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A New Day (And A New Acronym) For OTC Drugs

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The expansion of over-the-counter ("OTC") drug options has been a long time coming. Advocates in various fora, including within the U.S. Food and Drug Administration ("FDA" or the "Agency"), have focused on the potential for OTC medications to increase available, affordable options for patients.[1]

FDA has long been cognizant that the availability of OTC drugs is limited by both the rigid and decades-old OTC monograph framework and the understanding that certain types of prescription medicines could only be "switched" to OTC if novel mechanisms (*e.g.*, pharmacy kiosks or Internet questionnaires) can enable consumers' self-selection and safe use. FDA convened a public meeting in 2012 to discuss ways of "Using Innovative Technologies and Other Conditions of Safe Use to Expand Which Products Can Be Considered Nonprescription."[2] In 2018, FDA issued a draft guidance on Innovative Approaches for Nonprescription Drug Products (referred to as "NSURE") acknowledging that certain types of prescription medicines could be "switched" to nonprescription OTC use if manufacturers could identify such self-selection and safe use tools.[3] More recently, the 2020 CARES Act "reform[ed] and moderniz[ed] the way OTC monograph drugs are regulated in the United States," creating a user fee program for OTC monograph drugs ("OMUFA") and a new "administrative order process for issuing, revising, and amending OTC monographs."[4] The CARES Act did not, however, take on this additional issue.

Last month, on June 28, 2022, FDA issued a proposed rule, "Nonprescription Drug Product With an Additional Condition for Nonprescription Use," which seeks to establish requirements for nonprescription drug products with an additional condition for nonprescription use ("ACNU"). In short, ACNU stands for a drug product that may be marketed OTC if a manufacturer implements an additional condition to ensure appropriate self-selection and/or appropriate actual use by consumers without the supervision of a healthcare practitioner.[5]

Many questions spring to mind when confronted with this new concept (and its new acronym). We unpack some of those, below.

A. WHAT'S AN ACNU?

Currently, most OTC drugs are limited to those that can be labeled with sufficient information—within the limited space of a Drug Facts Label—to enable consumers both to "self-select" (*i.e.*, decide whether to use the drug product) and to use the drug product safely and effectively without the supervision of their healthcare practitioner.[6] In an apparent effort to spur additional development of OTC products, FDA has proposed a pathway for applicants to seek to market nonprescription drug products for which labeling alone may be insufficient to help consumers self-select and safely use OTC drugs.[7] FDA intends to define ACNUs broadly to offer applicants flexibility with respect to the types of "additional conditions" they may propose and how to implement them.[8] For example, an ACNU may require a consumer to complete a questionnaire using a mobile application or automated telephone response system, or to review labeling that describes how to appropriately use a nonprescription drug product and then respond to questions that verify their understanding.[9]

B. WHAT'S IN AN ACNU NDA?

The proposed rule is not related to the OTC monograph system. Instead, FDA seeks to establish a pathway for an applicant to submit a New Drug Application ("NDA") seeking approval for OTC marketing of a drug if it can demonstrate that: (1) the Drug Facts Label is insufficient to ensure a consumer could appropriately self-select and/or appropriately use the drug product without the supervision of a healthcare practitioner; (2) one or more ACNUs can enable self-selection and safe use; and (3) the ACNU(s) are necessary for such self-selection and safe use.[10]

The applicant of a nonprescription drug product with one or more ACNUs must file a separate NDA—even if the applicant is the holder of an NDA for an approved prescription drug product with the same active ingredient.[11] Importantly, this separate application requirement means that an NDA-holder can continue marketing the prescription drug product under the original NDA *and* an OTC drug product under the ACNU NDA, because the ACNU would be considered a meaningful difference between the prescription drug product and the nonprescription drug product—even if the drug products are otherwise the same.[12]

In addition to applicable, existing application requirements, an ACNU NDA must:

- State the purpose of the ACNU(s) (*i.e.*, appropriate self-selection and/or actual use by consumers without the supervision of a healthcare provider);[13]
- State the necessity of the ACNU(s) (*i.e.*, why labeling alone is insufficient)[14] and conduct or cite adequate testing to demonstrate the necessity of the ACNU(s) or, in instances when FDA has previously indicated that labeling would be insufficient to ensure appropriate self-selection and/or use, submit other information explaining the necessity of the ACNU for appropriate self-selection and/or use;[15]
- Describe the appropriateness of the ACNU(s) to ensure appropriate self-selection and/or use[16] and provide data or other information that demonstrates the effect of the ACNU(s) on consumers' ability to self-select and/or use the ACNU product safely and effectively;[17]
- Describe the key elements of the ACNU(s) (*e.g.*, the condition(s) implemented by the applicant to be fulfilled by the consumer, the labeling specifically associated with the ACNU(s), and the criteria used to evaluate whether the consumer satisfies the ACNU(s));[18] and
- Describe the specific way the ACNU(s) would be operationalized (*e.g.*, an ACNU that requires the administration of a questionnaire may be operationalized using a mobile application).[19]

We note that, although the proposed rule does not explicitly address what data or other information could support an ACNU, buried in the Preliminary Regulatory Impact Analysis ("PRIA"), FDA provides a glimpse of its expectations,

particularly with respect to technology-based ACNUs.[20] Specifically, FDA notes that one or more of the following would be needed:

- *Human Factors Studies*. Although performed infrequently for most nonprescription drug product applications, such studies would be necessary to elucidate interactions between consumers and the ACNU technology.
- *Actual Use Studies*. FDA anticipates that actual use studies would typically be longer and more complex for an ACNU product.
- *Self-Selection and Labeling Studies*. While the number of studies would likely not change, the complexity or nature of the study could increase.[21]

C. WHAT ABOUT AN ACNU ANDA?

Under the proposed rule, an ACNU NDA drug can serve as a reference listed drug ("RLD") for an Abbreviated New Drug Application ("ANDA"). As with NDAs, a separate ANDA would be required, even if the applicant is the holder of an approved ANDA for the prescription drug product, and that ANDA must:

- State the purpose of the ACNU(s) (*i.e.*, the same purpose as the ACNU(s) for the RLD);[22]
- Describe the key elements of the ACNU(s) that demonstrate they are the same as the RLD;[23] and
- Describe the specific way the ACNU(s) is operationalized with respect to the RLD.[24]

With respect to this last requirement, however, specific ways to operationalize ACNUs would not be considered "key elements" of the ACNU and otherwise are not considered a condition of use of the drug product. That means an ANDA applicant need not operationalize its ACNU in the same way as the RLD. Indeed, ANDAs may differ in operationalization when an NDA applicant operationalizes its ACNUs using proprietary means.[25] However, the ANDA must include information to show that, as operationalized, the proposed ACNU achieves the same purpose as the RLD and that the differences from the RLD are otherwise acceptable in an ANDA.[26]

D. HOW IS AN ACNU LABELED?

Certain labeling is envisioned for ACNU products under the proposed rule, in addition to existing labeling requirements. A nonprescription drug can only be approved with an ACNU if labeling alone is insufficient to ensure appropriate self-selection and/or actual use.[27] Therefore, by definition, it is not possible for these products to be labeled with adequate directions for use, as required under section 502(f) of the FD&C Act.[28] However, as explained in the proposed rule, given that the labeling and the ACNU together are sufficient to ensure appropriate self-selection and actual use, labeled directions alone would not be necessary for protection of the public health. Accordingly, under the proposed rule, FDA would exercise its authority to exempt nonprescription drug products approved with an ACNU from this statutory requirement if they include specified labeling.[29]

