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November 21, 2022

Dockets Management Staff (HFA-305)  
U.S. Food and Drug Administration  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852

Re: Nonprescription Drug Product With an Additional Condition for Nonprescription Use;  
Proposed Rule; 87 *Fed. Reg.* 38313-38331. Docket No. FDA-2021-N-0862.

Dear Sir or Madam:

The Consumer Healthcare Products Association<sup>1</sup> (“CHPA”) submits these comments on the proposed rule issued by the U.S. Food and Drug Administration (“FDA” or the “Agency”) on “Nonprescription Drug Product With an Additional Condition for Nonprescription Use” (“proposed rule” or “ACNU”)<sup>2,3</sup> published on June 28, 2022. For more than 141 years, CHPA has served as a vital advocate for the consumer healthcare products industry. A member-based trade association, CHPA represents the leading manufacturers and marketers of over-the-counter (OTC) medical products. Our members provide millions of Americans with safe, effective, and affordable therapies to treat and prevent many common ailments and diseases.

CHPA appreciates that FDA is proposing a process to facilitate approval of OTC medicines when labeling alone is inadequate to convey proper selection and/or use of these drugs. If implemented, sponsors will be able to utilize an ACNU to market, through the prescription-to-nonprescription switch (Rx-to-OTC<sup>4</sup> switch<sup>5</sup>) process, drugs that cannot currently be sold directly to consumers without the supervision of a healthcare professional (HCP). The use of an ACNU should not become a default approval pathway for all future Rx-to-OTC switches. We also envision the ACNU process could be used for non-switch product applications (e.g., direct approval for an OTC product, new indications for an existing OTC product). There could be situations where the sponsor determines that users are not able to properly select or use the drug based on labeling alone or where the ACNU enhances safe use of the product by consumers.

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<sup>1</sup> The Consumer Healthcare Products Association (CHPA), founded in 1881, is the national trade association representing the leading manufacturers and marketers of consumer healthcare products, including over-the-counter (OTC) medicines, dietary supplements, and consumer medical devices. CHPA is committed to empowering self-care by ensuring that Americans have access to products they can count on to be reliable, affordable, and convenient, while also delivering new and better ways to get and stay healthy. Visit [www.chpa.org](http://www.chpa.org).

<sup>2</sup> FDA Proposed Rule; Nonprescription Drug Product With an Additional Condition for Nonprescription Use, 87 *Fed. Reg.* 38313-38331 (June 28, 2022). Accessed from <https://www.govinfo.gov/content/pkg/FR-2022-06-28/pdf/2022-13309.pdf> on June 28, 2022.

<sup>3</sup> ACNU = Additional Condition for Nonprescription Use

<sup>4</sup> Rx = Prescription

<sup>5</sup> See glossary provided as Appendix A which lists select terminology, abbreviations, and definitions used throughout this document. (See page 33).

We do agree with the Agency that the proposed rule should not cover the use of technology (e.g., an alarm that reminds consumers to take their medication) to support OTC drugs under the existing Drug Facts Label (DFL) format.

CHPA agrees with many of the principles outlined in the proposed rule. However, we offer feedback in the following areas.

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## 1. General Feedback

### A. Sponsors Should Have the Ability to Propose Use of an ACNU

The Agency has indicated that for a sponsor to implement an ACNU, it must first demonstrate *and* FDA determine that labeling alone is not sufficient to ensure appropriate self-selection or use of the nonprescription drug product without the supervision of a healthcare practitioner.<sup>6</sup> CHPA asserts that sponsors may wish to propose an ACNU as part of an original switch application rather than awaiting FDA's review determination that an ACNU may be required. As part of its development program, a sponsor may ascertain that an additional condition for appropriate selection or use is needed. An applicant could assess the need for an additional condition at any stage during the research and development (R&D) process and, as part of its development program, provide its rationale for proposing the additional condition to the Agency. The rationale to support the use of the ACNU may include study data, publicly available information from prior FDA meetings, or other valid sources of information.

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<sup>6</sup> See 87 Fed. Reg. at 38318.

A sponsor may engage with the Agency, at any stage during the development program, to determine whether an ACNU will be pursued and request guidance regarding use of an ACNU. There may be instances where the need for an ACNU is obvious based on available information which would negate the necessity to generate new support to justify inclusion of a proposed additional condition. When a sponsor has determined an ACNU should be included in the overall drug development program, there should be clear, timely, and transparent communication between the sponsor and FDA to advance the program. It will be important that sponsors have clear advice from FDA during their interactions related to drug development programs so a sponsor does not spend valuable time and resources unnecessarily due to misunderstanding, miscommunication, or lack of or insufficient communication from the Agency.

Furthermore, there could be multiple applicants conducting development programs for the same or similar indication but utilizing different ACNU approaches. FDA should confirm it will continue to apply the current review standard of evaluating each program based on its own merits under the independent NDAs.

B. Concept of "Fail First" Should Be Removed as a Requirement in the Final Regulations

FDA has proposed to define an additional condition for nonprescription use (ACNU) as "...one or more FDA-approved conditions that an applicant of a nonprescription drug product must implement to ensure consumers' appropriate self-selection or appropriate actual use, or both, of the nonprescription drug product without the supervision of a healthcare practitioner *if the applicant demonstrates and the FDA determines that labeling alone is insufficient to ensure appropriate self-selection or appropriate actual use, or both*" (emphasis added).<sup>7</sup> We have interpreted this to mean that FDA expects that a sponsor must first generate data from a failed study (*i.e.*, "fail first") and that the Agency then must agree with the sponsor's assessment that labeling alone is insufficient to support appropriate self-selection or use. If this interpretation were adopted, the "fail first" concept would put the onus on the sponsor to prove a negative, rather than developing a program that addresses the key self-selection or use questions that trigger a need for an ACNU in the first instance. CHPA members strongly believe sponsors should have the ability to evaluate the need for, or use of, an ACNU in their switch or development programs, without seeking prior agreement from the Agency. Sponsors should have the ability to engage in reasonable dialogue or interaction with the Agency, at any stage of the R&D program prior to the ACNU being evaluated for its necessity and/or effectiveness, when a sponsor determines an additional condition may be warranted based on the specific development program and the totality of the evidence supporting the ACNU.

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<sup>7</sup> See 87 Fed. Reg. at 38318.

C. Sponsors Should Be Permitted to Present Alternative Sources of Information to Support an ACNU

The proposed rule states that "...the applicant can submit **information** explaining the necessity of the ACNU...*when FDA has previously signaled that labeling alone is not sufficient to ensure appropriate self-selection or appropriate actual use, or both.*"<sup>8</sup> (emphasis added) The Agency should clarify how it will determine and signal to the sponsor that labeling alone is insufficient. Having clear communication from the Agency on this point will allow the sponsor to proceed with including the ACNU in their development program without risk. Furthermore, we disagree that the use of "other information" beyond self-selection and label comprehension studies should be restricted to these instances alone. Sponsors should be free to utilize a variety of relevant information sources to demonstrate the necessity of the ACNU at any time during their development program.

Examples of other information to support incorporation of an ACNU into an applicant's R&D program may include but are not limited to:

- information generated from previous FDA advisory committee deliberations;
- black box warning on the prescription drug product;
- situations which may lead to complex DFL information (e.g., dosing regimens);
- situations that require additional tests, lab values, or other ancillary values or measurements as part of selection or use;
- publicly available information for previous failed switch applications;
- real world data (RWD)/real world evidence (RWE);
- literature and medical practice guidelines; and
- agreement between FDA and the sponsor that the specific indication, target population, or disease condition warrants information beyond labeling only to support OTC approval.

The sponsors will provide the complete rationale for their decisions to use an ACNU to the Agency at the time the application is filed. However, a sponsor may elect to share information supporting the inclusion of an ACNU in its development program prior to the filing. As noted above, a sponsor may choose to seek input from FDA about the ACNU any time during its development program.

CHPA members note that proposed §314.56(c)(1)(v) states "Adequate data or other information that demonstrates the necessity of the ACNU to ensure appropriate self-selection or appropriate actual use, or both."<sup>9</sup> However, in the preamble, the Agency makes several references to failed "robust studies" as the criterion for determining when an ACNU is needed. For the reasons outlined above, we ask the FDA to update the preamble to reflect that other information, not just "failed

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<sup>8</sup> See 87 Fed. Reg. at 38320.

