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Dockets Management Staff (HFA-305)
Food and Drug Administration (FDA)

Chris Wheeler, Pharm.D.
Center for Drug Evaluation & Research
US Food and Drug Administration
10903 New Hampshire Avenue
Building 51, Room 3330
Silver Spring, MD 20993

Re: Innovative Approaches for Nonprescription Drug Products; Draft Guidance for Industry; Availability. Docket No. FDA-2018-D-2281 (*Fed. Reg.* vol. 83, no. 138; pp 33938-33939)

Dear Dr. Wheeler:

On behalf of the Consumer Healthcare Products Association (CHPA)¹, comments are submitted to the United States Food and Drug Administration (FDA or Agency) regarding its draft guidance titled, “Innovative Approaches for Nonprescription Drug Products: Guidance for Industry” (Draft Guidance).² The *Federal Register* notice³ announcing the availability of this document notes that FDA intends to issue a proposed rule that will provide greater details about the use of additional conditions for nonprescription drug products. CHPA members look forward to publication of the final guidance and the companion proposed rule as expeditiously as possible. Together, when finalized, these regulatory documents will provide insights that sponsors can consider when designing research and development (R&D) proposals for prescription (Rx) to over-the-counter (OTC) switch programs where additional conditions are needed to ensure appropriate selection and/or use of the products.

We applaud the Agency for releasing this Draft Guidance and appreciate the flexibility it affords to sponsors as they design their switch programs. While this guidance will be helpful, CHPA members encourage release of the related proposed rule as soon as possible so that all stakeholders can understand the scope of the framework being considered. We appreciate the challenge in developing guidance in a rapidly evolving arena. Hopefully parameters set forward in the proposed rule will also support the use of innovative approaches as outlined in this Draft Guidance and enable continued evolution as the consumer environment advances technologically. When the proposed rule is issued, CHPA members will provide more detailed recommendations.

¹ The Consumer Healthcare Products Association (CHPA) is the 137-year-old national trade association representing the leading manufacturers and marketers of over-the-counter (OTC) medicines and dietary supplements. CHPA is committed to empowering consumer self-care by preserving and expanding choice and availability of consumer healthcare products.

² Draft guidance accessed at <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm613666.pdf> on July 23, 2018.

³ *Federal Register* notice accessed at <https://www.gpo.gov/fdsys/pkg/FR-2018-07-18/pdf/2018-15296.pdf> on July 27, 2018.

As written, the draft guidance allows sponsors to develop innovative approaches specific to their Rx-to-OTC switch program needs. These approaches are grouped in two categories:

1. Use of labeling tools in addition to the Drug Facts Label (DFL) (referred to herein as enhanced labeling)
2. Use of additional conditions to support safe and effective use

CHPA members offer the following points to consider as the Agency progresses to the next version of the guidance (either final or as a revised draft) and proposed rulemaking to allow for additional stakeholder input.

General Comments

- It is our understanding that the decision to utilize an innovative approach to labeling and/or additional conditions of use rests with the Sponsor, in consultation with the Agency. The need for enhanced labeling or support measures may become apparent as a Sponsor proceeds through the iterative label development program. There may also be circumstances that, due to their obviousness, might call for use of an innovative approach at the onset. As each switch program or program to expand indications or additional claims presents unique challenges, the specifics of individual programs should be subject to discussions between the Sponsor and the Agency.
- We note the principles of this Draft Guidance and anticipated regulation could potentially support both the introduction of new switch molecules to the OTC environment as well as innovations to existing nonprescription medicines (*e.g.*, new indications or new claims to drugs currently marketed under an approved application). The latter would apply the principles outlined in the guidance within an appropriate post-approval change framework. The precise regulatory mechanism and type of post-approval supplement needed would be driven by the nature of the change and the proposed innovative approach.
- The application of innovative approaches to support introduction of new nonprescription drugs (either through enhanced labeling and/or additional conditions of use) raises questions as to how follow-on applications (*e.g.*, second/third-in-class) might be managed. Future guidance and/or the proposed rule should be clear as to the Agency's thinking regarding follow-on submissions. These situations are explored separately in this document.
- There are currently numerous standard testing approaches that sponsors employ as part of the drug development process to evaluate and demonstrate the adequacy of the proposed product labeling to support the safe and effective use of the product in a nonprescription environment. It is assumed that the overall effectiveness of potential innovative approaches can be assessed using existing study methodology and that additional types of testing will not typically be required. CHPA members acknowledge that additional tests may be required for switch programs on a case-by-case basis (*e.g.*, studies or quality assurance (QA) processes to validate software).
- We interpret the conditions noted in Section III.B. of the Draft Guidance to suggest that some degree of restricted access would be permissible within the proposed regulatory framework (*e.g.*, a consumer must complete a certain action to obtain access to the product). CHPA members assume any criteria necessary for limiting product access would be negotiated between the Sponsor and the Agency.

