwise obtains information regarding an adverse drug experience associated with an ACNU failure before the submission of a report of an ACNU failure, an applicant must submit a report in the form of an individual case safety report (ICSR) that describes both the adverse drug experience and the associated ACNU failure. The ICSR must contain the information required in § 314.80(f) and paragraph (b)(3)(v)(A) of this section. If a previously submitted report of ACNU failure reports only an ACNU failure or if a previously submitted ICSR reports only an adverse drug experience, and the applicant subsequently receives or otherwise obtains information regarding an associated adverse drug experience or associated ACNU failure, the applicant must submit a follow up report to the previously submitted report with the new information. The follow-up report must include the information required in § 314.80(f) or paragraph (b)(3)(v)(A) of this section, as applicable.

(D) *Content of Report of ACNU failure.* The report of an ACNU failure must include the following:

(*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 ACNU failure.

(*2*) *Additional information if available to the applicant.* 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 follow-up report(s), if applicable.

(*iv*) ACNU failure term(s).

(*v*) Date of ACNU failure (or best estimate).

(*vi*) Date the ACNU failure was reported to the applicant.

(*vii*) Location of the ACNU failure, including business name and contact information.

(*viii*) Concise narrative summary of the ACNU failure including 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.

(*ix*) Description of the remedial action initiated or completed to address the ACNU failure, including the type of remedial action initiated or completed (for example, repair, replace, recall, inspection, modification, or adjustment).

(*x*) Description of the corrective action to prevent reoccurrence of an ACNU failure of the same nature.

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

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

(F) *Electronic format for submissions.* (*1*) The report of an ACNU failure 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)(F)(*1*) of this section in accordance with § 314.90 or § 314.99.

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

* * * * *

■ 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.

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■ 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: December 13, 2024.

Robert M. Califf,

Commissioner of Food and Drugs.

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