Demystifying the New Prescription Drug Use-Related Software Framework

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The Food and Drug Administration (FDA) unveiled its draft guidance on Regulatory Considerations for Prescription Drug Use-Related Software (PDURS) in September 2023. The document shed light on how the FDA intended to wield its drug-labeling authority over software outputs associated with prescription drugs and drug-device combination products.

We offered a preview of the PDURS framework in April 2023 in anticipation of the draft guidance release. Now, following the publication of the draft guidance, a review of submitted public comments and engaging extensively with both the FDA and pharmaceutical manufacturers on PDURS, we present an updated overview. The graphic below illustrates the framework.

EVERSANA	Non-PDURS Software	PDURS Promotional Software	PDURS FDA-Required Labeling	Drug-Software Combination
Description of Software	• Various intended uses or patient support functions • Can be used with general classes of drugs	• Disseminated with Rx drug • No added clinical effect to the drug or potential for harm	• Disseminated with Rx drug • Provides meaningful clinical benefit to Rx drug • Software is included on drug labeling (in clinical studies section)	• FDA approved as part of a drug-led combination product • The software is essential to the intended use of the drug • Software is included on labeling (in the drug/device description)
Sponsor	• Software or drug manufacturer	• Drug manufacturer	• Drug manufacturer	• Drug manufacturer
Regulatory Considerations	• No drug labeling considerations • Software subject to CDRH regulatory framework for SaMD	• Software output subject to promotional labeling requirements for Rx drugs • Software subject to CDRH regulatory framework for SaMD	• Software output subject to CDER/CBER FDA-required labeling regulations for prescription drugs • CDRH is consulted for review	• Drug-led combination product reviewed by CDER/CBER • CDRH is consulted for review
Regulatory Submission	• 510(k) or De Novo may be required if medical device	• Submit screen shots to OPDP prior to dissemination of software	• NDA or BLA Supplement	• New NDA or BLA
Clinical Evidence	• Clinical evidence may be required by CDRH if medical device	• Clinical evidence may be required by CDRH if medical device	• Adequate and well-controlled study required by CDER/CBER	• Phase 3 RCT generally required by CDER/CBER
Examples	• Unbranded companion apps • Insulin dosing calculator software • Digital therapeutics for MDD in patients on anti-depressants and OUD on buprenorphine	• Branded companion apps • Disease self-management • Medication/injection support	• Dose optimization • Side effect management • Behavioral support • Flare prediction	• No combos with “pure software” • Many drug-device combos with device-connected software (e.g., infusion pumps, autoinjectors)

*PDURS – Prescription Drug Use-Related Software

Overview of the PDURS Draft Guidance

The PDURS draft guidance introduces a new regulatory framework for software functions associated with the use of prescription drugs. The guidance document clarifies how drugs and biologics can leverage digital health technologies, specifically through integration within their prescribing information and promotional labeling. This is the first FDA guidance document focusing on the intersection of digital health and pharma from a commercial standpoint. It follows an earlier guidance on the use of digital health technologies in support of drugs in a clinical trial setting. The key takeaways from the PDURS draft guidance are as follows:

- **PDURS** is defined as software that (1) is **disseminated by or on behalf of a drug sponsor** and (2) produces an end-user output that **supplements, explains or is otherwise textually related to one or more of the sponsor's drug products**.
- **Regulatory Oversight:** The PDURS framework does not replace existing regulatory oversight for medical device software, which is generally led by the FDA's Center for Devices and Radiological Health (CDRH), but rather **is additive to it**. The new framework regulates software **output** from PDURS as drug labeling using existing regulations and falls under the purview of the FDA's Center for Drug Evaluation and Research (CDER), Center for Biological Evaluation and Research (CBER) and Office of Prescription Drug Promotion (OPDP.
- **PDURS Scope:** The FDA's focus is on software outputs that are **disseminated by or on behalf of a drug sponsor.** Third-party software, even if intended for use with specific prescription drugs, falls outside of this framework if it is not disseminated on behalf of the prescription drug manufacturer. Therefore, this framework is mainly intended for pharmaceutical manufacturers, not digital health startups or software developers, although they certainly can partner with pharma to commercialize PDURS.
- **PDURS Output as Labeling:** The PDURS draft guidance emphasizes that the software's end-user output constitutes labeling. This encompasses all forms of user-facing content, including static/dynamic displays, sounds and audio messages.