Therefore, an ACNU NDA or ANDA must include pre-specified statements that are intended to inform consumers that the OTC product includes an ACNU, instruct consumers how to fulfill the ACNU, and notify consumers that the product is not suitable for all persons and should only be used after fulfilling the ACNU.[30] For example, an ACNU label must include a statement under the heading "Directions," that says "[t]o check if this drug is safe for you, go to [insert where or how consumers can find information about the ACNU; for example, applicant's website, applicant's phone number, or specific retail location] and [insert action to be taken by consumer]. Do not take this drug without completing this step."[31] And, on the principal display panel and the immediate container surface that a consumer is most likely to view: "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."[32]

E. ARE THERE SPECIAL POSTMARKET REPORTING REQUIREMENTS?

The proposed rule would require the NDA- or ANDA-holder to submit postmarketing reports through the FDA Adverse Event Reporting System to inform the Agency about any "incident of failure in the implementation of an ACNU," including "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," regardless of whether the incident is associated with an adverse event.[33] This would include, for example, a consumer obtaining access to the ACNU product without first fulfilling the ACNU; a consumer fulfilling the ACNU conditions but failing to access or appropriately use the drug in a nonprescription setting; or a consumer being unable to meet the FDA-approved conditions due to a systematic, technological, or mechanical error in the applicant's implementation of the ACNU.[34] As acknowledged by FDA, quality assurance systems would likely be needed to capture these failures. However, neither the rule nor the PRIA account for such costs beyond the reporting requirements.

F. IS THERE EXCLUSIVITY FOR ACNU PRODUCTS?

The proposed rule is conspicuously silent on issues pertaining to exclusivity. Consistent with the way that FDA has handled exclusivity determinations in the context of Rx-to-OTC switches, we would expect ACNU NDAs to be eligible for 3-year, new clinical investigation exclusivity, presuming the applicable requirements are met. Additionally, given the rule's requirement that a drug product can only be approved with an ACNU if labeling alone is insufficient, a clinical investigation to support the necessity of the ACNU—even if no clinical investigation were conducted on the effect of the ACNU on appropriate self-selection and/or actual use—could arguably support such exclusivity.

Another unanswered question concerns eligibility for 180-day exclusivity for ACNU ANDAs—for example, whether an ACNU ANDA containing a paragraph IV certification could give rise to 180-day exclusivity even if the referenced drug product were originally approved as a prescription drug product. The proposed rule's requirement for the submission of a separate NDA and its position that the prescription drug product and nonprescription drug product with an ACNU are considered two different products, hint strongly that eligibility for 180-day exclusivity is on the table.

G. WHAT ABOUT BIOLOGICS?

As with importation,[35] the 505(b)(2)-type biologics license application ("BLA") pathway,[36] and other issues, it seems that biologics are not getting invited to the ACNU party. That may not be an oversight: OTC biologics may feel like a bridge too far already, let alone OTC biologics with specialized mechanisms for self-selection and consumer use. Then again, remember that since the Biologics Price Competition and Innovation Act NDA-to-BLA "transition" in March 2020,[37] the category of biologics has included insulin and insulin analogs (a small number of which already are approved as nonprescription), human growth hormones, pancreatic enzymes, and reproductive hormones. Maybe some of these types of products would like access to the ACNU pathway—if not now, then eventually. And is not too hard to imagine a near-term future in which a well-understood monoclonal antibody with decades-old history of safe use could be made available OTC with the right ACNU?

H. CONCLUSION

FDA has said that it does not expect a wave of ACNU drugs, at least initially,[38] but the creation of what is essentially a new approval pathway (albeit created through regulation) is still a sea change. The new pathway may hold great promise, particularly as more drug sponsors look to push into the OTC realm.