<sup>9</sup> See 87 Fed. Reg. at 38330.

robust studies," can be used to establish the need for an ACNU. Our proposed changes for one of the examples are noted below (in *blue italics* and strikethrough text). This language should be included for any other similar examples and references throughout the rule once finalized.

**Proposed § 314.56(c)(1)<sup>10</sup>**

"Drug X is proposed as a nonprescription drug product indicated for the treatment of symptom Y in adults who have a disease-specific risk score below the threshold for developing serious side effect E when taking Drug X. As part of the nonprescription development program, the applicant ~~conducted robust self-selection and label comprehension studies~~ *assessed the inclusion of an ACNU based on information from various sources, such as robust self-selection and label comprehension studies, or provided from other adequate data or information.* The results of the self-selection and label comprehension studies ~~demonstrated~~ *justified* that consumers cannot appropriately self-select Drug X with labeling alone. ~~FDA acknowledges these self-selection and label comprehension studies were well designed and conducted and concurs that consumers cannot self-select Drug X with labeling alone.~~ Results of the self-selection and label comprehension studies show that, although consumers recognize that they have symptom Y, they cannot appropriately calculate their disease-specific risk score for side effect E."

D. Allowing Simultaneous Marketing of Prescription and Nonprescription Drug Products Could Reduce Public Health Impact and Limit Expanded Product Access Due to Legal and Practical Reasons

**Legal Considerations**

The proposed regulation states that

An ACNU constitutes a meaningful difference between a nonprescription drug product and a prescription drug product, such that a prescription drug product and a nonprescription drug product with an ACNU may be simultaneously marketed even if there is not another meaningful difference between the two products that makes the nonprescription drug product safe and effective for use without the supervision of a healthcare practitioner licensed by law to administer the drug (e.g., a different active ingredient, indication, strength, route of administration, dosage form, or patient population).<sup>11</sup>

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<sup>10</sup> See 87 Fed. Reg. at 38319.

<sup>11</sup> See 87 Fed. Reg. at 38330.

If a prescription product and a nonprescription product have no meaningful differences, of course, they cannot be simultaneously marketed under Section 503(b)(3)(B) of the Food, Drug, and Cosmetic Act ("Act"). 21 USC 353(b)(3)(B). This is a question of great significance, as simultaneous marketing of a previously approved generic prescription product would undercut any incentive for companies to take on the enormous costs of a switch in the first instance, as discussed below. It may also lead companies with standard full OTC switch applications (which ordinarily would result in the generic prescription products being removed from the market) to withdraw those applications rather than proceeding with an ACNU in the event FDA determines that an ACNU would be required for approval (thus reducing rather than increasing access).

CHPA believes that there is insufficient legal basis for the Agency to conclude that the mere existence of an ACNU -- with no meaningful difference in indication, strength, route of administration, dosage form, or patient population -- constitutes a meaningful difference between the prescription drug product from which the switch application derived and the switched product.

The most instructive (and recent) relevant case on this question is FDA's decision to withdraw approval of ANDA<sup>12</sup> products that referenced the PEG-3350 product MiraLAX<sup>®</sup>. There, the Agency approved a full switch of PEG-3350 from prescription to nonprescription status. The holder of an ANDA for the prescription product refused to withdraw its ANDA, and FDA issued a Notice of Opportunity for Hearing (NOOH) on October 24, 2008, allowing the ANDA holder to request a hearing on whether the prescription and nonprescription drugs were the same, and therefore whether the prescription product was misbranded by virtue of Section 503(b)(3)(B) of the Act. 73 *Fed. Reg.* 63491.

In denying a hearing and determining in 2018 that the prescription and nonprescription products were the same drug, FDA acknowledged that there were some labeling differences between the prescription and nonprescription products, and even a difference in the duration of treatment. 73 *Fed. Reg.* 63491. Nevertheless, FDA found that the prescription and nonprescription products were the same, and withdrew approval for the prescription product. Several principles are apparent from the MiraLAX<sup>®</sup> decision:

*First*, 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." 83 *Fed. Reg.* 13996. The mere presence of an ACNU for a full switch does not implicate any of these factors. 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.

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<sup>12</sup> ANDA = Abbreviated New Drug Application

*Second*, FDA does not consider labeling changes "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)" to be meaningful differences. 83 *Fed. Reg.* 14007. These, of course, are just the kinds of labeling changes that would accompany a full switch with an ACNU, unless there were some additional meaningful difference(s) in "indication, strength, route of administration, dosage form, [or] patient population," between the products. 83 *Fed. Reg.* 13996.

*Third*, changes that inhere in the switch process itself -- such as requiring labeling for the nonprescription drug to comply with the rules generally applicable to nonprescription drugs -- do not qualify as meaningful differences. In MiraLAX®, for example, FDA noted that the difference in duration of treatment was merely based on "the OTC drug monograph system of having consistent labeling for OTC laxative groups." 83 *Fed. Reg.* 13997. Just so here: the mere existence of an ACNU and changes required to comply with products approved through this route is not itself a meaningful difference.

As recently as November 16, 2022, FDA reiterated these principles that simultaneous marketing is not permitted under the law where there is no difference in indication, strength, route of administration, dosage form, or patient population; or where labeling differences are due to different audiences. Nor do differences in a use setting constitute a meaningful difference. 87 *Fed. Reg.* 68711.

Under these principles, to say that *any* ACNU -- much less *every* ACNU -- renders a prescription product different from a nonprescription product with the same "indication, strength, route of administration, dosage form, [and] patient population," is a clear change in FDA's policy without sufficient rationale, or even acknowledgement that it is a change. 83 *Fed. Reg.* 13996. And it is unclear whether FDA could articulate a principle under which such a rule would not render Section 503(b)(3)(B) a nullity.

When finalized, the rule should 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, and that the existence of an ACNU by itself does not render two products different drugs.

### **Practical Considerations**

In addition to the legal considerations referenced above, CHPA objects to the simultaneous marketing concept for additional practical reasons. The proposed rule states that a separate application would be required for a nonprescription drug product with an ACNU (see §314.56(b)). If simultaneous marketing is no longer required based on the points CHPA has outlined above, we see no need to change the existing procedures under the Prescription Drug User Fee Amendments

(PDUFA).<sup>13</sup> Instead, the applicant would file a new drug application (NDA) or supplemental NDA according to the data package, and transmit the related PDUFA fee assessed during the fiscal year when the application is submitted to the Agency. Furthermore, if the Agency agrees with our position and eliminates the need for simultaneous marketing, §314.56(d) would be stricken from the regulations once finalized.

**1) The Purpose of the Proposed Rule is Nonprescription Access, Not Simultaneous Marketing**

FDA's own summary statements in the *Federal Register* notice point out that the proposed rule is intended to establish requirements for a nonprescription drug product with an additional condition for nonprescription use (ACNU) 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. FDA has also stated that the proposed rule is to allow applicants to develop safe and effective nonprescription drug products.

In the "Summary of Costs and Benefits" section of the Regulatory Impact Analysis<sup>14</sup>, the Agency has stated that an ACNU program would allow for a reduction in access costs. We agree, if simultaneous marketing is addressed as we recommend. Furthermore, the "Summary of Costs and Benefits" section states that government and private insurance payers may also experience cost saving because of the availability of OTC access. These cost savings will potentially be stifled or reduced if the Agency allows for simultaneous marketing.

CHPA strongly objects to allowing simultaneous marketing of the same drug as a prescription and nonprescription product where the only difference is the presence of an ACNU. As justification for simultaneous marketing, the proposed rule lists scenarios where persons may prefer not to use the ACNU to obtain their OTC medicine. If a consumer refuses to complete the ACNU directly or through an alternative mechanism, they would be able to speak to their HCP about other treatment options. Historically, and for different reasons, this situation would be similar to when a full switch has been approved and a consumer chooses not to purchase the OTC version of the drug. The consumer can speak with their HCP about other treatment options just as they could if the consumer declines or is unable to complete the ACNU required for product access. However, sponsors may provide alternate mechanisms for consumers to obtain the product beyond technology (e.g., mobile application or kiosk), such as an 800-number that also

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<sup>13</sup> See FDA Prescription Drug User Fee Amendments. Accessed from <https://www.fda.gov/industry/fda-user-fee-programs/prescription-drug-user-fee-amendments> on October 12, 2022.

