Overview of Proposed Rule: Nonprescription Drug Product With an Additional Condition for Nonprescription Use

Elisabeth Walther, PharmD, JD

Associate Director for Strategic Initiatives

Office of Nonprescription Drugs

CDER | FDA

The opinions and information in this presentation are my own and do not necessarily reflect the views and policies of the FDA

Learning Objectives

- Discuss regulatory pathways to market nonprescription drugs are marketed in the U.S.
- Explain the importance of nonprescription drug labeling
- Discuss the limitations of nonprescription drug labeling
- Discuss FDA's proposed requirements for nonprescription drug products with an additional condition for nonprescription use

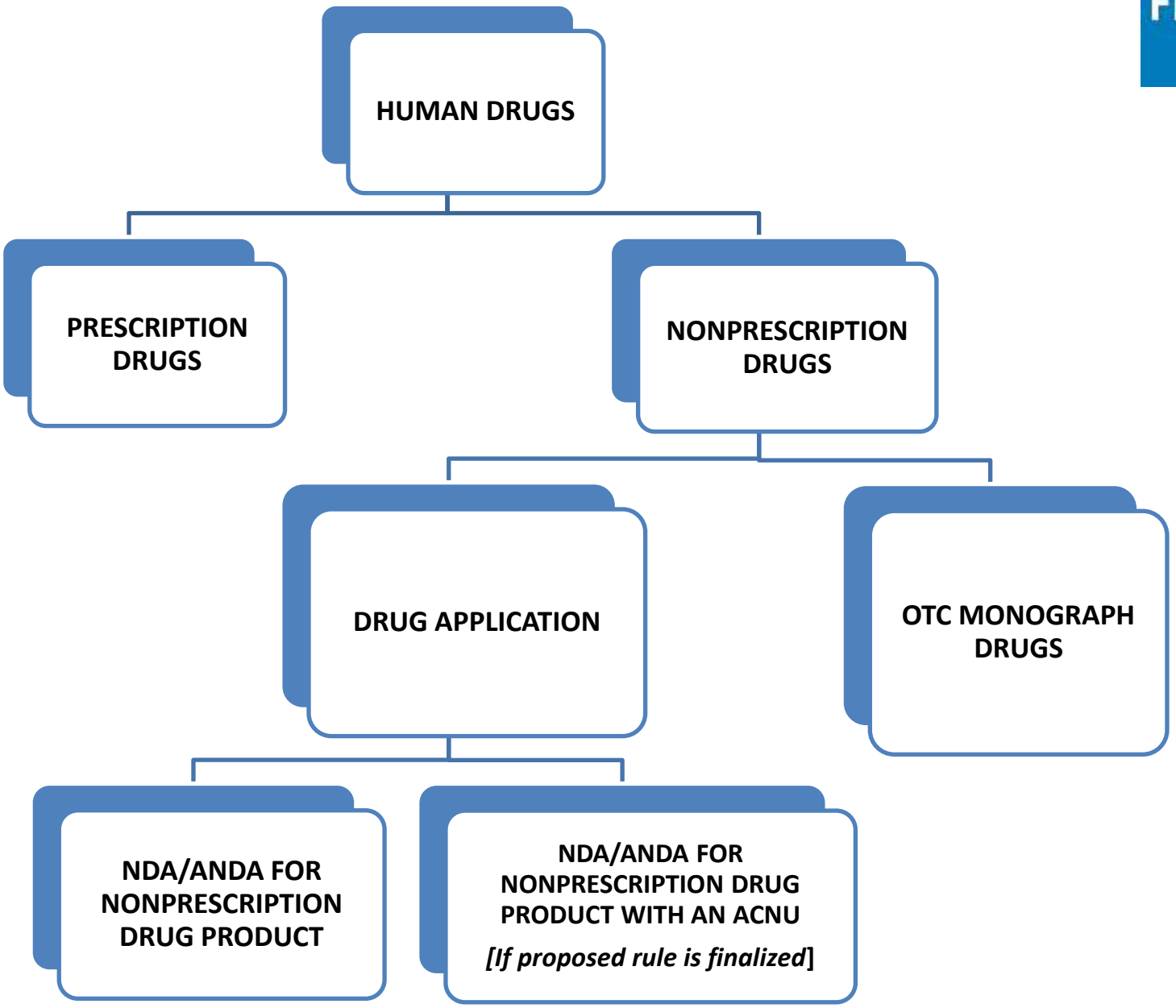
Classes of Drugs in the United States

- **Prescription Drug:** not safe for use except under supervision of a practitioner licensed to administer the drug because of
  - Toxicity or other potentially harmful effects
  - Method of use
  - Collateral measures necessary for use
- **Nonprescription Drug**: can be used safely and effectively by a consumer without the supervision of a health care practitioner and does not meet the criteria for prescription-only dispensing

Regulatory Pathways for Marketing Nonprescription Drugs

