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The Nucleus: Life Sciences Regulation and Enforcement Updates

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The Commercial Potential — and Practical Challenges — of Marketing OTC Drugs With 'Additional Conditions for Nonprescription Use'

The Food and Drug Administration's (FDA or Agency) final rule on Additional Conditions for Nonprescription Use (ACNU) paves the way for some drugs that are currently available only with a prescription to switch to OTC where a patient satisfies certain conditions.

However, there will be practical challenges to marketing these products:

- Screening patients for eligibility will require manufacturers to adopt innovative approaches.
- Restricting sales to eligible customers could impose staffing and other costs on pharmacies and other retailers.
- In practice, retailing the new category of drugs could be further complicated because the brand and generic are not required to have the same ACNU, and the final rule also allows for simultaneous marketing of prescription and OTC-with-ACNU versions of the same drug.
- FDA has been attempting to implement ACNU since 2012, and the final rule, issued in December 2024 (Final Rule), reflects significant stakeholder engagement on the myriad legal questions it raises.

While there certainly are particular classes of drugs that will benefit from the option of becoming OTC with ACNU, the practicalities of bringing these products to market will require manufacturers to weigh several strategic factors. In this article, we explore some of these considerations, including some of the key business and legal implications of this new product category:

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Background on ACNU

The market for OTC drugs in the U.S. was estimated at $43.4 billion in 2023. Over the past 20 years, many categories of drugs have successfully made the prescription-to-OTC switch, including modern allergy medicines, laxatives, overactive bladder medications, nasal corticosteroids, the morning-after pill, opioid overdose reversal medication and progesterone-only oral contraceptives. However, there are other categories of prescription drugs that sponsors and FDA believe should be available OTC, but that have not been able to make the switch due to lurking safety issues. These include: antibiotics, estrogen-containing oral contraceptives, statins, PDE-5 inhibitors for erectile dysfunction, albuterol inhalers, insulin and metformin, among others. Enter ACNU.

As noted above, FDA has been exploring this potential OTC category since 2012, when it hosted a public hearing on "Using Innovative Technologies and Other Conditions of Safe Use to Expand Which Drug Products Can be Considered Nonprescription" (77 FR 12059). FDA also issued a 2018 Draft Guidance for Industry on "Innovative Approaches for Nonprescription Drug Products" (83 FR 33938), which included suggestions similar to those ultimately adopted in the Final Rule. Indeed, prior to the Final Rule, FDA created a separate initiative under another unusual acronym — NSURE (the Nonprescription Drug Safe Use Regulatory Expansion) — and held workshops with the Brookings Institution to receive stakeholder feedback on the concept.

Under the Final Rule, FDA will allow a sponsor to make the switch from Rx to OTC, or even pursue the OTC market *de novo*, as long as the sponsor can demonstrate that any safety issues not addressed by the OTC Drug Facts Labeling (DFL) alone are addressed by an "additional condition." In its 2018 guidance, FDA provided the following examples of what the Agency believes would constitute an "additional condition":

- Prior to purchase, the consumer is required to respond to a set of questions on a self-selection test in a mobile application, and the outcome of the self-selection test affirmatively indicates that the consumer is an appropriate candidate to use the nonprescription drug product.
- Prior to purchase, the consumer is required to view and affirm that they viewed text or images in a video that describes how to appropriately use the nonprescription drug product.

In the proposed rule on ACNU issued in June 2022, the Agency provided a more in-depth hypothetical of an imaginary nonprescription drug product that is only safe for patients who do not have a high risk of developing a serious side effect. According to the hypothetical, when developing the drug, the sponsor conducted self-selection and label comprehension studies that demonstrated that consumers could not appropriately determine whether they were at risk of developing the serious side effect based on the DFL alone.

That's where the ACNU comes in. In FDA's hypothetical, the ACNU is a "questionnaire located on a secure website." The consumer answers questions that are then analyzed by an "underlying program or other operating information" to calculate a "risk score" to determine if the consumer should purchase the drug. If the ACNU determines the consumer can safely do so, the consumer would then be able to purchase the drug directly from the manufacturer via the website hosting the questionnaire, or "at a retail site specified by the applicant after presenting a barcoded voucher that can be printed or downloaded onto the consumer's mobile device from the applicant's secure website."

ACNU could be a game-changer for some products because it would allow consumers OTC access to products that otherwise would have to remain prescription-only. But, as FDA acknowledges, bringing this vision to life presents numerous real-world operationalization challenges that will require creativity on the part of the drug sponsor as well as the retail pharmacies and grocery stores where most OTC products are purchased.

The Final Rule also introduces some interesting strategic questions that sponsors considering the ACNU pathway will have to grapple with. As discussed further below, these include:

- The value of three-year exclusivity.
- Genericizing approved OTCs with ACNU.
- The possibility of simultaneous marketing of OTCs with ACNU and generic prescription versions of the same drug products due to a "meaningful difference" between the products.
- Potential new product liability issues given new labeling requirements for OTCs with ACNU.