<sup>14</sup> Nonprescription Drug Product with an Additional Condition for Nonprescription Use, Preliminary Regulatory Impact Analysis. Access from <https://www.fda.gov/media/159311/download> on October 13, 2022.



implements the ACNU. Having an alternative to obtain the OTC medicine would eliminate the need for the prescription version of the same drug.

During the development process, the sponsor may choose to initiate discussions with FDA about possible options for product access for persons who cannot or choose not to use the required ACNU process. Furthermore, there may be instances when a consumer is prevented from receiving an OTC+ACNU<sup>15</sup> drug which is in fact the intent of the ACNU, *i.e.*, to prevent consumers from gaining access to a drug that may not be appropriate for them. When a consumer is correctly blocked from accessing or using an OTC+ACNU product, there could be further explanation provided for what should be done next depending on the product involved. For example, a consumer may be advised to consult their HCP based on a specific lab value provided for the ACNU algorithm.

CHPA sees no reason for a sponsor to submit a separate full new drug application, as opposed to following existing processes, simply because an ACNU is part of the development program. In cases where an ACNU might be needed as part of an OTC switch application, the ingredients and formulation are not different, only the addition of the ACNU. It is unclear what studies, beyond consumer behavior studies typically included in switch applications, would be required to seek approval. The data that FDA reviews to decide whether to approve a new chemical entity as a drug is vastly different from reviewing an application for an Rx-to-OTC switch or supplement filed under an existing NDA. Typically, with Rx-to-OTC switch programs, a sponsor can cross-reference information contained in an FDA-approved NDA. Furthermore, it is rare that approval for a new OTC drug occurs without having first been marketed as a prescription drug. The application need only include the additional information relevant to the Rx-to-OTC switch itself and the ACNU as part of the complete data package. CHPA believes that in cases where there is a right of reference (RoR) letter, the Agency review would involve only new information as part of the switch application (not a full pharmacologic, CMC<sup>16</sup>, and safety review). FDA should not expend resources to review historical data.

## **2) Simultaneous Marketing Status Could Lead to Inaccurate Case Reporting Of Adverse Events for ACNU-Approved OTC Drug Products**

CHPA members are concerned that a potential identification of a true safety signal arising from an OTC+ACNU drug may not be accurately detected if there are both Rx and OTC versions of the drug product marketed, and the Agency or sponsor is unable to truly identify the source of purchase for the drug product in

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<sup>15</sup> Please see Appendix A: Glossary of Terms. As defined by CHPA members, an OTC+ACNU is a drug product with approval to be marketed without a prescription if an applicant implements an additional condition to enable appropriate self-selection, appropriate actual use, or both by consumers without the supervision of a healthcare professional.

<sup>16</sup> CMC = Chemistry, Manufacturing and Controls

question. This position assumes that when the rule is finalized, FDA continues to allow for simultaneous marketing status.

Furthermore, there is a risk that adverse event reporting accuracy could be compromised if simultaneous marketing is allowed. If the product assumed to be involved is not readily identifiable when a case report is filed by a consumer or HCP, CHPA is concerned that identification of a true safety signal arising from an OTC+ACNU drug could be delayed due to background noise if reports of the Rx and OTC versions are conflated. For example, there could be instances where both Rx and OTC versions of the same product are in the same household. Reporters are unlikely to have the exact product, SKU<sup>17</sup>, or lot/serial number, so an adverse event (AE) attributed to the OTC product could in fact be from the prescription version. Our proposed revisions to the regulations regarding adverse event reporting are suggested below and are intended to address these concerns (see pages 23-27)

### 3) Potential Consumer Confusion with Simultaneous Marketing Status Products

Prescription labeling is not identical in content and format to labeling for OTC products. Allowing simultaneous marketing of a prescription and OTC product that differ only with regard to the presence of the ACNU may lead to confusion with consumers since the labeling information will be different. Furthermore, there could be confusion resulting from direct-to-consumer (DTC) advertising for the prescription product competing with promotion for the nonprescription product.

### 4) Innovation to Provide Greater Consumer Access is Challenged by Simultaneous Marketing Status

The ACNU process will disincentivize OTC sponsors from pursuing a development program if simultaneous Rx and OTC marketing of the same drug is allowed, thus reducing the public health benefit desired by FDA and interested stakeholders, including industry. If simultaneous marketing is allowed, there are implications for the length of time and costs for R&D. These factors could stifle development thus minimizing public health benefit, expected cost savings, and the ability to address health disparities and inequities due to the anticipated additional costs for development and post-marketing activities (e.g., ACNU maintenance & updates). Incorporating an ACNU into a development program is expected to significantly increase the overall costs of R&D and time to market. If FDA expects sponsors to "fail first" (as written in the proposed rule), the expense and time factors of development programs would be even higher. In addition, when a new OTC drug is approved, there is typically a limited period of exclusivity for the sponsor when the product is first marketed. The incentive of exclusivity is an important consideration for a sponsor evaluating whether to proceed with a development program. Simultaneous

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<sup>17</sup> SKU = Stock Keeping Unit

marketing status could essentially eliminate the benefit of exclusivity, thereby deterring investment and innovation.

Sponsors who submit an NDA for review and approval do so after a considerable investment of time, staff, and financial resources. A sponsor of a first-in-class switch program without an ACNU may exceed 15-20 million dollars for necessary and required development costs alone depending on the drug involved (assuming there is a single round of review) and whether actual use studies are required to support approval, with costs increasing as complexity increases.<sup>18</sup> The addition of an ACNU will add millions of dollars to the overall R&D program due to expenses associated with technical development, documentation, testing, and lifecycle maintenance. Furthermore, sponsors currently invest heavily to support the successful introduction of a new switch into the OTC marketplace, educating consumers, driving product awareness, preparing the retail environment, supporting HCP education, etc. Based on industry experience, each additional development requirement adds to the costs and timeline, and reduces the likelihood for program support.

Finally, because the ACNU regulatory pathway is new, we anticipate there will be other expenses associated with an OTC+ACNU drug not currently incurred for OTC drugs approved for sale in the U.S. Without a means of recovering such an investment, sponsors cannot justify undertaking these significant investments.

E. Adverse Event Reporting Should Follow Established Processes for Drugs or Medical Devices

The current proposal establishes new procedures for reporting ACNU failures, even in the absence of an adverse event occurring. CHPA sees no reason to change from the existing adverse event reporting system currently used for drugs or medical devices because an ACNU is present. In the relevant section below, we have provided specific recommendations for improving the effectiveness of adverse event reporting requirements for an ACNU failure.

CHPA believes that one part of the adverse event reporting requirements set forth in the proposed rule is unnecessary, excessively burdensome, and beyond the Agency's scope of statutory authority. In particular, the rule requires reporting in, among other situations, instances in which "the consumer successfully fulfilled the ACNU but could not access ... the drug product in the nonprescription setting."<sup>19</sup> The rule contemplates that individual reports be filed for individual "failures" of this sort, even if numerous failures have the same cause. For example, if a kiosk with a questionnaire that is part of an ACNU fails to permit consumers to buy the product,

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<sup>18</sup> In addition to the drug development program, other potential costs associated with a first-in-class switch include the NDA filing fee, costs of preparing for an FDA advisory committee meeting if held, and expenses to educate consumers and retailers prior to and during initial launch activities.

<sup>19</sup> See 87 *Fed. Reg.* at 38322.

there may be numerous people who attempt to use the kiosk and report that they are unable to do so; rather than submitting a report indicating that the kiosk was inoperable for a period of time, the proposed rule contemplates a filing for each potential patient (or consumer).

Such a requirement is unnecessary because it requires duplicative information to be submitted, and in a format (*i.e.*, numerous identical reports) not likely to be helpful to the Agency. This all assumes, of course, that requiring reporting of ACNU failures that are not associated with adverse events is within the Agency's power under the statute. FDA's authority to require adverse event reporting for drugs derives from Section 505(k) of the Act, which permits FDA to require reporting if "such records and reports are necessary in order to enable the Secretary to determine, or facilitate a determination, whether there is or may be ground for invoking" the Secretary's NDA withdrawal authorities. 21 USC 355(k). FDA can invoke these findings based on determinations relating to safety and efficacy that may be informed by adverse event reports. 21 USC 355(e). But there is no basis under the statute to withdraw an NDA based on customers being unable to access the product in the first instance; perhaps for this reason, adverse event reporting is not (and could not be) required for other situations -- such as drug shortages and failure of REMS<sup>20</sup> systems to provide access to product -- in which patients are unable to get the drug products they seek.