Of course, we can also imagine myriad complexities that will play out as the ACNU pathway unfolds. For example, the increasing use of technology and its integration into drug development is not limited to ACNUs or to the OTC space. It will be very interesting to see how this approach dovetails with FDA's thinking regarding prescription drug use related software ("PDURS"), guidance for which is expected this year.[39] It also demands consideration of how high-tech or more

complex access aligns with efforts to reach underserved populations. We also expect myriad procedural challenges to arise. For example, the hazy line between "key elements" and operationalization, as well as the fuzzy concept of "achiev[ing] the same purpose" seem ripe subject matter for litigation and 505(q) petitions.[40]

It will be absolutely critical for stakeholders to engage and to help FDA shape the final rule appropriately so that the ACNU NDA and ACNU ANDA can be the best possible tools with the least fallout to other programs.

King & Spalding LLP regularly counsels pharmaceutical manufacturers on drug development and the submission of drug marketing applications to FDA. **Comments on the FDA proposed rule are due on October 26, 2022**. Please let us know if you have any questions regarding this proposed rule, or if you would like to consider submitting a comment.

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[1] *See, e.g.*, U.S. Food & Drug Admin., FDA Statement, FDA Commissioner Scott Gottlieb, M.D., on new efforts to empower consumers by advancing access to nonprescription drugs (July 17, 2018), https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-new-efforts-empower-consumers-advancing-access (positing that FDA is "considering all options for positively impacting both access and the cost of health care," such as "the implementation of additional conditions so that consumers appropriately self-select and use" to "therapeutic indications that have not, historically, been available for use without a prescription"); *Modernizing FDA's Regulation of Over-the-Counter Drugs: Hearing Before the Subcomm. on Health, H. Comm. on Energy and Commerce*, 115th Cong. 1 (2017) (statement of Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research) (recognizing that OTC drugs "have long provided an efficient, low-cost way for Americans" and discussing "potential reforms to the over-the-counter (OTC) monograph system and a new OTC monograph user fee program").
[2] *See* 77 Fed. Reg. 12059, 12059 (Feb. 28, 2012).
[3] *See generally* U.S. Food & Drug Admin., *Draft Guidance for Industry: Innovative Approaches for Nonprescription Drug Products* (July 2018).
[4] U.S. Food & Drug Admin., *Over-the-Counter (OTC) Drug Review: OTC Monograph Reform in the CARES Act*, https://www.fda.gov/drugs/over-counter-otc-nonprescription-drugs/over-counter-otc-drug-review-otc-monograph-reform-cares-act (last updated May 9, 2022).
[5] Nonprescription Drug Product With an Additional Condition for Nonprescription Use, 87 Fed. Reg. 38313, 38314 (proposed June 28, 2022) (to be codified at 21 C.F.R. pt. 201 and 314).
[6] *Id.* at 38315–16.
[7] *Id.*
[8] *Id.* at 38318.
[9] *Id.*
[10] *Id.* at 38316, 38318, 38320; 21 C.F.R. § 314.56(a)(1), (c)(1) (proposed).
[11] 87 Fed. Reg. at 38318; 21 C.F.R. § 314.56(b) (proposed). While the applicant cannot submit a supplement to an approved NDA (if any) for a prescription drug product, it may cross-reference information and studies in the approved NDA. *See* 87 Fed. Reg. at 38318.
[12] 87 Fed. Reg. at 38315–16; 21 C.F.R. § 314.56(d) (proposed). As explained by FDA, the Agency has interpreted section 503(b)(4) of the FD&C Act (21 U.S.C. § 353(b)(4)) to allow simultaneous marketing of drug products with the same active ingredient as prescription and nonprescription drug products if some meaningful difference, such as an indication, strength, route of administration, dosage form, or patient population, exists between the drug products. *See* 87 Fed. Reg. at 38315–16, 38321–22.
[13] 87 Fed. Reg. at 38319–20; 21 C.F.R. § 314.56(c)(1)(i) (proposed).
[14] 87 Fed. Reg. at 38319–20; 21 C.F.R. § 314.56(c)(1)(ii) (proposed).
[15] 87 Fed. Reg. at 38319–20; 21 C.F.R. § 314.56(c)(1)(v) (proposed).
[16] 87 Fed. Reg. at 38319–20; 21 C.F.R. § 314.56(c)(1)(iii) (proposed).
[17] 87 Fed. Reg. at 38319–20; 21 C.F.R. § 314.56(c)(1)(vi) (proposed).
[18] 87 Fed. Reg. at 38319–20; 21 C.F.R. § 314.56(c)(1)(iv) (proposed).
[19] 87 Fed. Reg. at 38319–20; 21 C.F.R. § 314.56(c)(1)(vii) (proposed).
[20] U.S. Food & Drug. Admin., *Nonprescription Drug Product with an Additional Condition for Nonprescription Use: Preliminary Regulatory Impact Analysis*, FDA-2021-N-0862, at 36–37 (June 2022).
[21] *Id.* at 37.
[22] 87 Fed. Reg. at 38321; 21 C.F.R. § 314.56(c)(2)(i) (proposed).
[23] 87 Fed. Reg. at 38321; 21 C.F.R. § 314.56(c)(2)(ii) (proposed).
[24] 87 Fed. Reg. at 38321; 21 C.F.R. § 314.56(c)(2)(iii) (proposed).