Impact on the Retail Sector

While OTC drugs are most often purchased at pharmacies, they are available throughout the retail sector at more than 750,000 outlets in the U.S. that sell OTC drug products. The sale of OTC drugs with ACNU will present logistical burdens for pharmacies and other retail outlets as these products must be inaccessible to customers who have not completed the ACNU. The easiest and least burdensome way for retailers to handle products with ACNU may be through a register block, which would require the ACNU to be presented before purchase. This has worked well for dextromethorphan (a common ingredient in cough medicine) and nicotine replacement therapy, which are age-restricted in certain states.

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Other options envisioned by FDA in the Proposed and Final Rules include storing OTC drugs with ACNU (1) in an automated kiosk that only dispenses the product when presented with a barcode obtained by adequately completing the ACNU, or (2) behind the pharmacy counter or in a locked area that can be accessed by a pharmacist or retail associate.[1]

While FDA assumes that the ACNU itself will be sufficient without additional help from retail associates, the options the Agency proposes unquestionably place a burden on retailers, especially those that sell more than one product subject to an ACNU, or sell similar products subject to different ACNUs (more on that later). Indeed, unless register blocks are feasible, the anticipated system is unlikely to be as fair as FDA envisions, as retailers will likely be unwilling to give up coveted floor space to multiple kiosks for the same drug or agree to pharmacists or retail associates spending additional time helping customers access these products.

Similar time commitments are required under state test-and-treat laws that allow pharmacists to prescribe medication after a rapid diagnostic test for things like strep and flu. However, pharmacists can seek reimbursement for the prescribing service they perform under these laws.

The Final Rule does not consider the potential business impacts that products with ACNU may have on pharmacies and retail stores. Consequently, it remains to be seen whether and how they will impact the dynamic between these retailers and manufacturers of OTC drugs with ACNU. While a manufacturer may be able to meet the regulatory standard for the ACNU, to successfully merchandize an OTC drug with ACNU, manufacturers will be required to get creative to ensure ease of access as well as frictionless operations at retail to make their products an attractive alternative.

Multiple ACNUs for the Same Product

In comments on the proposed rule, retailers asked FDA to clarify "whether consumers who satisfy the ACNU for the reference listed drug (RLD) (*i.e.*, branded drug product) could purchase the generic product" based on customer preference or product availability. Retailers also urged FDA to "only approve technology-neutral ACNUs and limit the proliferation of excessive proprietary platforms," noting that it might be difficult for pharmacies and other retailers to accommodate many different mechanisms. Comments from generic manufacturers also asked FDA to consider requiring shared ACNU in the same way that FDA requires shared-system Risk Evaluation and Mitigation Strategies (REMS).

FDA rejected these proposals in the Final Rule, instead requiring a distinct ACNU for each identical product from different manufacturers. As a result, if a brand product is introduced with ACNU, follow-on generics of the same product will have to develop their own ACNU. While FDA stressed that this approach was intended to allow generic manufacturers to "operationalize the ACNU in a different manner than the RLD," this requirement is likely to create a number of complications that are not addressed in the Final Rule.

In practice, requiring a different ACNU for each manufacturer of identical products could create confusion among consumers and increase the burden on the retailers. For instance, customers may complete the ACNU for the brand product but prefer to buy the generic/private brand due to price, or arrive at the store to find that the brand is not available, only to be required to complete a second ACNU prior to purchase. A similar challenge also may arise if a consumer regularly purchases an OTC drug with ACNU from one manufacturer and is required to repeat the ACNU prior to repurchase.

Although FDA notes that "we expect that a consumer who can fulfill the brand drug's ACNU would also be able to fulfill the generic drug's ACNU," this does not account for the consumer experience. Not only is the experience of completing multiple ACNUs likely to be frustrating for the consumer, it also may require additional training for retail associates or pharmacists to confirm customers have completed the correct ACNU for the product on hand. And, if a manufacturer chooses to use a kiosk to dispense an OTC drug with ACNU (consistent with one of FDA's suggestions), retailers may have to accommodate multiple kiosks to dispense identical products.

For all of these reasons, achieving sustainable access and competition in this space will require manufacturers to develop a specialized strategy to educate consumers and partner closely with retailers.

Impact on Generic Competition

In the past, an Rx-to-OTC switch has been an elegant lifecycle management tactic for branded drugs. The studies required to support an Rx-to-OTC switch — Label Comprehension and Actual Use Studies — qualify for three-year new clinical investigations exclusivity, but they are significantly less expensive than a Phase 3 clinical trial. In addition, an Rx-to-OTC switch can be effectuated via an efficacy supplement, which converts the entire New Drug Application (NDA) to nonprescription status and thus requires any Abbreviated New Drug Applications (ANDAs) referring to the switched NDA to convert to OTC status.