If FDA does include a provision in the regulation requesting these kinds of reports, sponsors should be permitted to file a single summary report with information regarding a single type of failure affecting numerous potential customers that includes the number of patients/consumers affected. As part of the application, the sponsor may provide system requirements documentation that would describe the anticipated availability of the ACNU to the public and any expected exceptions to availability for maintenance, repairs, updates, or cybersecurity activities.

In instances where a patient/consumer who is not qualified to receive drug does so and no adverse event occurs, we understand a risk may have occurred. We therefore agree sponsor submission of spontaneous reports of such incidents may be indicated. In the absence of an adverse event, we recommend sponsor submission of these spontaneous reports occur periodically, such as every 12 months, which is consistent with other current reporting requirements.

#### F. Postmarketing Technology Considerations

The proposed rule is silent about the process a sponsor would use to notify FDA when software upgrades and technology updates are needed for the ACNU. CHPA members believe the FDA should allow for most technical changes and software upgrades to be submitted in the sponsor's annual report. If the change is expected to result in a substantive change in how a consumer interacts with the ACNU,

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<sup>20</sup> REMS = Risk Evaluation and Mitigation Strategies

impacts the intended use, significantly improves safety and effectiveness of the ACNU, impacts risk controls, or increases risk to consumers, then the sponsor would be expected to seek prior approval from the Agency before proceeding. In general, FDA should continue to follow the principles for 510(k) devices. FDA’s Center for Devices and Radiological Health (CDRH) has existing guidance “Deciding When to Submit a 510(k) for a Software Change to an Existing Device”<sup>21</sup> that addresses the types of software upgrades and technology updates likely to be associated with an ACNU. The principles outlined in the CDRH existing guidances should apply to sponsors that may need to make technical or software changes for proper function when the ACNU is a device.<sup>22,23</sup> The FDA Center for Drug Evaluation & Research’s (CDER’s) Office of Nonprescription Drugs (ONPD) should issue new guidance to advise sponsors how to inform FDA of the changes needed when the ACNU does not involve software.

G. Other Issues Necessary to Address for a Successful ACNU Implementation Beyond the Control of Sponsors

While evaluating the proposed regulations to provide meaningful feedback to the Agency, CHPA has identified other areas that the Agency will need to address when finalizing the proposed rule. FDA should consider solutions for the following concerns which have implications for OTC drug manufacturers but are beyond their sphere of control:

1. Educational campaigns geared towards consumers, retailers, and healthcare professionals to explain the differences between the Rx, OTC, and OTC+ACNU products since the ACNU paradigm would be new. It is unclear if FDA intends to implement outreach to the various stakeholders, but we strongly encourage the Agency to do so for several years following implementation. Members of the Nonprescription Drugs Advisory Committee (NDAC) will also need training about how they should evaluate applications that include an ACNU.
2. Determination for when an additional condition for use is a medical device. It is unclear the criteria that FDA will use to determine when inclusion of an ACNU will and will not be classified as a device or part of a combination product. The Agency should issue companion guidance to explain the criteria that will be used to make determinations as to whether a nonprescription drug with an ACNU creates a combination product. Furthermore, the OTC industry requests FDA confirm that when an OTC+ACNU drug product is considered a combination product, the FDA’s CDER will continue to be the

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<sup>21</sup> FDA Deciding When to Submit a 510(k) for a Software Change to an Existing Device - Final Guidance (October 2017). Accessed from <https://www.fda.gov/media/99785/download> on October 20, 2022.

<sup>22</sup> FDA Deciding When to Submit a 510(k) for a Change to an Existing Device - Final Guidance (October 2017). Accessed from <https://www.fda.gov/media/99812/download> on October 20, 2022.

<sup>23</sup> FDA Postmarket Management of Cybersecurity in Medical Devices - Final Guidance (December 2016). Accessed from <https://www.fda.gov/media/95862/download> on October 22, 2022.

lead review center if the primary mode of action is attributed to the drug component, which aligns with current practices.

## 2. CHPA's Recommended Changes to Proposed Regulations for ACNU<sup>24</sup>

### Proposed Regulations for Part 201 Label

**Regulation and Text:** §201.67(b)(1) -*Additional condition for nonprescription use* (ACNU) means one or more FDA-approved conditions that an applicant of a nonprescription drug product must implement to ensure consumers' appropriate self-selection or appropriate actual use, or both, of the nonprescription drug product without the supervision of a healthcare practitioner if the applicant demonstrates and FDA determines that labeling alone is insufficient to ensure appropriate self-selection or appropriate actual use, or both.

**CHPA Proposed Text:** *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~~ *enable* 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~~ *determines* and ~~FDA determines~~ that labeling alone is insufficient to ~~ensure~~ *enable* appropriate *and adequate* self-selection or ~~appropriate~~ actual use, or both, *for the intended use of the product.*

**Additional Comments:** CHPA disagrees with the use of the term "ensure" as reflected throughout the proposed rule. We are interpreting this term to mean that any risk to consumers from the new OTC+ACNU product has been eliminated. However, as with any product (drugs included), there will always be residual risk regardless of any mitigation steps taken. Instead, we propose using the term "enable" throughout any final rule, which conveys the essence of what the ACNU is intended to do (i.e., allow consumers to appropriately select or use the OTC+ACNU product).

Furthermore, CHPA believes that the types of studies and/or information a sponsor would need to support an ACNU could vary depending on the individual development program. The sponsor and FDA may align on the information necessary to evaluate the success of the ACNU based on the specific risk-profile and other relevant factors for the drug product in question. The content of labeling (e.g., the DFL) could be part of the ACNU but new studies should be not required as a routine matter.

**Regulation and Text:** §201.67(d)(1) - The statement must appear on the principal display panel (see §201.60) and the immediate container surface that the consumer is most likely to view when seeking information about the drug product. If the immediate container is a bottle, the statement must appear on the surface that the

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<sup>24</sup> Comments refer only to those regulations where CHPA has suggested revisions. Proposed regulations not listed are acceptable as written. Italicized text in blue (e.g., *sample text*) reflects revisions recommended by industry. Text with double strikethrough (e.g., ~~sample text~~) reflects text recommended for deletion.

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

**CHPA Proposed Text:** *The statement alerting the purchaser that an ACNU must be completed for appropriate selection, appropriate actual use, or both, of the OTC drug product* 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 at the point of purchase. *The statement will be placed on the principal display panel (PDP) in a manner that is readily visible to purchasers and users.* If the immediate container is a bottle, the statement must appear on the surface that the consumer is most likely to consider the front of the bottle. If the immediate container is a blister card (including a card that contains more than one blister unit), the statement must appear on the blister card surface that the consumer would most likely view when removing the drug product from the blister card. If the blister card contains more than one blister unit (e.g., perforated blister card where individual blister units can be separated from one another), the statement does not need to be included on each blister unit of a blister card. However, the statement must remain intact and be readable on the blister card when the drug product is removed from each blister unit.

**Additional Comments:** CHPA agrees with the Agency's premise that consumers will need additional information about a new OTC drug product using an ACNU and that it should be the first statement in the "Directions" section of the Drug Facts Label. However, the FDA's proposed language (see §201.130) should be an example or template to help guide sponsors during their development program, not required text used on all OTCs incorporating an ACNU. As reflected in the proposed rule, the statement is lengthy. The FDA should provide the rationale or goal of the statement, including findings from any consumer behavior studies conducted when generating the proposed statement, so sponsors can identify language that is adequate and appropriate for each individual product. The language for specific development programs should be agreed to by the FDA and sponsor during the review and approval process and be based on the information most relevant to consumers selecting or using the specific OTC+ACNU drug product.

Additionally, many OTC drugs are sold in convenience or small pack sizes which may have limited space for the ACNU statement listed in §201.130(a)(1). Furthermore, existing drug regulations under §201.10(h)(2)(i-iv) allow sponsors to provide limited information when the container is too small to bear all of the



required information. A similar exemption or allowance should be included in the ACNU rule when finalized.