- **New Drug Application/Abbreviated New Drug Application (NDA/ANDA)**
  - Application is submitted to FDA for premarket approval
    - Drug product cannot be marketed until FDA approves the drug application
  - FDA determines whether the information submitted as part of an application is sufficient to ensure that the drug product is safe and effective for nonprescription use under the conditions prescribed, recommended, or suggested in its proposed labeling

- **OTC Drug Review (OTC Monograph)**
  - Drug product is marketed without an approved drug application if the drug complies with the requirements in section 505G of the Federal Food, Drug, and Cosmetic Act (FD&C Act), including any applicable conditions in an OTC Monograph


HUMAN DRUGS
PRESCRIPTION DRUGS
NONPRESCRIPTION DRUGS
DRUG APPLICATION
OTC MONOGRAPH DRUGS
NDA/ANDA FOR NONPRESCRIPTION DRUG PRODUCT
NDA/ANDA FOR NONPRESCRIPTION DRUG PRODUCT WITH AN ACNU
[If proposed rule is finalized]

Nonprescription Drug Labeling

- Currently, nonprescription drugs must be labeled with adequate directions for use so that the consumer:
  - Can use the nonprescription drug product safely and effectively and for the purpose for which it is intended
  - Self-select and use the nonprescription drug product appropriately