[1] Retailers have historically found that locked cabinets are disincentives for customers.

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Through the combination of these two mechanisms, a brand can achieve three years of market exclusivity without OTC or prescription generic competition. ACNU is poised to dramatically change this landscape, thereby requiring considerable strategic analysis for manufacturers contemplating an Rx-to-OTC switch.

Meaningful Difference

FDA has long interpreted Section 503(b) of the Food, Drug, and Cosmetic Act (21 U.S.C. §355(b)) to preclude the same active ingredient to be simultaneously marketed in both a prescription drug product and an OTC drug product, unless a "meaningful difference" exists between the two that makes the prescription product safe only under the supervision of a licensed practitioner. The issue of what constitutes a "meaningful difference" came to a head in connection with the Rx-to-OTC switch of the brand PEG 3350 laxative product. When FDA moved to withdraw the prescription ANDAs through a Notice of Opportunity for a Hearing (NOOH), the ANDA holders argued to FDA that differences in the conditions of use of the Rx and OTC products constituted a "meaningful difference" that would allow the ANDAs to remain prescription-only.

FDA denied the ANDA holders' request for a hearing and withdrew the ANDAs, noting that:

> The factors FDA generally considers in determining whether there is a meaningful difference are indication, strength, route of administration, population, and dosage form. As the labeling for the prescription and nonprescription PEG 3350 products shows, they have the same indication, strength, route of administration, population, and dosage form. As explained in the NOOH, if FDA were to include the differences between prescription and nonprescription labeling requirements as a factor in determining whether there is a meaningful difference sufficient to allow the same active ingredient to be marketed in prescription and nonprescription products, FDA would never be able to exempt a drug product from the prescribing requirements of section 503(b). This result would be in contravention of the plain language of section 503 of the FD&C Act and the purpose of Congress in enacting that provision.

FDA encountered a similar issue when naloxone 4 mg nasal spray converted from Rx to OTC status. In that case, FDA preemptively issued a Federal Register notice in advance of the RLD's switch, stating "at this time, we do not believe that any clinically meaningful differences could exist between currently approved prescription and potential nonprescription naloxone nasal spray products (up to 4 mg), or between currently approved prescription and potential nonprescription naloxone autoinjector products (up to 2 mg)." This declaration from the Agency was a signal to the approved naloxone 4 mg nasal spray ANDA products that they would need to switch to OTC status when the naloxone NDA switched. The naloxone NDA did switch to OTC in March 2023.

In the Final Rule, FDA takes a dramatically different approach with ACNU. The Agency, in an attempt to preserve generic competition and avoid some of the challenges in genericizing a product with ACNU (discussed further below), declared that ACNU constitutes a "meaningful difference" that will allow for simultaneous marketing of an OTC drug with ACNU and prescription-only generic versions of the same product, "even if they do not have other meaningful differences, such as different indications or strengths." In other words, if the brand switches to OTC with ACNU, generics may remain Rx-only.

Resulting Lifecycle Management Considerations

This differing approach appears driven by a policy choice. In the preamble to the Final Rule, the Agency explains that, "while many consumers will benefit from the availability of nonprescription drug products with ACNUs, FDA also recognizes that some may not be able to access the nonprescription drug product with an ACNU. For example, a consumer may not be able to access the technology that operationalizes the ACNU. Therefore, continued availability of the prescription drug product along with the nonprescription drug product with an ACNU promotes the greatest access to needed drug products."

Regardless of the motivation, the Agency's approach to meaningful difference is likely to render an Rx-to-OTC switch involving ACNU much less attractive as a lifecycle management option. Especially considering the expanded availability of telehealth, it is unclear if obtaining a prescription will actually be more arduous than meeting the ACNU requirements as FDA envisions. OTC drugs also generally are not reimbursed by insurance and can be significantly more expensive than a prescription generic, which may lead patients with insurance to continue to opt for the generic Rx-only option. And, while ACNU will still likely garner three years of market exclusivity, that would only block the approval of other OTC drug products with the same ACNU and will not stop the marketing of prescription generics. Finally, FDA will require a separate application (rather than an efficacy supplement) — and sponsors will therefore have to pay a full Prescription Drug User Fee Amendments (PDUFA) fee — to switch a drug from prescription to OTC with ACNU.

Taken in combination, these factors may make the ACNU pathway less appealing to brand manufacturers.

