Biotechnology Innovation Organization
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December 18, 2023

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

**Re: FDA-2023-D-2482; Regulatory Consideration for Prescription Drug Use-Related Software**

Dear Recipient:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments regarding the request for information and comments on the draft guidance "**Regulatory Consideration for Prescription Drug Use-Related Software**."

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers, and related organizations across the United States and in more than 30 other nations. BIO's members develop medical products and technologies to treat patients afflicted with serious diseases, to delay the onset of these diseases, or to prevent them in the first place.

Sincerely,

/s/
Steve Berman
Sr. Director, Science & Regulatory Affairs
Biotechnology Innovation Organization

## General Comments

BIO applauds the FDA's efforts regarding defining the categories of end-user output created by prescription drug use-related software, and what end-user outputs meet the definition of FDA-required labeling. However, BIO recommends that FDA clarify the PDURS definition and narrow the scope of PDURS output considered to be labeling. BIO urges FDA to reconsider its proposed position that all PDURS output that is not included in FDA-required labeling constitutes a form of regulated promotional labeling. FDA's definition of PDURS output appears intended to be coextensive with the definition of "labeling," because FDA states that both "accompany" a prescription drug. We also request clarity on what exact PDURS could be considered "supplementing" a drug product.

Irrespective of whether a particular communication is "promotional," we are concerned this proposed approach reflects an overbroad conception of "labeling" and could discourage innovation in the digital health space, particularly given that FDA's proposed Guidance would add an additional layer of digital health regulation on top of the existing, already complex to navigate layer that both Congress and FDA have put in place over the last several years. We believe that only software output that includes safety or effectiveness claims or dosing and administration information for a drug could be regarded as labeling and thus PDURS output. Such a tailored and focused conception of PDURS and labeling would be risk-based, protect public health, and promote innovation, consistent with FDA's guiding principles and longstanding legal precedent governing what constitutes "labeling" under the Federal Food, Drug, and Cosmetic Act (FD&C Act). Further, to the extent that FDA continues to apply a broader conception of labeling in this context, we believe that much PDURS output would be reminder labeling.

We reference the following Agency's recommendation from the draft guidance that, "FDA considers end-user output a type of prescription drug labeling". While we agree with the intention of this proposal to ensure Sponsors' communications about a product via software are consistent with labeling requirements, we recommend that the Agency take a singular, risk-based approach to regulating all software output(s) regardless of the developer or the origin of the software product. Such an approach would ensure that there is a clear and better-optimized regulatory path for any developer developing prescription drug use-related software.

## Specific Comments

As the draft guidance is currently written, BIO is concerned that it does not adequately address emerging software categories like chatbots (e.g., ChatGPT). These software platforms are commonly used by the general public to receive information on a variety of topics and are not created on behalf of an individual sponsor, nor are they created in collaboration with a sponsor. These chatbot services represent an information pathway where patients could potentially receive out-of-date or poorly summarized (mis)information about their prescription drug products. We recommend that FDA consider issuing guidance on chatbot and other artificial intelligence services unaffiliated with sponsors, prior to finalizing the Prescription Drug Use-Related Software guidance.

Additionally, we ask that the Agency clarifies what "disseminated [...] on behalf of a drug sponsor" entails. There are various examples of situations where a drug sponsor might engage

with a third-party entity on software output. In some cases, the sponsor will intentionally partner with a third party on the development of the PDURS. However, that will not always be the case. Indeed, software developed independently by a third party could include information about a sponsor's drug and, if it is erroneous, the sponsor would engage with the third party to correct such information. In such cases, it is unclear whether the Agency would consider that outreach to the third party-developed software as "disseminated [...] on behalf of a drug sponsor".

BIO recommends the Agency to take a risk-based approach to its review of modifications made to PDURS. Low-risk/minor changes related to the UI of PDURS should not require regulatory submission to the Agency as the potential for harm caused by such changes is low. Therefore we ask the Agency to clarify what exact types of modifications would "alter the end-user output" and therefore trigger a regulatory submission (PI change or Form 2253).

We ask the Agency to clarify how evidence of clinical benefit of PDURS might include benefits associated with the effectiveness and/or the safety of the drug. We also request the Agency to include examples of different clinical benefits. For example, clinical benefit of PDURS associated with the effectiveness of the drug could include symptom management software, whereas examples of clinical benefit associated with the safety of the drug could include the management of adverse events associated with the drug.

We appreciate that the guidance describes multiple scenarios for use of different types of PDURS, as well as types of evidence associated with each potential use. However, we note with concern that a key scenario when the PDURS is a standalone non-medical device software is not addressed. Therefore, we ask the Agency to elaborate and clarify the type of submission required of the drug sponsor in the case of a stand-alone non-medical device PDURS

The guidance notes in Footnote 21 that *"If an applicant for an ANDA proposes a generic product with prescription drug use-related software considerations (e.g., prescription drug use-related software accompanies the proposed generic product and/or the reference listed drug (RLD)), FDA will consider, among other things, the proposed labeling. Labeling differences that stem from permissible differences in design between the user interface for a proposed generic product and its RLD may fall within the scope of permissible differences in labeling for a product approved under an ANDA."* We appreciate FDA noting that that generics and their associated PDURS may be slightly different from the RLD and its associated PDURS. BIO notes that it would be helpful if FDA could expand on its thinking, in particular their views on how PDURS may be written/re-written to cover the range of products on the market within a category to best ensure products are taken as directed.