**Regulation and Text:** §201.67(d)(2) - The statement must appear in boldface and black type.

**CHPA Proposed Text:** ~~The statement must appear in boldface and black type.~~

**Additional Comments:** In lieu of the criteria proposed in §201.67(d)(2-5), a universal, short statement, should be generated to enhance consumer awareness that an ACNU is required for OTC+ACNU drugs. This statement would apply to *any* OTC drug product using an ACNU with specific details provided under the directions section of the OTC Drug Facts Label. The statement should also help consumers understand whether the ACNU applies to appropriate self-selection, use, or both. Development of a validated symbol(s) to represent the requirement of an ACNU should also be considered.

For OTC drug products in general, trade dress is an important element in the consumer's retail shopping experience. Therefore, to require that the ACNU statement appear in boldface and black type against a yellow background, regardless of the product in question, is overly prescriptive. The sponsor should ensure that the statement has appropriate prominence and contrast on the PDP to be seen by consumers. The current format and content requirements for OTC drug product labeling allow the sponsor to choose a type that is all black or one color printed on a *white or other contrasting background (emphasis added)* for the Drug Facts Label with some exceptions (see 21 CFR 201.66(d)(3)). Similar flexibility with regards to the ACNU statement should be allowed.

Furthermore, there will likely be differences in the types of ACNU implemented for OTC+ACNU drugs. Therefore, having flexibility in the font type and color will be important to establish the information relevant to the purchaser and user is readily visible. The relevant ACNU statement would still be prominently displayed on the PDP based on the product packaging.

Lastly, CHPA members offer their technical expertise to FDA to help develop a shorter ACNU statement and/or validated symbol(s) that accomplish the spirit of these regulations.

**Regulation and Text:** §201.67(d)(3) - The statement must appear in a yellow background banner. No other information or statements may be included within the yellow background banner.

**CHPA Proposed Text:** ~~The statement must appear in a yellow background banner. No other information or statements may be included within the yellow background banner.~~

**Additional Comments:** See comments above related to §201.67(d)(2).

**Regulation and Text:** §201.67(d)(4)(ii) - At least 12 point font (1 point = 0.0138 inches)

**CHPA Proposed Text:** At least 12 point font (1 point = 0.0138 inches). *Sponsors will use font size for the ACNU statement that is at least 25% of the brand name unless it is not feasible to do so due to the package size (i.e., convenience or small size packaging). In such instances where there is limited space on the packaging, the sponsor and FDA would agree to the appropriate font size for the ACNU statement.*

**Additional Comments:** CHPA's proposed changes to this regulation assume that a shorter ACNU statement and/or validated symbol(s) will be developed that can be used on product packaging.

**Regulation and Text:** §201.130(a)(1) - The label of the drug: Bears, as the first direction under the "Directions" heading required in §201.66(c)(6), the statement "To check if this drug is safe for you, go to [insert where or how consumers can find information about the ACNU; for example, applicant's website, applicant's phone number, or specific retail location] and [insert action to be taken by consumer]. Do not take this drug without completing this step." The statement must be followed by the other information required in §201.66(c)(6).

**CHPA Proposed Text:** The label of the drug: Bears, as the first direction under the "Directions" heading required in §201.66(c)(6), ~~the a~~ statement *that alerts purchasers and users that the nonprescription drug product with an ACNU has a requirement that must be fulfilled to ensure safe or effective use. For example, "To check if this drug is safe [OR] right for you, go to [insert where or how consumers can find information about the ACNU; for example, applicant's website, applicant's phone number, or specific retail location] and [insert action to be taken by consumer]. Do not take this drug without completing this step."* The statement must be followed by the other information required in §201.66(c)(6).

**Additional Comments:** The ACNU statement as written is not consumer friendly and should be significantly streamlined. For example, instead of the original ACNU statement in the proposed regulation, FDA should consider using language contained in, or similar to, language in its final guidance "Self-Selection Studies for Nonprescription Drug Products" (i.e., "Is it okay for you to use this medication?"<sup>25</sup>). CHPA also notes that the ACNU statement proposed by FDA does not distinguish

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<sup>25</sup> See FDA Final Guidance: Self-Selection Studies for Nonprescription Drug Products at page 7. Accessed from <https://www.fda.gov/media/81141/download> on October 18, 2022.

between an ACNU used for adequate self-selection, use, or both. With input from FDA, we offer to conduct consumer studies to identify standard text and/or a validated symbol(s) that clearly and concisely convey the purpose of the ACNU to consumers and to provide mock labels for the Agency's consideration.

See also comments above related to §201.67(d)(1).

**Regulation and Text:** §201.130(a)(2) - Bears, in the form and manner required by §201.67(d), the statement "You must complete an extra step to see if this drug is safe for you before you use it. Do not take this drug without completing this step. See the Drug Facts labeling for more information."

**CHPA Proposed Text:** See additional comments.

**Additional Comments:** See comments above related to §201.67.

**Regulation and Text:** §201.130(a)(3) - Complies with other applicable labeling requirements for nonprescription drug products under this part, including the format and content requirements for nonprescription drug product labeling under §201.66.

**CHPA Proposed Text:** Complies with other applicable labeling requirements for nonprescription drug products under this part, including the format and content requirements for nonprescription drug product labeling under §201.66. *This requirement would not apply when an exemption has been granted or approved.*

**Additional Comments:** Sponsors that have been granted an exemption should not be expected to comply with §201.130(a)(3).

### Proposed Regulations for Part 314 Applications for FDA Approval To Market a New Drug

**Regulation and Text:** §314.56(a)(1) - *Additional condition for nonprescription use* (ACNU) means one or more FDA-approved conditions that an applicant of a nonprescription drug product must implement to ensure consumers' appropriate self-selection or appropriate actual use, or both, of the nonprescription drug product without the supervision of a healthcare practitioner if an applicant demonstrates and FDA determines that labeling alone is insufficient to ensure appropriate self-selection or appropriate actual use, or both.

**CHPA Proposed Text:** *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~~ *enable* consumers' to appropriately self-select or appropriately use, or both, of the nonprescription drug product without the supervision

of a healthcare practitioner if an applicant ~~demonstrates~~ *determines* an ACNU is needed to achieve appropriate self-selection, appropriate actual use, or both, *for the intended use of the product*.

**Additional Comments:** Sponsors should determine when an ACNU is necessary for an OTC drug product subject to the switch application process or to facilitate safe and effective use of the product by consumers. However, ACNUs should not be required for all future Rx-to-OTC switches or OTC application approvals. It should be available for any development program where the sponsor has determined an ACNU may be needed along with its rationale for doing so.

There may be instances where information already exists that suggests that an ACNU is likely to be needed (e.g., previous FDA Advisory Committee meetings, pre-IND<sup>26</sup> discussions with the Agency, denial letter for an NDA). In such cases, there should be no expectation for the same or a different sponsor to generate new data solely for the purpose of demonstrating that consumers are unable to appropriately select, use, or both, the drug product in question. To require companies to generate this type of data would be duplicative and result in unnecessary use of resources (e.g., staff and monetary) and needless delay of development timelines.

The ACNU rule, when finalized, should not prescribe the types of studies that should be performed to assess when an ACNU may be needed to enable appropriate self-selection or use of an OTC drug product. Adequate data should also not be restricted solely to prospective consumer behavior studies if the sources cited by the sponsor are reliable and fit for purpose. A sponsor should be permitted to seek FDA advice any time during the development process regarding the use of an ACNU.

Lastly, although an ACNU may be necessary for several years immediately following approval of an application with an ACNU, it may not need to be permanent. A sponsor should be permitted to submit an amendment to an approved application requesting the revision to or removal of the ACNU as a condition of OTC marketing. The sponsor would provide its rationale and supporting documentation for this request as part of the amended application.

**Regulation and Text:** §314.56(a)(2) - None

**CHPA Proposed Text:** *A sponsor marketing an OTC drug approved with an ACNU may submit an amendment to an approved application requesting the revision to or removal of the ACNU. The sponsor will provide its rationale and supporting documentation for the request(s) to FDA as part of the amended application.*

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<sup>26</sup> IND = Investigational New Drug Application

**Additional Comments:** We are proposing a new regulation (*i.e.*, §314.56(a)(2)) to establish a process to revise or remove an ACNU that was part of a new OTC drug application approval. In-market experience or additional information about the drug may provide sufficient data or other information to support changes or removal of an ACNU. An ACNU should not be expected to be unchanging or permanent simply because it was an initial element required for approval.