Nonprescription Consumer Studies

Label Comprehension Study

- Understanding the key label message

Self- Selection Study

- Choosing the right product

Actual Use Study

- Using according to labeled directions

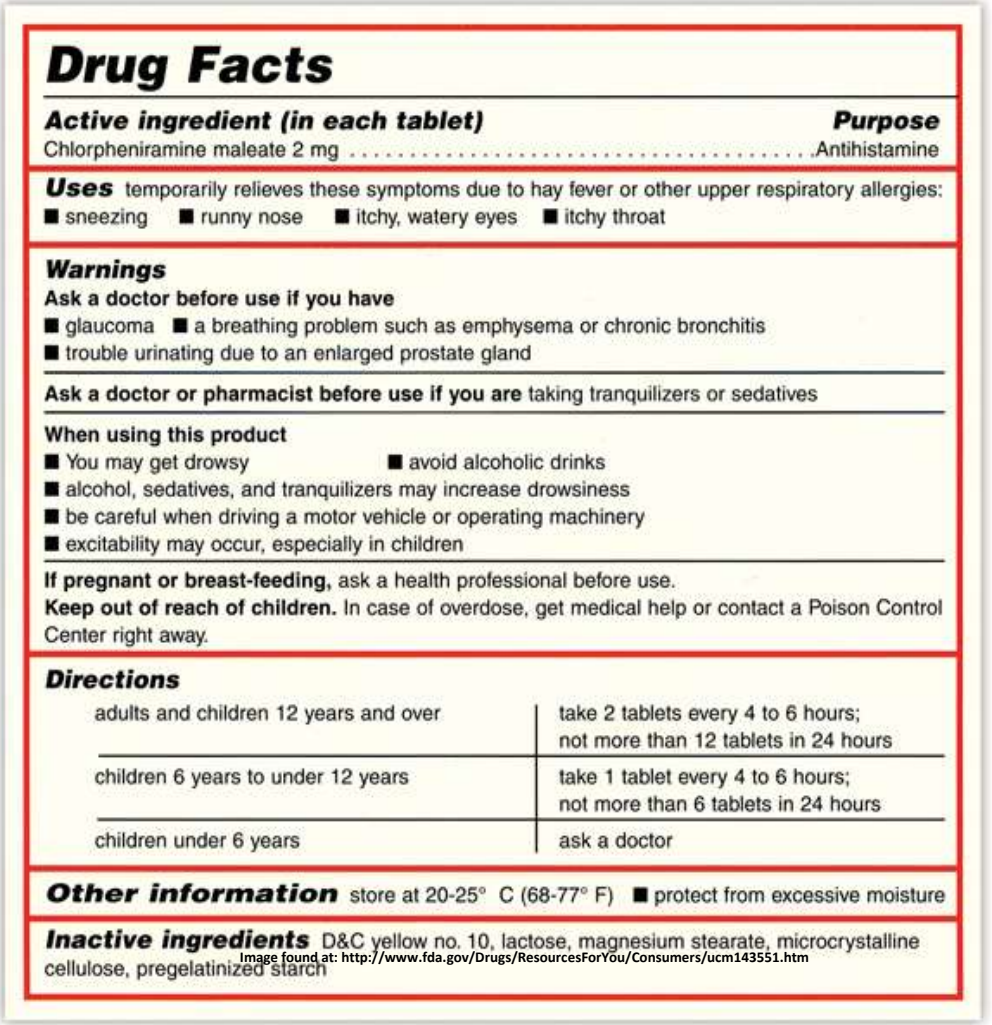
Human Factors Study

- Interacting with the product

Drug Facts Labeling

- Nonprescription drug products are subject to the Drug Facts labeling (DFL) requirements

- The DFL is intended to help enable consumers to appropriately self-select and use the nonprescription drug product safely and effectively



Drug Facts

Active ingredient (in each tablet) — **Purpose**
Chlorpheniramine maleate 2 mg ..... Antihistamine

Uses temporarily relieves these symptoms due to hay fever or other upper respiratory allergies:
■ sneezing ■ runny nose ■ itchy, watery eyes ■ itchy throat

Warnings
Ask a doctor before use if you have
■ glaucoma ■ a breathing problem such as emphysema or chronic bronchitis
■ trouble urinating due to an enlarged prostate gland

Ask a doctor or pharmacist before use if you are taking tranquilizers or sedatives

When using this product
■ You may get drowsy ■ avoid alcoholic drinks
■ alcohol, sedatives, and tranquilizers may increase drowsiness
■ be careful when driving a motor vehicle or operating machinery
■ excitability may occur, especially in children

If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

adults and children 12 years and over	take 2 tablets every 4 to 6 hours; not more than 12 tablets in 24 hours
children 6 years to under 12 years	take 1 tablet every 4 to 6 hours; not more than 6 tablets in 24 hours
children under 6 years	ask a doctor