- We note the Draft Guidance does not cover the potential enhanced role of the pharmacist and other healthcare providers as mentioned in earlier NSURE⁴ communications^{5,6}. It would be helpful to understand FDA's intent in this regard.
- As FDA finalizes the guidance and drafts regulations, we encourage the Agency to consider how the use of a technology, in the context of studies essential to approval, would qualify for exclusivity.

Enhanced Labeling

- Section III.A. of the Draft Guidance cites the use of leaflets or other documents inside or on the container as innovative approaches to labeling (see lines 79-85). We agree with the value that this supplemental labeling can provide and note that there are several examples of currently-approved products that have used this approach to support appropriate consumer use. We view the other examples noted in the Draft Guidance which highlight different technological solutions as building on this established practice.
- We note in Section III.A. the examples cited by the Agency such as websites and video displays (see lines 87-89 in the Draft Guidance). We understand that these items have historically not been reviewed and approved by FDA in connection with approval of a new drug application (NDA). Our assumption is that the new regulatory scheme under consideration is not intended to alter this practice and that formal designation as labeling, and consequent review and approval, would be limited only to those innovative approaches deemed essential to supporting safe and effective use. Furthermore, CHPA members assume the Sponsor and Agency would agree to the terms of approval during the course of development and NDA review.
- The Draft Guidance notes that FDA may consider and approve additional labeling that goes beyond the Drug Facts Label and other standard OTC labeling requirements to promote the safe and effective use of the product "...when labeling alone is not sufficient for this purpose" (see lines 97-98 of the Draft Guidance). As previously stated under General Comments, we would anticipate that the criteria for determining the need for innovative approaches would be determined on a case-by-case basis in collaboration between the Sponsor and the Agency. Factors to consider may include, but are not limited to:
 - overall complexity/length of the label;
 - ease of navigation,
 - desire to provide supporting educational messages;
 - insights/feedback from qualitative and/or quantitative consumer research; and
 - actual performance of the standard DFL⁷ (sDFL) in relation to pre-specified performance standards in formal label testing.

We would request that the Agency provide clarity regarding these factors.

⁴ FDA Center for Drug Evaluation & Research's Nonprescription Safe Use Regulatory Expansion initiative.

⁵ FDA 2nd Annual Health Professional Organizations Conference (October 2012). Presentation accessed from <https://www.fda.gov/downloads/ForHealthProfessionals/UCM330650.pdf> on September 5, 2018.

⁶ FDA Presentation by Dominic Cirincione at 2016 CHPA Regulatory, Scientific & Quality Conference (RSQ) on May 19.

⁷ As defined in 21 CFR §201.66

Additional Conditions of Use

The Draft Guidance indicates that sponsors should "...consider how to ensure proper implementation of any additional condition necessary for safe and effective use" (see lines 114-115). It is CHPA's position that consistent with the process in place for the creation, evaluation, review and approval of product labeling, the design, and performance of any proposed conditions of use would be evaluated within the context of the Sponsor's development program to characterize likely real-world experience. In terms of implementation in the marketplace, the extent to which the proposed conditions of use inform, influence, guide, and/or affect consumer behavior should be determined based on specific circumstances unique to each product under consideration.

Follow-On NDAs

For follow-on products in the same therapeutic class as a first-in-class switch (FIC), the Agency has historically implemented a class-related approach to key elements of the label, while allowing differences to exist among individual products where appropriate and supported by data within an individual Sponsor's NDA. Industry would expect a similar approach to be applied to the consideration of innovative approaches for nonprescription drugs. Namely, that the process for approval of follow-on products (e.g., second/third-in-class switches) would allow harmonization among class labels where appropriate, but afford sufficient flexibility to enable alternative approaches to achieve the desired outcomes of safe and effective use in an OTC environment. The evidence required to support the follow-on product should be influenced by the nature and magnitude of its difference from the FIC drug.