[25] 87 Fed. Reg. at 38321.
[26] *Id*.
[27] *Id*. at 38322 ("FDA would refuse to approve an application for a nonprescription drug product with an ACNU if FDA has determined that the applicant failed to demonstrate that labeling is insufficient to ensure consumers' appropriate self-selection and/or appropriate actual use, of the nonprescription drug product without the supervision of a healthcare practitioner ...."); *see also id*. at 38324.
[28] *See* 21 U.S.C. § 352(f).
[29] 87 Fed. Reg. at 38324. Marketing a nonprescription drug with an ACNU without the required labeling or implementation of the ACNU would render the nonprescription drug product misbranded. *Id*. at 38324–25; 21 C.F.R. §§ 201.67(e), 201.130 (proposed); *see* 21 U.S.C. § 352(f).
[30] 87 Fed. Reg. at 38323–25.
[31] *Id*. at 38323–38324; 21 C.F.R. § 201.130(a)(1) (proposed).
[32] 87 Fed. Reg. at 38324; 21 C.F.R. §§ 201.67(d), 201.130(a)(2) (proposed).
[33] 87 Fed. Reg. at 38322; 21 C.F.R. § 314.81(b)(3)(v) (proposed).
[34] 87 Fed. Reg. at 38322; 21 C.F.R. § 314.81(b)(3)(v) (proposed).
[35] *See* Kyle Sampson et al., Client Alert, *FDA Finalizes Rule and Guidance to Implement Safe Importation Action Plan Aimed at Lowering Prescription Drug Prices* (Oct. 2, 2020), *available at* https://www.kslaw.com/attachments/000/008/232/original/FDA_Finalizes_Rule_and_Guidance_to_Implement_Safe_Importation_Action_Plan_Aimed_at_Lowering_Prescription_Drug_Prices.pdf?1601664611.
[36] *See* Generics Bulletin, *Could US FDA User Fee Bill Include the Long-Sought 505(b)(2) Pathway for Biosimilars* (May 27, 2021), *available at* https://generics.pharmaintelligence.informa.com/GB150953/Could-US-FDA-User-Fee-Bill-Include-The-LongSought-505b2-Pathway-For-Biosimilars.
[37] *See* 42 U.S.C. § 262 note.
[38] *See* 87 Fed. Reg. at 38327.
[39] *See* U.S. Food & Drug Admin., *CDER Guidance Agenda, New and Revised Draft Guidance Documents Planned for Publication in Calendar Year 2022* (Jan. 2022).
[40] Relatedly, the proposed rule also solicited comment on whether patents claiming aspects of the ACNU for the nonprescription drug product may be submitted for listing in the Orange Book and "other issues FDA should consider in implementing this proposal that will help avoid unnecessarily delaying the entry of" an ANDA. 87 Fed. Reg. at 38321.