**Regulation and Text:** §314.56(b) - *Separate application required for a nonprescription drug product with an ACNU.* An applicant must submit a separate application for a nonprescription drug product with an ACNU. Initial approval for a nonprescription drug product with an ACNU cannot be obtained through a supplement to an approved application.

**CHPA Proposed Text:** See discussion under simultaneous marketing. (See Section 1.D. above at page 5)

**Additional Comments:** None

**Regulation and Text:** §314.56(c)(1)(i) - *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— A statement regarding the purpose of the ACNU: ensure appropriate self-selection or appropriate actual use, or both, by consumers of the nonprescription drug product with an ACNU without the supervision of a healthcare practitioner;

**CHPA Proposed Text:** *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— A statement regarding the purpose of the ACNU: ~~ensure~~ *enable* appropriate self-selection or appropriate actual use, or both, by consumers of the nonprescription drug product with an ACNU without the supervision of a healthcare practitioner;

**Additional Comments:** FDA should advise sponsors where it expects information regarding the ACNU to be included within the existing structure of an NDA.

**Regulation and Text:** §314.56(c)(1)(v) - Adequate data or other information that demonstrates the necessity of the ACNU to ensure appropriate self-selection or appropriate actual use, or both;

**CHPA Proposed Text:** Adequate data or other information that demonstrates the ~~necessity of~~ *rationale for* the *use of* the ACNU to ~~ensure~~ *enable* appropriate self-selection or appropriate actual use, or both.

**Additional Comments:** Due to the speed at which technology evolves, the regulatory framework for OTC+ACNU drug products needs to provide guidelines for implementing an ACNU while retaining the flexibility needed to allow innovation for different types of ACNUs in the future.

**Regulation and Text:** §314.56(c)(1)(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

**CHPA Proposed Text:** None

**Additional Comments:** See comments above related to §314.56(c)(1)(v).

**Regulation and Text:** §314.56(c)(2)(ii) - Include information demonstrating that the key elements of the proposed ACNU are the same as the key elements of the ACNU for its reference listed drug (RLD); and

**CHPA Proposed Text:** Include information demonstrating that the key elements of the proposed ACNU are ~~the same~~ *equivalent to* as the key elements of the ACNU for its reference listed drug (RLD); and

**Additional Comments:** None

**Regulation and Text:** §314.56(c)(2)(iii) - Include information on the way the ACNU would be operationalized. If an applicant believes the ACNU is operationalized in the same way as the RLD, include information demonstrating that the ACNU is operationalized in the same way as the RLD. If a different way to operationalize the proposed ACNU is used, include information to show that this different way to operationalize the proposed ACNU achieves the same purpose as the ACNU for its RLD and that the differences from the RLD are otherwise acceptable in an ANDA.

**CHPA Proposed Text:** Include information on the way the ACNU would be operationalized. If an applicant believes the ACNU is operationalized in *an the same equivalent* 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~~ *an equivalent* purpose as the ACNU for its RLD and that the differences from the RLD are otherwise acceptable in an ANDA.

**Additional Comments:** The Agency should provide guidance to sponsors about the types of data it expects to review to establish that one ACNU functions in a way that is equivalent to another ACNU for an RLD. CHPA believes typical consumer

behavior studies would be sufficient to demonstrate equivalent outcomes for ACNUs.

**Regulation and Text:** §314.56(d) - *Simultaneous marketing of nonprescription and prescription products.* An ACNU constitutes a meaningful difference between a nonprescription drug product and a prescription drug product, such that a prescription drug product and a nonprescription drug product with an ACNU may be simultaneously marketed even if there is not another meaningful difference between the two products that makes the nonprescription drug product safe and effective for use without the supervision of a healthcare practitioner licensed by law to administer the drug (e.g., a different active ingredient, indication, strength, route of administration, dosage form, or patient population).

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

**Additional Comments:** CHPA strongly opposes permitting simultaneous marketing of Rx and OTC products. See also comments above related to simultaneous marketing status. (See Section I.D. above at page 5)

**Regulation and Text:** §314.81(b)(3)(v) - *Report of failure in the implementation of an additional condition for nonprescription use.* The applicant must submit a report when a failure in the implementation of an additional condition for nonprescription use (ACNU) for a nonprescription drug product occurs. A report of a failure in implementation of an ACNU includes any event that results from a deviation in an applicant's implementation of the ACNU that may cause or lead to inappropriate medication use or consumer harm. All failures in implementation of an ACNU must be reported to the FDA Adverse Event Reporting System (FAERS), whether or not the failure in implementation of an ACNU is associated with an adverse event. If an applicant becomes aware of both a failure in implementation of an ACNU and an associated adverse event before the submission to FAERS, a single individual case safety report (ICSR) that describes both the failure in implementation of an ACNU and the associated adverse event must be submitted and must contain the information as required in § 314.80(f) and paragraph (b)(3)(v)(A) of this section. If a previously submitted report to FAERS describes only a failure in implementation of an ACNU or a previously submitted ICSR reports only an adverse event, and the submitter subsequently becomes aware of an associated adverse event or associated failure in

implementation of an ACNU, the submitter must supplement the original report to FAERS with the new information. The supplement must include the information required in § 314.80(f) or paragraph (b)(3)(v)(A) of this section, as applicable.

~~CHPA Proposed Text: §314.81(b)(3)(v) - Report of failure in the implementation of an additional condition for nonprescription use. The applicant must submit a report when a failure in the implementation of an additional condition for nonprescription use (ACNU) for a nonprescription drug product occurs. A report of a failure in implementation of an ACNU includes any event that results from a deviation in an applicant's implementation of the ACNU that may cause or lead to inappropriate medication use or consumer harm. All failures in implementation of an ACNU must be reported to the FDA Adverse Event Reporting System (FAERS), whether or not the failure in implementation of an ACNU is associated with an adverse event. If an applicant becomes aware of both a failure in implementation of an ACNU and an associated adverse event before the submission to FAERS, a single individual case safety report (ICSR) that describes both the failure in implementation of an ACNU and the associated adverse event must be submitted and must contain the information as required in § 314.80(f) and paragraph (b)(3)(v)(A) of this section. If a previously submitted report to FAERS describes only a failure in implementation of an ACNU or a previously submitted ICSR reports only an adverse event, and the submitter subsequently becomes aware of an associated adverse event or associated failure in implementation of an ACNU, the submitter must supplement the original report to FAERS with the new information. The supplement must include the information required in § 314.80(f) or paragraph (b)(3)(v)(A) of this section, as applicable.~~

**CHPA Proposed Text:** §314.81(b)(3)(v) - Report of failure in the implementation of an additional condition for nonprescription use.

*Individual case reporting for ACNU failures- Failure of an ACNU that results in an adverse event will be reported based on existing postmarketing reporting requirements.*

*Aggregate case reporting for ACNU failures - Failure of an ACNU that does not cause an adverse event but is likely to cause an adverse event if not addressed by the Sponsor.*

*Non-reportable ACNU failures - Failure of an ACNU that is anticipated to occur or is unlikely to cause a non-serious adverse event. Failure of an ACNU that results in a consumer being unable to purchase the drug would not be reported. During the application review process, the sponsor shall propose a Service Level definition that describes the anticipated availability of the ACNU to the public (e.g., 99.9% of the time) and any expected exceptions to availability for maintenance, updates, or cybersecurity activities. Once approved, the sponsor will provide periodic reports of failures in the availability of the ACNU in excess of the Service Level agreed with FDA. The sponsor and FDA may agree on the additional type(s) of failures related to an ACNU failure that do not need to be reported to the FDA Adverse Event Reporting*



*System (FAERS) database. Failures that are not specifically related to the ACNU would not be subject to reporting.*

***Additional considerations** - If an applicant becomes aware of both a failure in implementation of an ACNU and an associated adverse event before the submission to FAERS, a single individual case safety report (ICSR) that describes both the failure in implementation of an ACNU and the associated adverse event must be submitted and must contain the information as required in §314.80(f) and paragraph (b)(3)(v)(A) of this section. If a previously submitted report to FAERS describes only a failure in implementation of an ACNU or a previously submitted ICSR reports only an adverse event, and the submitter subsequently becomes aware of an associated adverse event or associated failure in implementation of an ACNU, the submitter must supplement the original report to FAERS with the new information. The supplement must include the information required in § 314.80(f) or paragraph (b)(3)(v)(A) of this section, as applicable.*

**Additional Comments:** As proposed, CHPA disagrees with the creation on an alternative reporting system and request that Agency use the current reporting systems as outlined in 21 CFR 314.80 for drugs and 21 CFR Part 803 for medical devices. We are concerned about the precedent the Agency would be setting by requiring reporting of errors not related to adverse events or failures for drug products as well as the potential number of reports that would be submitted for ACNU failures that result in the consumer not being able to access a product. As with adverse event reporting, safety should drive failure reporting.