Generic Drug Products (Abbreviated New Drug Applications)

CHPA members encourage FDA to provide clarity regarding how OTC products marketed under an abbreviated new drug application (ANDA) would be evaluated for regulatory approval and implementation. Consistent with current practice, we assume that a generic version of an innovator product approved using an innovative approach will be subject to employing the same or similar enhanced labeling and/or conditions of use as the innovator or be required to support differences through a suitable regulatory mechanism (e.g., suitability petition).

Alignment with Other Agency Disciplines & Initiatives

- We appreciate that regulatory approval and oversight of OTC medications primarily resides within FDA's Center for Drug Evaluation and Research (CDER) Office of Drug Evaluation (ODE) IV Division of Nonprescription Drug Products (DNDP). It is assumed that this role will remain unchanged as we look to leverage emerging technologies and innovative approaches to support OTC drugs while retaining the historical experience of regulating nonprescription medications.
- We do acknowledge that other areas within FDA, such as the Office of Combination Products (OCP), the Center for Devices and Radiological Health (CDRH), and therapeutic review divisions may also provide input on regulatory decisions associated with OTC medicines. Therefore, Industry requests further guidance and understanding of the roles that OCP, specific subject matter review divisions (SSMRDs), and CDRH may play as they relate to the submission and review of any application. Guidance and

examples are requested as to when or if CDRH would be expected to oversee any submission. For example, would an OTC drug using an innovative approach (such as a mobile application) still be classified as a drug only, or as a drug/device combination product and therefore under the purview of the OCP? In this context, what role would CDRH play in the review process and how will this be coordinated with the activities of DNDP?

As mentioned above, CHPA members assume that DNDP would retain regulatory oversight, except in limited circumstances, and engage with other FDA offices and divisions as necessary. The Agency is asked to provide clarity about how the pre-market review and post-market regulation of these products will be managed within the various Centers within the FDA and how these processes will be communicated to sponsors.

- We hope that factors associated with additional conditions of safe use for OTC medicines would be considered across the various Centers within FDA to ensure harmonization to the extent possible, and to minimize potentially duplicative or unnecessary regulatory requirements. For example, CDRH recently published its Digital Health Innovation Action Plan⁸ which references the Agency's implementation guidance for 21st Century Cures and its policy on mobile medical applications, medical device data systems used for electronic transfer, storage, display or conversion of medical device data, and low-risk general wellness products. The current Draft Guidance references questions or statements in a mobile application (see line 91). We would expect that the new draft guidance for 21st Century Cures implementation (see page 4 of the Digital Health Innovation Action Plan) and this Draft Guidance would be consistent whenever possible.
- We acknowledge the Agency's progressive actions to implement reasonable, pragmatic, and risk-based approaches to the review and approval of medical devices and wellness products available within the consumer space. We hope that the Agency's actions to enable innovation in drug development and broaden access to important OTC medicines would support assessment of technologies and/or conditions of use based on overall evaluation of both the benefits and risks for these products.

CHPA members look forward to FDA's issuance of the final guidance and the companion proposed rule as soon as possible. We encourage the Agency to designate these actions as priority items on its regulatory agenda. As FDA Commissioner Scott Gottlieb, M.D., suggested in his press statement about this initiative, the hope is that a modernized framework will "...contribute to lower costs for our health care system overall and provide greater efficiency and empowerment for consumers by increasing the availability of certain products that would otherwise be available only by prescription."⁹ CHPA members who market OTC medicines under approved applications agree with the potential benefit of these proposals to the public's health.

⁸ FDA Center for Devices and Radiological Health (CDRH) Digital Health Innovation Action Plan. Access at <https://www.fda.gov/downloads/MedicalDevices/DigitalHealth/UCM568735.pdf>. Additional information on digital health from the Agency is available at <https://www.fda.gov/medicaldevices/digitalhealth/default.htm>. Accessed on August 15, 2018.

⁹ FDA Press Statement titled "Statement from FDA Commissioner Scott Gottlieb, M.D., on new efforts to empower consumers by advancing access to nonprescription drugs," released July 17, 2018. Accessed at <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm613692.htm> on July 27, 2018.

Your time and attention to our comments are greatly appreciated. My contact information is provided below should you need to reach me or if questions arise.

Sincerely,

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