**Combination
Products
Coalition**

1227 25th St. NW #700
Washington, DC 20037
combinationproducts.com
202.861.4199

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<u>**VIA ELECTRONIC SUBMISSION**</u>

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

Re: <u>Docket Number FDA–2018–N–3017: Prescription Drug-Use-Related Software;</u>
<u>Establishment of a Public Docket; Request for Comments</u>

Dear Sir or Madam:

The Combination Products Coalition ("CPC")[1] welcomes the opportunity to provide input (including both general comments and responses to the specific questions posed by FDA) regarding the Federal Register Notice entitled "Prescription Drug-Use-Related Software; Establishment of a Public Docket; Request for Comments," dated November 20, 2018 (the "Notice").

While the CPC applauds the Agency's efforts to develop a proposed framework to address the ever-increasing array of digital innovations associated with pharmaceuticals that are focused on improving patient health and the delivery of health care, we have certain concerns regarding the proposed framework, as discussed below.

General Comments

In the Notice, FDA defined a new term, "prescription drug-use-related software" ("PDURS"), as software disseminated by or on behalf of a drug sponsor that accompanies one or more of the sponsor's prescription drugs. The term does not include software deemed to be a medical device or software developed by a third party that is unaffiliated with the drug sponsor.

As discussed in our responses to FDA's specific questions below, the CPC agrees with FDA that the regulatory approach here should be "risk-based." We further believe that a streamlined and predictable regulatory approach is needed to foster innovation and best serve patients.

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[1] The CPC is a group of leading drug, biological product, and medical device manufacturers with substantial experience and interest in combination product issues. One of our top priorities is to work collaboratively with FDA on issues affecting combination products to advance our common mission: providing the best possible health care to patients. Our diverse, cross-industry membership permits the CPC to bring a special, broad, and unique perspective to these issues.

However, we are concerned that a few aspects of the proposed framework will have the potential to severely inhibit innovation or create a public health disparity. We highlight the following points with regard to our responses to FDA's specific questions below:

- FDA should apply the same regulatory framework for software regardless of who develops and distributes it.

- Regarding the development of software, a single unified FDA policy should be adopted. CDER should recognize and adopt the applicable CDRH guidance documents.

- The proposed utilization of a voluntary advisory comment process is significantly underestimated and, based on current turnaround timelines, prohibitive to fast-paced needs.

- Pharmaceutical fees for clinical study reviews of software innovation are prohibitive to innovation.

Responses to FDA's Specific Questions

1. **FDA is seeking to foster innovation in the use of digital technology with prescription drugs while maintaining a consistent approach to communications by sponsors about their drugs. Does the proposed approach to prescription drug-use related software adequately foster innovation by drug sponsors?**

   The CPC applauds the efforts of FDA in providing this proposed framework for prescription drug-use related-software products and appreciates FDA's recognition of digital health and its potential in drug use-related applications. The CPC agrees with several underlying principles of the proposed framework, including a "risk-based" regulatory approach and fostering innovation while maintaining a consistent approach to communication by sponsors about their drugs. However, the CPC is concerned that the proposed framework contains specific policies that could ultimately hold back innovation in digital health and prescription drug-use-related software.

   The proposed framework draws a distinction between drug sponsor-owned software and third-party software, which results in artificial categorization of software produced by a third party as inherently lower risk than software developed by or on behalf of drug sponsors. This has significant potential to disincentivize digital health innovation among drug sponsors as it disproportionately increases the regulatory burden on drug sponsors developing software for use with prescription drugs. The CPC believes any framework adopted by FDA should apply to all software for use with prescription drugs regardless of the software manufacturer.

   In addition, the proposal states that there is no change to the definition of a medical device. However, once a drug is involved, CDER has been firm that it would weigh in. The CPC believes greater clarity would be achieved with a single Agency policy regardless of standalone device or device constituent. This would leverage and recognize the authority and software expertise of CDRH with consultation of CDER as required, similar to the process of consultation used for combination products. A single policy that remains consistent regardless of the software, while recognizing the expertise of the various centers within FDA, would allow

for optimal innovation by all parties, including the drug sponsors themselves who hold the most information concerning their drug products.