The clinical outcome of a failure is considered in the reporting requirements and is risk-based for adverse event reporting for medical devices. The FDA CDER's Office of Nonprescription Drugs should use a similar risk-based approach for establishing adverse event reporting requirements for ACNUs.

ACNU failures resulting in an adverse event should be the primary focus of AEs reported to the Agency. This approach should help with identifying true safety concerns more efficiently and effectively, without contributing to background noise that could obscure true safety signals. Non-significant failures will be captured and investigated under existing complaint handling processing.

FDA CDER ONPD should look to its sister center, the Center for Devices and Radiological Health (CDRH), and its Voluntary Malfunction Summary Reporting Program (VMSRP) for a more streamlined reporting procedure that does not compromise public health. Announced on August 17, 2022, the VMSRP<sup>27</sup> allows the manufacturer to report certain medical device malfunctions in summary form on a quarterly basis. Separate summary reports are submitted for each unique

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<sup>27</sup> Food and Drug Administration 21 CFR Part 803 Medical Devices and Device-Led Combination Products; Voluntary Malfunction Summary Reporting Program for Manufacturers; Notification; order granting alternative. 83 Fed. Reg. 40973-40985. Accessed from <https://www.govinfo.gov/content/pkg/FR-2018-08-17/pdf/2018-17770.pdf> on August 31, 2022.

combination of brand name, device model, and product codes, and identifies the total number of reportable malfunctions. A similar approach should be developed for what are anticipated to be common ACNU failures regardless of the specific ACNU involved.

To the extent that CDRH is involved, FDA should be clear which Center is designated for adverse event reporting to avoid duplicative submissions.

**Regulation and Text:** §314.81(b)(3)(v)(A)(1)-(2)(v) - (A) *Content*. The report must include the following for a failure in implementation of an ACNU: (v) The remedial action taken or completed to address the failure in implementation of an ACNU, including the type of remedial action initiated or completed (for example, repair, replace, recall, inspection, modification, or adjustment) and a description of how the applicant will prevent failures of the same nature in the future.

**CHPA Proposed Text:** (A) *Content*. The report must include the following for a failure in implementation of an ACNU: (v) The remedial action taken or completed to address the failure in implementation of an ACNU *depending on the type of failure and the consequences of the failure*, including the type of remedial action initiated or completed (for example, repair, replace, recall, inspection, modification, or adjustment) and a description of how the applicant will prevent failures of the same nature in the future.

**Additional Comments:** It is unclear if FDA expects a sponsor to implement remediation for *each and every* failure that occurs related to a failure in implementation of an ACNU. Sponsors should determine when remediation should be implemented based on their safety assessment and not be expected to report on complaints that are solely based on the failure of an ACNU. Reporting should be based on the failure of an ACNU that results in an adverse event. FDA CDER ONPD should establish a reporting structure for common ACNU-related failures similar to the CDRH Voluntary Malfunction Summary Reporting Program (VMSRP).

See also related comments above under §314.81(b)(3)(v).

**Regulation and Text:** §314.81(b)(3)(B)(1-2) - (B) *Submission*. (1) The applicant must submit the report for each failure in implementation of an ACNU as soon as possible but no later than 15 calendar days from the date when the applicant has acquired the minimum dataset for a failure in implementation of an ACNU. (2) The applicant must also investigate any new information it obtains or otherwise receives about previously submitted reports and assess the relationship or impact of the new information on the initial report. The applicant must submit follow-up reports as soon as possible but no later than 15 calendar days after obtaining the new information.

**CHPA Proposed Text:** (B) *Submission.* (1) *In accordance with 21 CFR 314.80*, the applicant must submit the report for each failure in implementation of an ACNU *that results in an adverse event* as soon as possible but no later than 15 calendar days from the date when the applicant has acquired the minimum dataset for a failure in implementation of an ACNU. (2) The applicant must also investigate any new information it obtains or otherwise receives about previously submitted reports and assess the relationship or impact of the new information on the initial report. The applicant must submit follow-up reports as soon as possible but no later than 15 calendar days after obtaining the new information.

**Additional Comments:** CHPA recommends FDA implement quarterly aggregate reporting for the first three years after approval for ACNU failures with clinical significance, and annually thereafter. Reporting should be based on the category or type of ACNU failure.

See also related comments above under §314.81(b)(3)(v).

### **3. The Favorable Economic Impacts of the Proposed Rule Will Be Undermined If Simultaneous Marketing Remains in the Rule**

As FDA notes in the proposed rule, Rx-to-OTC switch, including with an ACNU, can provide greater access to drugs and reduce costs to consumers, saving consumers \$26.70 per consumer per purchase (within a range of \$0 - \$53.40). Past switches have repeatedly underscored the increased utilization that flows from nonprescription availability. For instance, Stomberg, *et al.*, found utilization increased 27 percent when a new OTC therapy is introduced.<sup>28</sup> In the era of several switches for allergy symptoms, the percentage of allergy sufferers using OTC medicines increased from 66 to 75 percent.<sup>29</sup> The introduction of OTC smoking cessation products provides the most powerful example, with utilization increasing 150 percent in the first year post-switch.<sup>30</sup> However, as discussed in section I.D. of these comments, simultaneous marketing of Rx and OTC drugs with an ACNU presents several challenges with implementation of the proposed rule that may differentially impact patients and that will undercut incentives for sponsors to pursue this path.

A model using two common Rx drugs described in detail below reached two conclusions: First, yes, switches with an ACNU would likely increase the number of patients/consumers accessing the medicines in the model. But second, for the modeled drug classes, just under half to two-thirds of users would be projected to use a generic Rx, rather than the OTC with an ACNU. In many instances, the reduction in OTC utilization will have a significant chilling effect on a sponsor's incentive to undertake the lengthy process involved in developing and seeking approval of an ACNU, and could similarly chill a sponsor's incentive to pursue an Rx-to-OTC switch program where an ACNU versus a traditional label-based switch program was in question. These incentives are further undercut when one considers that one component of launching a new OTC drug product is raising consumer and healthcare professional awareness. In the case of simultaneous marketing of an Rx product, the sponsor's awareness-building efforts will have the perverse impact of raising awareness about a competing Rx generic drug. In essence, a sponsor of a drug with an ACNU would undertake additional development costs, likely increased time in the development process, and no change in in the effort involved with a launch weighed against a de facto elimination of exclusivity.

#### ***Model Structure***

To better understand precisely how the proposed rule will impact patients, CHPA asked Avalere Health<sup>31</sup>, a healthcare consulting and advisory firm specializing in strategy, policy, and data analysis for life sciences, health plans, and providers, to develop a model focusing on product volume shifts under the current approach to switch and Rx or OTC with the proposed simultaneous Rx and OTC market.

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<sup>28</sup> Stomberg C., *et al.*, Utilization effects of Rx-OTC switches and implications for future switches. *Health*. 2013.

<sup>29</sup> Nielsen for CHPA, Assessing consumer benefit of allergy Tx-to-OTC switches. Self-published. 2017.

<sup>30</sup> Shiffman S., *et al.*, Public health benefit of over-the-counter nicotine medications. *Tobacco Control*. 1997. See also Keeler T., *et al.*, The benefits of switching smoking cessation drugs to over-the-counter status. *Preventive Health Care*. 2002.

<sup>31</sup> Avalere Health, memo to CHPA on file, October 25, 2022.

Avalere Health prepared this assessment by looking at two common drug types – a low-dose statin and an oral combination contraceptive. The model was structured as a decision tree analysis at a micro- and macro-level, demonstrating the volume changes that may occur under specific types of insurance coverage as well as overall between Rx and OTC.