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Combination Product, Device and IP Issues

Even though FDA has preserved the option for Rx-only generics to remain on the market once an OTC with ACNU is approved, there may be reasons for a sponsor to seek approval of a generic OTC drug with ACNU. Generics can potentially earn 180 days of marketing exclusivity for being the first generic approved, if their sponsors have challenged patents. But there are a number of IP-related considerations presented by ACNU that could impact the generic path to market:

- Brands may choose to design their ACNU as medical devices, triggering combination product requirements for ANDAs. Regardless, FDA confirms that OTC drugs with ACNU will be drug-led combination products.
- If an ACNU is considered a medical device, it also may have patents appropriate for listing in the Orange Book (although the FTC has recently challenged improper device listings in the Orange Book and courts have agreed).
- ACNU are similar conceptually to REMS with Elements to Assure Safe Use (ETASU). In many cases for REMS products, the brand chooses to patent the REMS and list those patents in the Orange Book. This has been a successful strategy to protect a product beyond just the patents on the drug formulation or method of use.
- If the brand lists any device or ACNU patents in the Orange Book, generics would be required to either challenge, design around, or wait for those patents to expire before coming to market.

FDA has made clear that "the ACNU can be operationalized in different ways provided it reliably meets the objective." While generics may be able to easily design around any ACNU patents listed in the Orange Book, this also raises the questions related to consumer confusion discussed above.

In addition, the cost to individually operationalize an ACNU on top of the cost of patent litigation may be too high to justify pursuing generic entry. However, there may be unique opportunities for private brand products in this space since retailers could work with the manufacturer to design an ACNU that works best for their system and associates, which would make the opportunity more attractive for generic manufacturers.

Labeling and Product Liability

The Final Rule establishes a few specific labeling requirements for OTC drugs with ACNU. These products must contain both:

- The ACNU Instruction (in the Drug Facts Label): "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"; and
- The ACNU Statement (on the principal display panel (PDP) and immediate container): "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"

The Final Rule also specifies the format for the ACNU Statement, requiring that it be:

- On the PDP and the immediate container surface that the consumer is most likely to view when seeking information about the drug product, including the bottle or blister pack.
- In boldface and black type.
- In a yellow background banner alone.
- In 12-point font or font that is 25% as large as the largest font on the PDP, whichever is greater.

Because these requirements are written into FDA's regulations, the labeling will be approved as part of the NDA or ANDA and FDA will evaluate the adequacy of the ACNU as part of the review process. This review will presumably give OTC drugs with ACNU greater preemptive protection from a product liability standpoint than OTC monograph products currently enjoy.

However, in the Final Rule, FDA explains that it is requiring the ACNU Statement to be in black font with a yellow background because it wants "consumers to know that there is something different about an ACNU drug product." In particular, FDA explains that the goal of the ACNU Statement is "to provide immediate notice to consumers and for other people who may have access to the drug product ... but did not fulfill the ACNU" that the "drug may not be right for that person and using the drug product without fulfilling the ACNU could put the person at risk for side effects and medication errors."

This explanation highlights interesting product liability considerations relating to ACNU products given that, once they are outside the retail setting, they may be accessible without fulfilling the ACNU. Unlike other OTC drug products, which are intended to be used safely by any consumer pursuant to the DFL, OTC drugs with ACNU are not necessarily safe for anyone to use. In addition, retailers who choose to develop private brand products with ACNU — especially if the ACNU is proprietary to their system — should be aware of heightened product liability exposure associated with OTC drugs with ACNU versus those without.

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Retailers also will want to update their compliance programs to mitigate the risk of customers inappropriately accessing products subject to ACNU, which also could carry product liability exposure. Without appropriate training and controls, associates may inadvertently allow customers who have not adequately fulfilled the ACNU to purchase a product, exposing the customer to risks the labeling was intended to avoid.

Conclusion: The Business Case for ACNU

While the discussion above highlights the many complications that ACNU may present, there certainly are drugs for which OTC with ACNU may be an attractive option, such as older off-patent branded drugs or generics that have an established safety record and use case. There likewise are products that would be especially beneficial for uninsured or under-insured patients to be able to access OTC. For instance, the likely front-runner for a switch from Rx-only to OTC with ACNU is estrogen-containing birth control, which carries a boxed warning regarding cardiovascular risks for patients who are over 35 and smoke. It seems possible to imagine an ACNU that could manage this risk by asking patients their age, if they smoke, and requiring them to get their blood pressure taken before accessing the product.

Switching an older, genericized product to OTC with ACNU could well present business upside, including a new patient population and new pricing for the OTC market. Especially for a drug with an established safety profile, the process to switch to OTC with ACNU would involve Label Comprehension and Actual Use studies, and therefore would result in three years of OTC exclusivity without requiring expensive clinical trials. If the manufacturer also was able to tailor the ACNU to a branded and white-label format, it could minimize friction with retailers while capturing more of the market because the branded and private label products could either share an ACNU (even if just on the back end), or it may limit the overall number of OTCs with ACNU.

It is clear from FDA's enthusiasm for ACNU that it has some drugs in mind for this category, so we may see the potential benefits and challenges of the category begin to play out in the real world very soon.