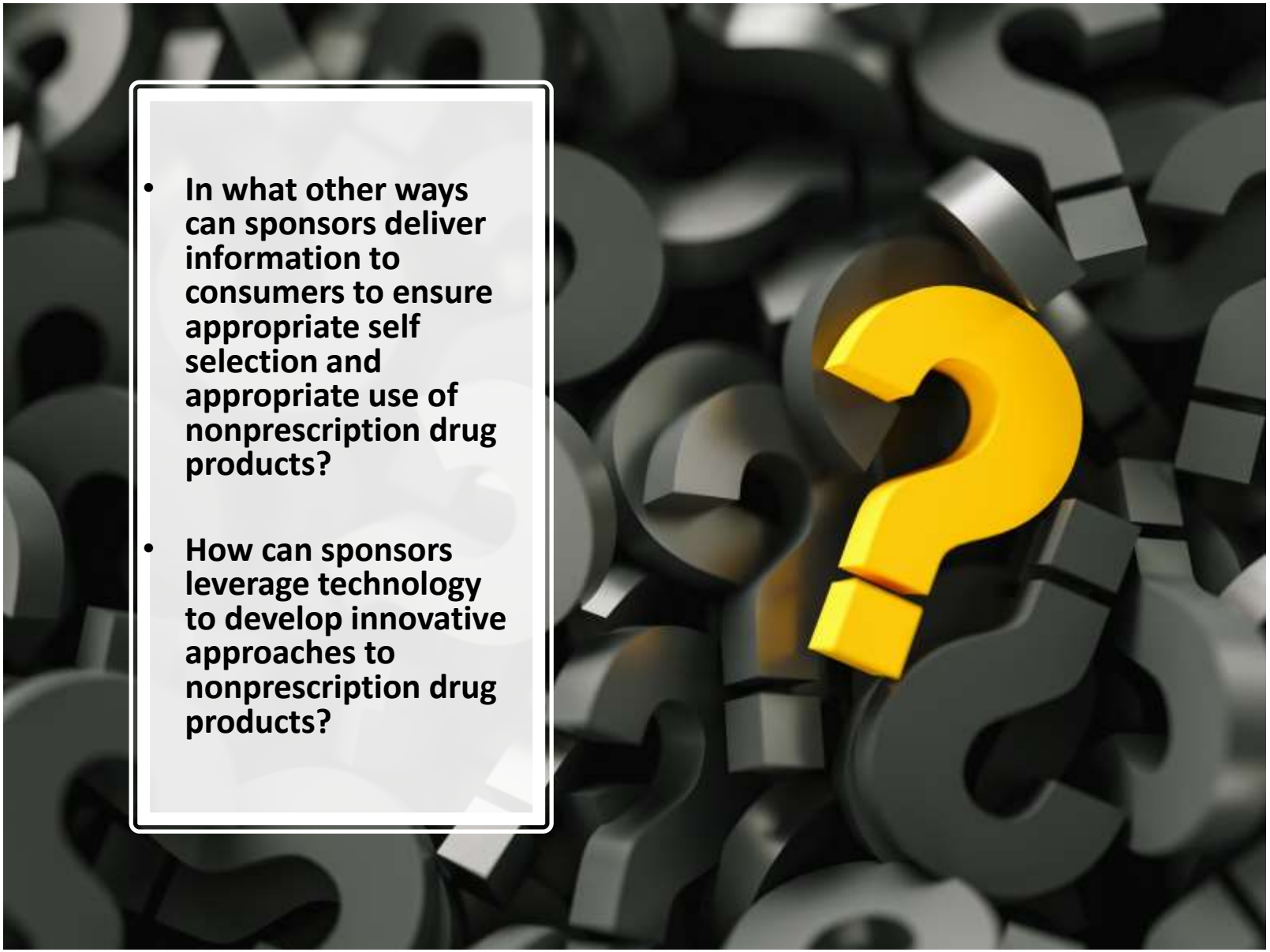
Other information store at 20-25° C (68-77° F) ■ protect from excessive moisture

Inactive ingredients D&C yellow no. 10, lactose, magnesium stearate, microcrystalline cellulose, pregelatinized starch

Image found at: http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143551.htm

Limitations of Nonprescription Drug Labeling

- Consumers' purchasing decision based on information in DFL and on principal display panel of product's carton/container
- For certain drug products, limitations of labeling present challenges for adequate communication of information



- In what other ways can sponsors deliver information to consumers to ensure appropriate self selection and appropriate use of nonprescription drug products?
- How can sponsors leverage technology to develop innovative approaches to nonprescription drug products?