## Model Methodology

The model projects the shift and growth in volume that could be seen in the current Rx or OTC paradigm, compared to the proposed simultaneous Rx and OTC market for two common drugs – a low-dose statin and an oral combination contraceptive. The model was structured as a decision tree analysis at a micro- and macro-level, demonstrating the volume changes that may occur under specific types of insurance coverage as well as overall across all types of insurance coverage. The model used common deductible and copay design elements for Medicare, commercial insurance, and Medicaid; total market growth and price reductions for Rx to OTC as identified in the literature; and elasticities of demand developed by the Congressional Budget Office to develop a decision matrix for patients and determine at a payer and product level how volume could shift and increase.

### ***Influence of Coverage Segment on Model Outputs***

While the model demonstrates that a simultaneous Rx and OTC market generally lowers patient costs and provides a higher volume of product utilization (see *Table 1*), this increase in access is highly dependent on several factors, including patients' insurance coverage.

- *Medicare* and *commercially* (particularly employer sponsored) insured patients may see out-of-pocket (OOP) costs increase in an OTC environment. These plans tend to have lower patient cost liability. However, this will vary for different classes of drugs, depending on the typical co-pay required under these plans.
- *Medicaid* patients for the most part would not be economically impacted by the availability of OTC products. Medicaid is the only common type of insurance that covers OTC products. In order to purchase an OTC product under Medicaid coverage, patients require a physician 'prescription' (in some states, referred to as a 'fiscal order'). In this situation, OTC transactions still flow through the benefit adjudication process.
- *Uninsured* patients are likely to benefit the most from an Rx product being available as OTC. The outputs of the model in *Table 1* show this increase in volume. These patients usually have significantly higher OOP costs for Rx products compared to patients with Medicare, commercial, or Medicaid coverage. In an OTC environment, the cost of a medicine would be expected to be lower compared to the cost in an Rx pathway without health plan coverage, thus driving a shift in volume.

Table 1: Current and Projected Volumes Under Existing and Proposed Regulation for Rx and OTC Marketing					
	<u>Current Rx Volume</u>	<u>Switch to OTC Under Existing Regulation</u>	<u>Rx and OTC Under Proposed Rule</u>		
	Rx	OTC	Rx	OTC	Total
<i>Low-Dose Statin</i>					
Medicaid	59,000	62,000	53,000	11,000	64,000
Medicare	5,591,000	-	4,193,000	-	4,193,000
Commercial	10,684,000	-	6,211,000	-	6,211,000
Cash Pay	860,000	21,258,000	86,000	12,004,000	12,090,000
<b>Total</b>	<b>17,193,000</b>	<b>21,320,000</b>	<b>10,543,000</b>	<b>12,015,000</b>	<b>22,558,000</b>
<i>Oral Combination Contraceptive</i>					
Medicaid	108,000	126,000	97,000	35,000	132,000
Medicare	15,000	-	14,000	-	14,000
Commercial	14,163,000	-	12,747,000	-	12,747,000
Cash Pay	752,000	18,522,000	75,000	6,763,000	6,838,000
<b>Total</b>	<b>15,039,000</b>	<b>18,648,000</b>	<b>12,933,000</b>	<b>6,798,000</b>	<b>19,731,000</b>

***Considering Current and Future Patient Behavior***

This decision tree analysis is based on “rational consumer behavior.” The cost savings that would lead to increased access for patients through a simultaneous Rx and OTC marketing paradigm would be fully realized only if stakeholders have the appropriate information at hand to determine which pathway would be most cost-effective, which is an assumption not explicitly highlighted in the FDA proposed rule.

Acquiring a medicine through the Rx pathway requires a greater number of steps, any one of which can reduce adherence to therapy: visiting a provider, receiving a prescription, receiving any relevant authorization from the insurance plan, finding an in-network pharmacy, and being aware of any OOP liability. This process requires a patient’s time commitment and an awareness of those steps and

relevant information (e.g., how to access and understand the plan's benefit design). Conversely, acquiring an OTC product provides patients with a more direct access route.

As a result of the different access pathways, including the time and awareness elements, some individuals may choose to acquire a product as an OTC even where its availability as Rx could provide out of pocket drug cost savings under many Medicare and commercial plans. Of course, relative cost savings between a Rx and OTC product will vary across classes of drugs. For example, many contraceptives have a \$0 co-pay under Affordable Care Act compliant plans; for this class of drugs, patients would experience increased costs if acquiring the product as OTC rather than as Rx under their insurance plan. But the point of the model remains: If out of pocket is less for the Rx, many will remain with the Rx.

### ***Marketplace Competition and its Potential Impact***

The relative benefit of the Rx and OTC pathways are further complicated by market dynamics in specific classes of drugs. For drugs that have generics competing in the market, pricing pressures across the Rx supply chain can reduce patients' out-of-pocket costs. This can result directly from drops in list prices of competing products or, once multiple generics are on the market, a maximum allowable cost (MAC) at which pharmacies can be reimbursed for generics. The MAC tends to fall in between the price of the lowest and highest generic available for a given drug, which has indirect downstream cost saving implications for patients. These structures can provide reductions in spending in the Rx market that may not directly transfer in an OTC environment.

In the proposed rule, FDA also notes potential savings from a simultaneous Rx and OTC pathway due to a decrease in future medical costs and insurance claims. While an expectation of lower costs is reasonable as a result of fewer provider visits and reduced Rx claims, patients purchasing an OTC may still be encouraged to discuss diagnoses and treatment options with a healthcare provider and be monitored for progress regarding their condition. Thus, the cost savings may be diminished if such safety parameters are followed.

## Conclusion

CHPA appreciates the opportunity to provide input for Agency consideration as it works to finalize the regulations for ACNU. We hope our recommendations are incorporated into the final rule as we believe they will lead to the intended outcome of increased public health access to new OTC products, including access for the underserved.

Our contact information is listed below if there are any questions.

Sincerely,

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### Appendix A - Glossary of Terms

Term	Abbreviation	CHPA Member Definition
Additional Condition for Nonprescription Use	ACNU	An additional condition that must be fulfilled which facilitates appropriate selection, appropriate use, or both by consumers without the supervision of a healthcare professional. The ACNU may be implemented in various ways including a mobile application, tool, process, or technology provided by the sponsor beyond the product labeling.
Healthcare Professional; Healthcare Practitioner	HCP	A licensed medical or osteopathic doctor, dentist, nurse practitioner, physician assistant, or pharmacist permitted to deliver healthcare to consumers and patients.
Nonprescription Drug Product With an Additional Condition for Nonprescription Use	OTC+ACNU drug	Drug product with approval to be marketed without a prescription if an applicant implements an additional condition to enable appropriate self-selection, appropriate actual use, or both by consumers without the supervision of a healthcare professional.
Over-the-counter Drug	OTC drug	Drug product that can be marketed to and purchased by consumers without a prescription and without supervision by a healthcare professional.

Term	Abbreviation	CHPA Member Definition
Prescription to Nonprescription Switch	Rx-to-OTC Switch or Switch	The process to change the marketing status of an FDA-approved prescription drug to nonprescription initiated by a sponsor through the new drug application (NDA) process.
Reference Listed Drug	RLD	A Reference Listed Drug (RLD) is an approved drug product to which new generic versions are compared to show that they are bioequivalent. A drug company seeking approval to market a generic equivalent must refer to the Reference Listed Drug in its <a href="#">Abbreviated New Drug Application</a> (ANDA). By designating a single reference listed drug as the standard to which all generic versions must be shown to be bioequivalent, FDA hopes to avoid possible significant variations among generic drugs and their brand name counterpart. <sup>32</sup>
Right of Reference Letter	RoR	A right of reference letter is a formal document authorizing FDA to cross reference the NDA, including underlying study data, from one sponsor in support another sponsor’s 505(b)(2) application.

[https://consumerhealthcare.sharepoint.com/sites/Shared/Shared Documents/General/RSA/FDA/ACNU NPRM/Comments/Proposed Rule/Final/CHPA Comments\\_FDA NPRM for ACNU\\_FINAL 11212022.docx](https://consumerhealthcare.sharepoint.com/sites/Shared/Shared Documents/General/RSA/FDA/ACNU NPRM/Comments/Proposed Rule/Final/CHPA Comments_FDA NPRM for ACNU_FINAL 11212022.docx)

<sup>32</sup> FDA Drugs@FDA Glossary of Terms. Accessed from <https://www.fda.gov/drugs/drug-approvals-and-databases/drugsfda-glossary-terms#R> on October 4, 2022.