2. What alternative regulatory approaches could the Agency consider?

FDA should leverage the existing regulatory approaches for "non-essential" prescription drug-use-related software and clarify the regulatory pathway as a standalone device subject to CDRH regulation, or whether it may be subject to enforcement discretion.

3. What should FDA take into consideration with respect to applying prescription drug labeling requirements in this context (e.g., the requirement that labeling bear adequate directions for use)?

FDA should provide the maximum flexibility for PDURS outputs with respect to "adequate directions for use." PDURS outputs need not be verbatim to USPI directions for use but may enhance or go beyond the FDA-required labeling to provide a benefit in comprehension of the directions for use.

FDA should take into consideration the limitations of the mobile app user interface ("UI"), and the impact of certain labeling rules on user experience. The layout of information would frequently be presented in sections as opposed to as printed material or as pdf format of the printed material.

For example, boxed warnings and prescribing information are needed due to FDA labeling requirements any time the brand name is used. This makes an app user interface (or text messages) very clunky given the limited characters or screen real estate. Users find this annoying. A bad/annoying UI may lead to increased risk since the user's mental model is not used to such things with apps.

Further, promotional labeling can include training materials submitted to OPDP that are consistent with product use and are of benefit to patients and health care providers.[2] In the past, these have included, for example, training videos; however, more sophisticated software platforms and mobile apps can, and are, being developed with interactive software for training on more complex drug delivery devices and dosing regimens. FDA's proposal should look to provide some guidance in this area, for example, providing for consistency and allowed expansion of FDA-required labeling for Instructions for Use.

For outputs that are considered FDA-required labeling and which have meaningful clinical impact, FDA may wish to consider user-testing, Failure Mode Effects Analysis, software validation/limitations and software security/privacy.

In addition, further clarity is needed in Section I.B. of the Notice, where it is stated that the proposed framework does not apply to software developed by companies or individuals who

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[2] FDA's expectations for training materials are stated in the "Instructions for Completing Form FDA 2253 – Transmittal of Advertisements and Promotional Labeling for Drugs and Biologics for Human Use," which lists items for submission including: "Training Materials - Training Materials (e.g. learning modules, training video/brochure/other piece(s) provided to health care professionals or patients)," http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf.

are unaffiliated with the drug sponsor. Has FDA considered the situation where an unaffiliated company or individual interacts with the pharmaceutical company to develop the software? Would the proposed prescription drug labeling requirements apply?

Does the proposed approach adequately preserve FDA's ability to ensure that existing prescription drug labeling requirements are met?

With the additional clarity that is being requested in this response, the proposed labeling approach seems reasonable.

4. **In a situation where the output of prescription drug-use-related software includes a benefit claim about the drug, what should FDA consider when providing recommendations on how to appropriately address the balancing of benefit information and risk information?**

FDA may wish to consider whether it is acceptable for benefit claims about the drug to be accompanied on the display screen with only links to the product indication, ISI, and full prescribing information (meaning, no portion of the indication or ISI would be visible) when the following conditions are met:

- Upon completion of initial APP enrollment and user consent, the full product indication and ISI (forced scroll through) are displayed, as well as a link to the full prescribing information.
  - Subsequently, the full product indication and ISI (forced scroll through) will be displayed, as well as a link to the full prescribing information upon first use of the APP after changes to either the indication, ISI, or PI have been made.

- Product indication, ISI, and full prescribing information will be available at all times and can be accessed through the APP menu.

5. **Does the proposed framework appropriately characterize the types of prescription drug-use-related software output that should be submitted for advisory comment (See Section II.C., Prescription Drug-Use-Related Software Output That Constitutes Promotional Labeling)? Are there other examples for which advisory comment should be recommended because there is a strong potential that the prescription drug use-related software output will increase the potential for harm to health if used with a drug?**

The CPC believes that the Agency has provided an appropriate characterization of the types of prescription drug-use-related software output that should be submitted for advisory comment; however, the CPC believes that the Notice should have provided more detail around the intent and purpose of using OPDP Form FDA 2253 and the Request for Advisory Comment process for Agency evaluation of prescription drug-use-related software output. The CPC recommends that future Agency guidance, or policy related to prescription drug use-related software output, address the following considerations:

- **Expected output of the Request for Advisory Comment process:** It is unclear what assessment the Agency would be providing for drug use-related software output. Would

this assessment simply be an evaluation of whether the proposed drug-use-related software output is consistent with FDA-required labeling or would additional detail be provided? Ideally, this advisory process would provide sponsors not only with advice related to promotional labeling, but also would include an assessment of whether the software output is considered to meet the definition of a medical device and/or combination product. Further, it is unclear how the Advisory Comment process will handle scenarios where a software output is consistent with FDA-required labeling, but where the Agency believes the prescription drug-use-related software output may increase the potential for harm.