History of Rulemaking

- **March 2012 Public Hearing**
  - "Using Innovative Technologies and Other Conditions of Safe Use to Expand Which Drug Products Can be Considered Nonprescription"
- **Engelberg Center for Health Care Reform at Brookings Institution Workshops**
  - "Nonprescription Medications with Conditions of Safe Use as a Novel Solution for Undertreated Diseases or Conditions" (Nov. 2012)
  - "Innovative Technologies and Nonprescription Medications: Addressing Undertreated Diseases and Conditions through Technology Enabled Self-Care" (May 2013)
  - "Exploring Implications of the Nonprescription Drug Safe Use Regulatory Expansion Initiative on Reimbursement and Access" (Nov. 2013)

Proposed Rule: *Nonprescription Drug Product with An Additional Condition for Nonprescription Use*

- Published in the Federal Register of June 28, 2022 (87 FR 38313)
- The proposed rule, if finalized:
  - would establish requirements for a nonprescription drug product with an additional condition for nonprescription use (ACNU) that an applicant must implement to ensure appropriate self-selection or appropriate actual use, or both, by consumers without the supervision of a healthcare practitioner
  - is intended to increase options for applicants to develop and market safe and effective nonprescription drug products, which could improve public health by broadening the types of nonprescription drug products available to consumers

The proposed rule **does not** create a third drug class.

INTRODUCTION TO THE PROPOSED RULE

What is an Additional Condition for Nonprescription Use (ACNU)? (Proposed §§ 314.56(a) and 201.67(b))

- 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

ACNU Examples

- In order to purchase the nonprescription drug product, consumers must respond with specific answers to a set of questions on a self-selection test available by either a mobile application or an automated telephone response system

- Before purchasing the nonprescription drug product with an ACNU, a consumer be required to view labeling (for example, text or images in a video), that describes how to appropriately use the nonprescription drug product and to respond to questions to confirm understanding

ACNU ≠ Labeling

- An ACNU may, however, utilize labeling to effectively implement the ACNU.
- For example:
  - **ACNU**: requirement that the consumer respond with specific answers to a set of questions on a self-selection test to purchase the drug product
  - **Labeling**: the list of questions to be answered by the consumer in the self-selection test

When Can an Applicant Propose an ACNU?

When the applicant demonstrates that labeling alone is not sufficient to ensure that the consumer can appropriately self-select or appropriately actually use, or both, a drug product correctly in a nonprescription setting

Evidentiary Standard

- Evidentiary standards that an application must meet under the FD&C Act and current FDA regulations for demonstrating safety and effectiveness would continue to apply to nonprescription drug products approved with an ACNU
  - A drug will only be approved for nonprescription use if the FDA determines that it is safe and effective to use without the supervision of a healthcare practitioner

Applicability

- The proposed rule would apply to NDAs and ANDAs for nonprescription drug products with an ACNU
- Currently marketed NDAs and ANDAs for nonprescription drug do not need an ACNU
- The proposed rule would not apply to OTC monograph drugs

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

- Applicants would be required to submit a separate application for a nonprescription drug product with an ACNU
  - Enables continued marketing of the prescription product under the original NDA and would allow it to serve as a reference listed drug for ANDAs for the prescription product
  - Continued access to the prescription drug product, along with availability of the nonprescription drug product approved with an ACNU, would ensure greater access to needed drugs by providing flexibility in how to obtain them

HIGHLIGHTS OF PROPOSED APPLICATION REQUIREMENTS FOR A NONPRESCRIPTION DRUG PRODUCT WITH AN ACNU

Specific Requirements for an NDA for a Nonprescription Drug Product with an ACNU (Proposed § 314.56(c))

(1) a statement regarding the purpose of the ACNU

(2) a statement of the necessity of the ACNU

(3) a description of how the ACNU ensures appropriate self-selection or appropriate actual use, or both

(4) a description of the key elements of the ACNU

(5) adequate data or other information that demonstrate the necessity of the ACNU