The FDA recognizes two distinct labeling categories for PDURS:

- **Promotional Labeling:** Most PDURS end-user outputs are categorized as promotional labeling. A software output that supplements, explains or is otherwise textually relate to one or more of a sponsor's drug products will generally be considered promotional labeling as long as it (1) is not essential to the safe and effective use of the drug, (2) does not provide a clinical benefit to the drug or (3) does not rely on data directly transferred from the device constituent part of a combination product. **Essentially, promotional labeling includes software outputs that are promotional in nature or serve patient support functions that do not make medical claims** or otherwise impact safety or effectiveness.
- **FDA-Required Labeling:** Here is the interesting part: When a drug sponsor can demonstrate that PDURS output provides a **clinically meaningful benefit to a prescription drug**, the drug sponsor can choose to submit the clinical evidence to the FDA and **add the software output to the required drug labeling**. As we described in a recent article discussing the commercial promise of PDURS, this is a new opportunity for pharmaceutical manufacturers to pair software with a medication without the same level of rigor and risk as a drug-software combination product

Examples of Software Paired With Drugs

There are already many examples of drug-adjacent software that are used to support patients on various medications and that do not fall under the category of PDURS promotional software, because they are not branded or disseminated with specific prescription drugs. There are also examples of drug-adjacent software that make medical claims that are not considered PDURS FDA-required labeling because they are intended for use with general classes of drugs. These include insulin dosing calculators from multiple manufacturers and digital therapeutics and digital therapeutics that must be used adjunctively with prescription drugs, such as Pear

Therapeutics' reSET-O (with buprenorphine) and Otsuka's Rejoyn (with antidepressants). All of these solutions fall under the **"non-PDURS software"** column in the table above, and they may or may not be regulated by the CDRH.

Until the introduction of the PDURS framework, the only other way to formally pair software with a prescription drug was with a **combination product**. However, pharma is generally allergic to this approach for companion software because these solutions must be rigorously tested; clinically validated, typically with a phase 3 randomized controlled trial; and submitted as a New Drug Application – all introducing unacceptable risk to the drug. For these reasons, there is not yet a single example of an FDA-approved drug-led combination product where the device constituent is stand-alone software (i.e., there is no hardware).

The PDURS **promotional labeling category** does not necessarily provide any benefit to manufacturers other than to provide clarity on how these software outputs are regulated. Anti-kickback laws further limit their value and adoption. There are several examples of branded companion apps today that have patient support functions, such as for injection training.

The PDURS **FDA-required labeling category**, on the other hand, is a **new opportunity** that allows manufacturers to be more innovative by pairing clinically validated software with drugs and to make medical claims by virtue of their addition to the drug label. This comes with less rigor and risk than combination products and with considerably greater clinical and commercial value than non-PDURS software and promotional software. Another key benefit is that PDURS FDA-required labeling can **optionally be prescribed with the drug**, unlike with combination products, where the software is by definition essential to the intended use of the drug and therefore must be prescribed with the drug.

Mechanics

PDURS that is **promotional labeling** must be submitted to the FDA's OPDP using Form 2253 at the time of initial dissemination. Software updates that do not alter the user-facing content, such as security patches, would not necessitate Form 2253 submission. Despite this being draft guidance, it is possible to submit PDURS promotional labeling to the OPDP today; in fact, this framework has been in place for years.