- **Implications if the Request for Advisory Comment process finds that prescription drug-use-related software output is not consistent with FDA-required labeling:** It is unclear how sponsors should proceed if the Request for Advisory Comment process finds that proposed drug-use-related software output either is not consistent with FDA-required labeling or may increase the potential for harm. The CPC recommends that if either scenario is encountered, the Agency also provide advice on how the proposed drug use-related software output must be submitted for Agency review and/or approval prior to dissemination. The CPC also recommends that the Agency publish information about appealing comments provided through this process for reconsideration.

- **Questions related to the binding nature of advisory comments and timelines to receive responses to advisory comment requests:** The CPC recommends that there be a process put in place to allow the submitter to provide clarification or discussion when a voluntary FDA advisory comment is disagreed with. Further, it will be critical that performance timelines for each step of the process be established, so that feedback to a requestor is timely, as to not stall innovation. The CPC proposes that such feedback timeline be less than 60 days. FDA should also consider the potential resulting increase in workload and anticipate staffing accordingly.

6. **Does the proposed framework appropriately identify the materials and information that should be submitted by drug sponsors as part of a voluntary request for comment under § 202.1(j)(4)?**

The CPC requests that FDA provide further clarity regarding the materials and information that should be submitted. The proposed submission of screenshots may not adequately represent the user experience. For example, is it adequate to just provide a link to a proposed app?

Are there other materials or information FDA should consider in its evaluation of whether prescription drug-use-related software output submitted by drug sponsors is consistent with FDA-required labeling and is truthful and not misleading (e.g., human factors study results)?

According to the CDRH FDA guidance, "human factors validation testing is primarily a qualitative rather than a quantitative exercise. The goal is to evaluate users' interactions with a device user interface by observing their performance and simultaneously collecting subjective user assessments of their experience using the device to assess the adequacy of the user

interface design."[3] With this, the CPC believes that the human factors study results should not be used to determine whether labeling is truthful and not misleading. Current evaluation methods should be used to establish if labeling is truthful and not misleading.

7. Regarding software functions, FDA's proposed expectation is that sponsors are responsible for ensuring that prescription drug-use-related software reliably produces its output as intended. Is this approach sufficient to ensure patient safety?

The CPC agrees that sponsors are responsible to have objective evidence on file that PDURS products perform as intended accurately and reliably to ensure patient safety. To achieve this effectively, a consistent Agency-wide regulatory policy on analytical validation of software is important to facilitate development and commercialization of innovative software solutions for patients who need them. The CPC strongly recommends CDER recognize and adopt the applicable CDRH guidance documents. The list of guidance documents includes, but is not limited to:

- *General Principles of Software Validation; Final Guidance for Industry and FDA Staff (January 2002)*

- *Design Considerations and Premarket Submission Recommendations for Interoperable Medical Devices (September 2017)*

- *Content of Premarket Submissions for Management of Cybersecurity in Medical Devices (October 2014)*

- *Postmarket Management of Cybersecurity in Medical Devices (December 2016)*

- *Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices (May 2005)*

Discussed below are two examples of software use cases with different intended uses. Given the intended uses:

- Use Case 1 is regulated as drug labeling; and

- Use Case 2 is regulated as a medical device.

In Use Case 1, the drug sponsor would develop the PDURS using good software practices to ensure the reliability of the software without having to apply software design controls (21 CFR 820.30), which are required for Use Case 2.

The CPC strongly recommends that FDA provide clarity in the future CDER software guidance on the software development approach that covers various uses, including the two examples provided herein. Clarity in the software development and maintenance regulatory requirement (if applicable) will ensure the applicability of the future CDER software guidance.

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[3] FDA, *Applying Human Factors and Usability Engineering to Medical Devices: Guidance for Industry and Food and Drug Administration Staff* (2016), https://www.fda.gov/downloads/medicaldevices/.../ucm259760.pdf.