(6) adequate data or other information that demonstrate the effect of the ACNU

(7) a description of the specific way the ACNU is operationalized

Drug X

- **Indication:** 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
- **ACNU Necessity:** robust self-selection and label comprehension studies demonstrated that consumers cannot self-select Drug X with labeling alone
  - Consumers could not calculate their risk of developing side effect E
- **ACNU:** consumer questionnaire on a secure website
- **Consumer Access:** consumer with an acceptable risk score can purchase Drug X on the applicant's secure website

Statement Regarding Purpose of ACNU (Proposed § 314.56(c)(1)(i))

- Statement indicated whether ACNU is intended for:
  - Self-selection
  - Actual Use
  - Self-selection and actual use

Statement of the Necessity of the ACNU (Proposed § 314.56(c)(1)(ii))

- Explain why the ACNU is necessary to ensure self-selection, actual use, or both
  - Explain why labeling alone is not sufficient
  - Include summary of adequate data or other information in the NDA

Description of how the ACNU ensures Self-selection, Actual Use, or Both (Proposed § 314.56(c)(1)(iii))

- **Drug X**
  - Describe that the ACNU requires a consumer to complete a questionnaire that would assist in calculating a consumer's risk score for developing side effect E
  - Justify the appropriateness of the of the self-selection questions
    - Criteria and/or considerations used to calculate the risk score of the consumer
    - Description of the algorithm in the underlying program or other operating information used by the website to calculate the risk score
  - Describe how the consumer with an acceptable risk score can purchase

Description of the Key Elements of the ACNU (Proposed § 314.56(c)(1)(iv))

1) The additional condition(s) implemented by the applicant to be fulfilled by the consumer to be able to obtain or use the nonprescription drug product with an ACNU condition(s) implemented

2) The labeling specifically associated with the ACNU

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

Adequate Data or Other Information that Demonstrate the Necessity of the ACNU (Proposed § 314.56(c)(1)(v))

- Include data or other information that demonstrates the necessity of the ACNU to ensure self-selection or actual use, or both
  1) Applicant must conduct or reference adequate testing to show that labeling alone is not sufficient or
  2) Submit information explaining the necessity of the ACNU when FDA previously signaled that labeling alone was not sufficient (e.g. FDA previously approved a nonprescription drug product for the same indication with a similar ACNU)

Adequate Data or Other Information that Demonstrate the Effect of the ACNU (Proposed § 314.56(c)(1)(vi))

Data must show that consumers can self-select or use the drug product safely and effectively with the ACNU

Description of the Specific way the ACNU is Operationalized (Proposed § 314.56(c)(1)(vii))

- ACNU can be operationalized in different ways provided it reliably meet the objective
  - Drug X's ACNU is operationalized by the administration of a questionnaire on the website
  - Drug X's ACNU might include the following alternatives to the way the ACNU is operationalized:
    - A display screen at a pharmacy kiosk
    - A mobile application
    - Automated telephone response system

Refusal to Approve an Application with an ACNU (Proposed §§ 314.125(b)(20) and 314.127(a)(15))

- FDA would refuse to approve an NDA for a nonprescription drug with an ACNU if:
  - NDA fails to meet the requirements in 21 CFR 314.56 applicable to NDAs
  - FDA determines that labeling is sufficient to enable self-selection and actual use
- FDA may approve the NDA with technologies (e.g., a mobile application) that do not meet the definition of an ACNU

Specific Requirements for ANDA for a Nonprescription Drug Product with an ACNU (Proposed § 314.56(c)(2))

(1) state the purpose of the ACNU (the same purpose as the ACNU for the RLD),

(2) include information demonstrating that the key elements of the proposed ACNU are the same as the key elements of the ACNU for its RLD, and

(3) include information on the way the ANDA applicant intends to operationalize the proposed ACNU

- If an applicant proposes to operationalize the ACNU in the same way as the RLD (*e.g.,* both use a mobile application), the ANDA must include information demonstrating the operationalization of the ACNU is the same as the RLD
- If the applicant proposes a different way to operationalize the proposed ACNU, the ANDA must include information to show that this different operationalization of the proposed ACNU achieves the same purpose as the ACNU for its RLD and the differences from the RLD are otherwise acceptable in an ANDA