We ask the Agency to clarify that this framework does not apply to Software in a Medical Device as such software is reviewed by CDRH as part of a medical device, despite them potentially displaying information about a drug.

In the scenario where there is evidence of clinical benefit associated with the use of the PDURS, which would allow the inclusion of its output in the PI, we ask the Agency to clarify what exact information about the output would be included. We request the Agency to explicitly state whether there be a mention of the specific software that was used in the adequate and well controlled study or just the content of the output irrespective of the software. This clarity is necessary to adequately communicate this section of the PI with HCPs and Patients.

LINE-BY-LINE RECOMMENDED EDITS

| SECTION/LINE | ISSUE | PROPOSED CHANGE |
|---|---|---|
| **I. Introduction (Section 1)** | | |
| **67-70** | We reference the following text from the draft guidance: “Rather, it focuses on the application of drug labeling authorities to the end-user output of prescription drug use-related software, regardless of whether such software is regulated as a device under the Federal Food, Drug, and Cosmetic Act (FD&C Act)”. | BIO recommends the Agency to be explicit about the type of submission requested of drug sponsors if PDURS constitute a medical device under enforcement discretion, referencing CDRH’s software regulatory framework.<br><br>Further, we request clarity on what type of labeling PDURS would constitute in this case. Indeed, we ask the Agency to confirm if the presence of evidence of clinical benefit would allow inclusion of PDURS output in the drug PI or if the lack of evidence of clinical benefit make PDURS promotional labeling. |
| **II. Background** | | |
| **III. Prescription Drug Use-Related Software Functions and End-User Output** | | |
| **124** | Promotional labeling must be truthful and non-misleading, convey balanced information about a drug’s efficacy and its risks, and reveal material facts about the drug, including facts about the consequences that can result from use of the drug as suggested in a promotional piece. | BIO recommends clarification in the final guidance (or references to another guidance) for achieving balanced information about a drug’s efficacy and its risks within a software app. There is not current specific FDA guidance about achieving ‘fair balance’ in a software application, especially on User Interface screens that may be providing important information, such as recommended drug doses, warnings, and/or cautions associated with use of the device. |
| **170-176** | We reference the following text from the draft guidance: “When a prescription drug use-related software function receives input data from the device constituent part of a combination product (i.e., device-connected software function), FDA intends to assess whether the combination product used with the software can accurately and reliably provide the data, perform analyses, and display the end-user output (regardless of whether the end-user output is FDA-required or promotional labeling). 20 Sponsors should | The footnote 20 refers to the Design Controls section of FD&C (21 CFR 820.30(g)). BIO asks the Agency to clarify what exact parts of the interface between the PDURS and the device constituent would need to be done under design controls, as well as indicate whether regression studies would be deemed sufficient to prove that the combination product used with the PDURS will not lead to medication errors. |

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| | provide information to support how the combination product used with the software will not lead to medication errors, such as inappropriate administration of extra doses". | |
| **IV. Describing Prescription Drug Use-Related Software Functions and End-User Output in the Prescribing Information** | | |
| **A. When the Drug Sponsor Submits Evidence Demonstrating That the Use of Prescription Drug Use-Related Software Leads to a Clinically Meaningful Benefit** | | |
| **B. When the Drug Sponsor Does Not Submit Evidence of a Clinically Meaningful Benefit** | | |
| **260 - 269** | There is a lack of clarity on acceptable language to be addressed in the PI. | BIO recommends FDA elaborate on what would be acceptable language or key points that must be addressed in the PI. For example, FDA should clarify if the sponsor is able to include QR codes or web links for mobile application downloads. |
| **C. Additional Considerations Relating to Review of End-User Output** | | |
| **Appendix A: Examples of Prescription Drug Use-Related Software Functions and End-User Output** | | |
| **Appendix B: Examples of Device Software Functions That Are Regulated By FDA Under an Appropriate CDRH Marketing Submission and Where the End-Use Output is Considered Promotional Labeling** | | |
| **Glossary** | | |
| **Glossary** | The draft guidance document defines 'end-user output' as any material/content that the prescription drug use-related software presents to the end user and that FDA considers such end-user output as prescription drug labeling. | BIO recommends that the final guidance state that content presented to an end-user that could be considered 'transactional' is exempt from meeting promotional labeling requirements.<br>For example, customer support program registration pages where a product name or indication are mentioned to clarify what a patient is signing up for are not meant to be promotional in nature. Similarly, HIPAA authorization screens, privacy consent, and opt-in screens for texts or emails are not meant to be promotional in nature even though a product name or indication is included. |