	Software Use Case 1	Software Use Case 2
Intended use	Enables patients to record and track their prescription drug use with the app.	Enables HCPs to determine the drug treatment regimen of a patient using baseline data and advanced analytics (not peer-reviewed).
Regulatory framework	Regulated as drug labeling pursuant to Section 201(m) (21 U.S.C. 321(m)) of the Federal Food, Drug, and Cosmetic Act ("FD&C Act").	Regulated as a medical device pursuant to Section 201(h) (21 U.S.C. 321(m)) of the FD&C Act.
Software development and maintenance regulatory requirement	No specific regulatory requirement. However, good software practices according to a recognized consensus standard (i.e., IEC 62304) may be applied at the discretion of the sponsor.	Develop and maintain under 21 CFR 820.30 (Design Controls).

8. **FDA recognizes that software will have frequent updates, many of which will not alter prescription drug-use-related software functionality. FDA proposes that for prescription drug-use-software output that is considered promotional, if changes in the software do not alter the output experienced by the user, FDA would not need to be notified of those changes. Does this approach strike an appropriate balance between allowing for software innovation while providing adequate oversight of sponsor communications about their prescription drugs?**

The CPC supports the proposed approach regarding changes in the PDURS not altering output experienced by the user and believes that it will strike an appropriate balance between allowing for software innovation while providing adequate regulatory oversight. The CPC commends FDA in taking this pragmatic approach as PDURS routinely go through iterative refinements in their outputs (i.e., change of color of an icon, location of an icon, etc.) that do not impact the PDURS functionality experienced by the users. Further, the CPC believes that changes in PDURS functionalities that do not impact the overall safety profile or clinical performance would not require prior approvals or notifications to FDA.

Similarly, the CPC encourages FDA to apply a pragmatic, risk-based framework on lifecycle management for software as a constituent of a combination product, as software often undergo routine refinements as well. An effective regulatory framework that allows timely and efficient introduction of software changes is important to the quality, safety, and availability of innovative software products. It is acknowledged that software changes vary from low to high potential risk with respect to their impacts on product safety and/or efficacy. The regulatory reporting mechanisms associated with the changes should be commensurate with the potential risk. The guiding principles associated with the regulatory reporting mechanisms are described below:

- Prior approval – software changes that could result in high risk are submitted to FDA for review and approval prior to implementation.

- Notification – software changes that could result in moderate to low risk are submitted to FDA, but formal approval is not required prior to implementation.

- Lowest risk software changes are managed and documented within the Pharmaceutical Quality System but may be verified during routine inspections.

The CPC urges FDA to describe a pragmatic, risk-based approach to ensure the applicability and utility of the draft guidance.

9. **What can be done to ensure that the end user has access to the prescription drug-use related software that is appropriate to the specific drug dispensed at the pharmacy (e.g., in cases of generic substitution)?**

It is important for end users to use the appropriate software intended to be used with the appropriate drug. It is particularly important when use of the software can lead to a clinically meaningful outcome or when the software provides a function or information essential to one or more intended uses of the drug.

The framework proposes that, in these cases, the drug sponsor will be required to submit a new application for review. As part of the submission, the drug sponsor should be required to indicate the software appropriate for use with the drug.

If the software output is necessary for the intended use of the drug, or to achieve clinically meaningful outcomes, ANDA holders should be required to make available comparable software. This approach would ensure that the appropriate software is available even if the Reference Listed Drug is discontinued. If the output is NOT necessary for use of the drug, then making the output available would not be required.

For PDURS that falls under promotional labeling (and does not require prior FDA approval), the end user may choose to use the software as advertised by the drug sponsor promoted in the material.

10. **What issues should the Agency consider as it develops this proposed framework in order to facilitate timely generic competition for prescription drugs that are approved with prescription drug-use related software output included in the FDA required labeling?**

The CPC recommends that FDA issue guidance regarding any expectations of generic companies, ensuring requirements are transparent and clear.

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We appreciate the opportunity to provide input on the proposed framework detailed in the Notice and are happy to meet with the Agency to clarify or discuss any of our suggestions.

Yours truly,

Bradley Merrill Thompson,
On behalf of the Combination Products Coalition