Simultaneous Marketing (Proposed § 314.56(d))

- A prescription drug product and a nonprescription drug product with an ACNU that contain the same active ingredient could be *simultaneously marketed* even if the two products do not have other meaningful differences, such as different indications or strengths

- ACNU = Meaningful Difference

HIGHLIGHTS OF PROPOSED LABELING REQUIREMENTS FOR A NONPRESCRIPTION DRUG PRODUCT WITH AN ACNU

General Labeling Requirements (Proposed § 201.67(c))

- A nonprescription drug product with an ACNU:
  - Must comply with applicable labeling requirements for nonprescription drug products under 21 CFR part 201, including the DFL requirements
  - May be approved with additional labeling that supplements the DFL

Required Labeling Statement in DFL (Proposed § 201.130(a)(1))

- The labeling for all nonprescription drug products approved with an ACNU to include the following statement as the first statement under the heading “Directions” in the DFL:

  “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.”

ACNU Statement
(Proposed § 201.130(a)(2) and 201.67(d))

- The following statement must appear on principal display panel and the immediate container surface that the consumer is most likely to view when seeking information about the drug product:

  "**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.**"

Exemption from Adequate Directions for Use (Proposed § 201.130)

- Nonprescription drug products with an ACNU would be exempt from the statutory requirement for adequate directions for use, if certain conditions are met
  - Section 502(f)(1) of the FD&C Act requires that drug products need to be labeled with adequate directions for use, but FDA may exempt certain drug products through regulation
  - A drug product can only be approved with an ACNU if labeling alone is insufficient to ensure self-selection or actual use, or both.
- FDA has proposed that labeling and the ACNU are sufficient to ensure consumers' appropriate self-selection and actual use of the nonprescription product

PROPOSED POSTMARKETING REPORTING REQUIREMENTS FOR A NONPRESCRIPTION DRUG PRODUCT WITH AN ACNU

Reports of Failure in Implementation of the ACNU (Proposed § 314.81(b)(3)(v))

NDA and ANDA applicants would be required to submit a report with information concerning any incident of ***failure in the implementation of an ACNU*** defined as

- any event that results from a deviation in an applicant's implementation of the ACNU that may cause or lead to inappropriate medication use or consumer harm such as
  - (1) the consumer accessed or used the drug product without successfully fulfilling the ACNU,
  - (2) the consumer successfully fulfilled the ACNU but could not access or appropriately use the drug product in the nonprescription setting, or
  - (3) the consumer was unable to make an attempt to fulfill the ACNU due to systematic, technological, or mechanical errors in the implementation of the ACNU

Public Comment Period

- Closed November 28, 2022
- Federal Register notice (87 FR 38313)
  - Docket No. FDA-2021-N-0862
  - https://www.federalregister.gov/documents/2022/06/28/2022-13309/nonprescription-drug-product-with-an-additional-condition-for-nonprescription-use

Challenge Question 1

True or False.

Currently, there are 2 classes of drugs in the U.S. -- Prescription and nonprescription. If the proposed rule is finalized, there will be 3 classes of drugs in the U.S.

Challenge Question 2

True or False.

An ACNU is labeling.

Contact Us

CDER Division of Drug Information:

druginfo@fda.hhs.gov

Resources

- **Press release**
  - https://www.fda.gov/drugs/over-counter-otc-nonprescription-drugs/fda-announces-proposed-rule-nonprescription-drug-product-additional-condition-nonprescription-use
- **Draft guidance**
  - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/innovative-approaches-nonprescription-drug-products
- **Proposed rule**
  - https://www.federalregister.gov/documents/2022/06/28/2022-13309/nonprescription-drug-product-with-an-additional-condition-for-nonprescription-use
- **Docket**
  - Docket No. FDA-2021-N-0862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