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Expanding US OTC Switches Turns On Flexibility In FDA Drug Approval Process And For Consumers

by Malcolm Spicer

"Nonprescription Drug Product with an Additional Condition" for OTC use proposed rule would add to drug firms' workloads for some OTC switches. Along with NDAs, sponsors would need to show a DFI isn't sufficient to ensure a consumer can appropriately self-select and use a drug OTC and how an "additional condition" system would work.

Increasing OTC switches in the US will add "ACNU" to regulatory jargon and flexibility to the Food and Drug Administration's drug approval process, allowing the same ingredient at the same dose to remain available Rx after being approved for nonprescription sales, according to a proposed rule.

The FDA's "Nonprescription Drug Product with an Additional Condition for Nonprescription Use" *proposed rule* published on 27 June – its first proposal after a decade of considering changes targeting making more drugs available OTC, particularly ingredients indicated for chronic conditions – also would add to drug firms' workloads for approval of some OTC switches. (Also see "*Before Asking FDA For Novel OTC Switch, Be Sure DFL Alone 'Can't Get There'*" - HBW Insight, 23 May, 2019.)

Switch sponsors would be required to submit, along with new or abbreviated drug applications, separate documents supporting making drugs available through an additional condition for nonprescription use (ACNU) approval, which will be needed when a firm convinces the agency that labeling on a package isn't sufficient to ensure a consumer can appropriately self-select and use a drug as a nonprescription product.

An ACNU proposal would show "a meaningful difference between a prescription drug product

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and a nonprescription drug product that makes the nonprescription drug product safe and effective for use without the supervision of a healthcare practitioner," states the agency's Center for Drug Evaluation and Research.

Sponsors also must conduct post-market monitoring of products and submit reports to the agency "concerning any incident of failure in the implementation of an ACNU," such as a consumer gaining access to the product despite not fulfilling or meeting ACNU restrictions, "whether or not the failure is associated with an adverse event," the agency says.

Although it's the first proposed rule, the publication isn't the agency's first stemming from its "novel switches" initiative launched in 2012 as a potential for making more drugs available OTC. It published a draft guidance in 2018 suggesting sponsors tap into digital media and other tools to help demonstrate consumers can assess whether an OTC drug is appropriate and they can use it safely *(see related story)*.

Self-Selection Test In Questionnaire

The ACNU component adds a step to the process consumers are expected to follow when determining whether to buy and use an OTC drug.

In addition to information on Drug Facts labels about a product's ingredients, indications and use and warnings against use or about potential side effects, an ACNU switch would provide consumers with a questionnaire as an extended self-selection test to determine whether they should use the product.

Operationalizing: 'Not Key Element Of ACNU'

Operationalizing an ACNU, part of the information the FDA requires from a sponsor, comprises the system and technology used not only to guide a consumer through an extended self-selection step, but also to provide approval the consumer needs to buy a product from retailers.

The CDER grants ACNU switch sponsors room for designing and implementing those operations.

"While it is important for FDA to understand how the ACNU is operationalized because this is part of achieving appropriate self-selection or use, the specific way an ACNU is operationalized is not a key element of the ACNU," the center states.

In addition to administering questionnaire using a website, systems could offer questionnaires pharmacy kiosk on display screens and make it available through mobile applications or through automated telephone response technology.

A consumer's pass to present at the point of sale would be a barcoded voucher printed or downloaded onto a mobile device from the ANCU drug marketer's secure website.

Consumers must respond with specific answers in order to purchase an ACNU OTC drug product.

In its introduction to the proposed rule, the CDER notes examples of a sponsor proposing an ACNU switch requiring a consumer to respond to a set of questions on a test available by either a mobile application or an automated telephone response system, or available at a store's kiosk viewing labeling, such as text or images in a video, describing how to appropriately use the product and to respond to questions to confirm understanding.

"These examples differ in the way the ACNU is operationalized ... but the key elements (including the questions in the questionnaire and responses that ensure appropriate self-selection) remain the same," the center states.

However, it also indicates it anticipates questions on ACNU components moving consumers from selection to purchase. "FDA seeks comment on any unique issues that might arise for retailers or consumers based on the way the applicant operationalizes the ACNU ... e.g., in a store kiosk, online, or otherwise," the proposal states.

Consumers "who prefer to continue interacting with their healthcare providers and obtain the drug by prescription would have" that option after the drug is made available OTC through the ACNU pathway, according to the proposal.

"While FDA would generally expect any technology that is used to operationalize an ACNU to be easily usable to the majority of consumers, there may be some consumers who may not be comfortable using such technology. Continued availability of the prescription drug product would provide greater flexibility in obtaining the drug and enable these patients to continue their care without potential interruption."