For **FDA-required labeling**, PDURS with meaningful clinical benefit to a drug would be added to the CLINICAL STUDIES section of the prescribing information of the drug label. For existing FDA-approved drugs, the PDURS would be reviewed by the FDA as any label changes are: via an NDA supplement (or potentially an NDA annual report, depending on benefit/risk). The biggest remaining question is, what clinical evidence is required to demonstrate a "meaningful clinical benefit"? The draft guidance states that "adequate and well-controlled studies" are required, with "adequate" essentially referring to good clinical practice and "well-controlled" including several control options that depend on benefit/risk. Most companion apps have low to minimal risk, and we anticipate based on initial discussions that well-designed real-world phase 4 studies will suffice for certain intended uses.

Device-Connected Software

The draft guidance also introduces the concept of device-connected software, which refers to "software functions that rely on data directly transferred from the device constituent part of a sponsor's combination product." Examples include software linking a mobile app with an inhaler or autoinjector to monitor and display patient usage data, and software providing information on drug ingestion from embedded tablet sensors. In these examples, the software would be included in the HOW SUPPLIED/STORAGE AND HANDLING section of the drug label, unless the drug sponsor is also claiming a clinical benefit from the software. These functions may also be subject to medical device regulation, potentially necessitating premarket device submissions.

Industry Reaction

Stakeholders in the pharmaceutical industry have expressed divergent views on the FDA's use of drug labeling authority for PDURS in the public comments. The most frequent recommendation in the public comments was to narrow the scope of PDURS promotional labeling, as many stakeholders suggested that this new requirement added unnecessary burden to manufacturers while having neglible impact or risk to the drug.

This concern was shared by the Pharmaceutical Research and Manufacturers of America (PhRMA), the Biotechnology Innovation Organization (BIO), the Combination Products Coalition (CPC), Medical Information Working Group (MIWG), Teva Pharmaceuticals, and Eli Lilly and Company.

Many groups, including PhRMA, BIO, Teva, and Lilly, pointed to an "asymmetric regulatory burden" in which PDURS oversight only applied to drug sponsors, while non-drug sponsors with similar drug-facing products would not be subject to any regulatory scrutiny from the PDURS framework.

Several stakeholders, including PhRMA, the Digital Therapeutics Alliance (DTA), and the Academy of Managed Care Pharmacy (AMCP), suggested that the clinical evidence requirements for PDURS FDA-required labeling implied in the draft guidance is overly burdensome and that it would discourage innovation in this field. Multiple groups instead recommended risk-based evidence generation requirements, including alternative approaches such as real world evidence (RWE) studies. As we stated above, in our discussions with FDA, they may already be leaning in this direction.

Additional suggestions in the public comments were to clarify how to engage with the FDA on PDURS, to provide more flexibly on how software outputs can be described on the labeling, to address how PDURS would apply to emerging technologies such as generative AI, to provide guidance on how to separate PDURS software outputs from non-PDURS software outputs in multi-function software, and to provide additional illustrative examples of both promotional and FDA-required labeling.

Commercial Implications

As we discussed in a recent article, the PDURS FDA-required labeling framework could have considerable commercial impact for pharma. This approach allows pharmaceutical manufacturers to enhance a drug's label by enabling an HCP to prescribe software alongside the drug at the HCP's discretion if the software has meaningful clinical benefit to the drug. Potential clinical use cases include dose optimization, side effect monitoring and management, behavioral health support and prognostics for disease severity and flares. Commercial benefits beyond the clinical benefits include brand differentiation, improved adherence and demand retention post loss of exclusivity. For software developers, PDURS FDA-required labeling also unlocks a new go-to-market option for digital health software.

The commercial benefit of the PDURS framework for promotional software is less clear and potentially adds more burden than value, as the public comments suggest. The benefit of the PDURS framework for device-connected software is also modest because a drug-device combination submission would still generally be required, and these products already allow a description of the software on the labeling.