Rule Change To Exempt ACNU OTCs From Misbranding Violation

Allowing a drug ingredient to be available Rx and OTC at the same dose and indication and in the same delivery format, a flexibility the CDER notes in multiple references, requires changing the FDA's regulation for drug approvals.

The agency proposes adding Sec. 314.56 to CFR Title 21, part 314, subpart B, to establish additional application requirements for a nonprescription drug with an ACNU approved under an NDA or an ANDA.

The change is needed, the center explains, because separate Food, Drug and Cosmetic Act rules which form a basis for the differences in the agency's regulation of Rx and OTC drugs "effectively [mean] that absent a meaningful difference between the products, simultaneous marketing of two drug products with the same active ingredient as both a prescription and a nonprescription

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drug would result in one of the two products being misbranded."

While Sec. 503(b)(4)(A) of the FD&C Act "requires prescription drug products to bear the 'Rx only' symbol," Sec. 503(b)(4)(B) provides that nonprescription drugs "will be deemed to be misbranded if at any time before dispensing, the label of the drug bears the 'Rx only' symbol," the CDER states.

However, the FD&C Act also provides a pathway for the agency to allow an exemption to the prohibition against simultaneous Rx and OTC approval of the same drug at the same dose.

After 10 Years, US FDA 'Additional Conditions' Proposed Rule Offers 'Novel Switch' Pathway

By Hannah Daniel

27 Jun 2022
Publication of "ACNU" proposed rule wasn't reached in straight line and featured coining another term with more of a regulatory sound, "NSURE," and detours on explaining where the agency wouldn't steer OTC drug manufacturing and marketing.

Read the full article here

Sec. 502(f) deems a drug misbranded when it lacks labeling with adequate directions "necessary for the protection of users," including indications and use instructions and adequate warnings against use, unsafe dosage or methods or duration of administration or application.

Without additional, extra-label information, an ACNU switch wouldn't be packaged with all necessary labeling and would be noncompliant with Sec. 502(f).

The section, however, also provides a solution, the CDER states.

Because Sec. 502(f) authorizes "exempting a drug or device from the requirement to bear adequate directions for use upon a determination that such directions are not necessary for the protection," the FDA is proposing exempting OTC drugs approved with an ACNU from the requirement when labeling alone cannot provide adequate directions for use.

Describe ACNU, Prove It Works

In addition to a drug application, sponsors also would be required to submit

Sponsors Must Report 'Implementation' Failures

The CDER also likely anticipates stakeholder questions about the proposed rule's post-market monitoring requirement for ACNU sponsors to "submit a report when a failure in the implementation of an [ACNU] for a nonprescription drug product occurs."

information describing an ANCU and data supporting it.

A description should include statements regarding an ACNU's purpose, key elements and necessity, or why it rather than a conventional DFl is needed; on how it ensures appropriate self-selection or appropriate actual use, or both if needed for a particular application; and on the specifics of operationalizing an ACNU.

The data and information to support the description statements should show an ACNU's effect on appropriate self-selection or appropriate actual use, or both, and that it's needed to ensure for consumers' correct selection and use.

The necessity of an ACNU to ensure appropriate self-selection or appropriate actual use, or both, would be supported from testing conducted or referenced adequate showing labeling alone would not support safe and effective use.

The information could include "robust self-selection studies and label comprehension studies that demonstrate that consumers could not appropriately self-select [an ACNU product] with labeling alone."

An implementation failure "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, regardless of whether they are associated with an adverse event, must be reported to the FDA Adverse Event Reporting System (FAERS). Description of an implementation failure associated with a prior adverse event can be reported to FAERS in a single individual case safety report (ICSR).

If a report previously submitted to FAERS describes only a implementation failure or an ICSR reports only an adverse event, and an associated adverse event or implementation failure become known, a firm must supplement its original report to FAERS with additional information.

The CDER acknowledges in the proposal, though, that not all consumers will have access to information provided online or through other digital connections or will be comfortable using certain drugs without doctors' referrals.

Sponsors also could submit information about FDA previously signaling labeling alone wasn't sufficient for safe and effective OTC use of a particular drug, the CDER states. This type of proposal "might apply if FDA has previously approved multiple nonprescription drug products for the same indication with a similar ACNU."

Data or other information supporting an ACNU's effect on selection and use must show consumers can appropriately self-select or use the drug product safely and effectively, or both,

with the ACNU. The CDER notes as an example, a sponsor submitting "adequate data from robust self-selection studies that demonstrate that consumers could appropriately self-select [a drug] with the ACNU."

The FDA asks for comments on the proposed rule – docket FDA-2021-N-0862 – to be submitted within 120 days of its publication in the Federal Register, scheduled for 28 June.

HBW Insight will publish additional articles about requirements of the "Nonprescription Drug Product with an Additional Condition for Nonprescription Use" proposed rule and stakeholders' response to it.