

December 3, 2018

Aiming to Foster Innovation, FDA Proposes Regulatory Framework Specific to Prescription Drug Software

On November 20, 2018, the U.S. Food and Drug Administration (“FDA”) issued a [Federal Register notice](#) seeking public comment on FDA’s proposed framework for regulating prescription drug-use-related software (“PDURS”), the agency’s latest move in modernizing the regulatory requirements for digital health technologies (see prior Ropes & Gray alerts summarizing FDA’s [Digital Health Innovation Action Plan and new Software Precertification Program](#) and discussing [two digital health software draft guidances](#)). Under the proposed framework, which FDA intends to develop into a draft and, ultimately, a final guidance document, FDA would regulate the output of PDURS—software “disseminated by or on behalf of a drug sponsor that accompanies one or more of the sponsor’s prescription drugs (including biological drug products)”—as drug labeling. As such, the software output would be subject to FDA’s regulations for FDA required labeling or promotional labeling, as applicable.

The proposed framework is intended to align with FDA’s ongoing digital health initiatives and foster innovation while also ensuring that drug sponsors’ communications (in the form of software outputs) are consistent with applicable labeling requirements. In [public remarks](#) announcing the proposed framework, Commissioner Gottlieb expressed his view that the “flexible concepts” described in the proposed framework will encourage more drug sponsors to advance beneficial and innovative software apps with their products. He added that FDA “is committed to considering and weighing all comments as we develop draft guidance.”

The Proposed Framework

Relevance of Existing Digital Health Device Policies. The proposed framework does not address whether particular software constitutes a medical device and would not affect FDA’s existing policies in this area, such as FDA’s guidance documents relating to mobile medical applications and clinical and patient decision support software. FDA anticipates that some PDURS will meet the definition of a device, while other PDURS will not. Separate and apart from whether PDURS is considered a device, the proposed framework would regulate the output of such software as drug labeling (*i.e.*, the software may be regulated as a device in addition to its output being regulated as drug labeling).

Scope and Applicability. The proposed framework would only apply to software disseminated by or on behalf of a drug sponsor and explicitly would not apply to “third party software developers who independently develop or disseminate software for use with prescription drugs.” However, if a drug sponsor licenses software originally developed by a third party and then disseminates the software for use in conjunction with the sponsor’s drug, such software would be subject to the proposed framework. Additionally, software that is branded with the name of a drug product is considered to be disseminated by or on behalf of the sponsor, even if the software is otherwise available or is not solely related to the specific product’s use, such as an app that provides medication reminders, symptom tracking, or general information about the disease. The “output” of PDURS is described as the material presented to the end user and includes screen displays, alerts, reminders, audio messages, vibrations, or sounds. FDA asserts that such outputs constitute drug labeling because they “accompan[y] a drug, for example by explaining how to use the drug . . . or by supplementing the use of the drug.” This assertion is based upon FDA’s historically broad view of “labeling” under the Federal Food, Drug, and Cosmetic Act and its expansive interpretation of *Kordel v. United States*, 355 U.S. 345, 350 (1948), the seminal Supreme Court case addressing the proper scope of “labeling.”

When PDURS Information May Be Included in FDA-Required Labeling. FDA generally classifies drug labeling as either (a) FDA-required labeling (*e.g.*, prescribing information, medication guide), which contains information essential to the provider’s decision to prescribe the drug or the patient’s safe and effective use of the drug, or (b) promotional labeling, which encompasses any other labeling devised for product promotion. FDA anticipates that most forms of PDURS

output would be considered promotional labeling and not subject to prior FDA approval. Nevertheless, the proposed framework contemplates two scenarios in which PDURS information may be included in the FDA-required drug labeling and therefore subject to prior FDA approval:

- i. when use of the PDURS with the drug results in a clinically meaningful improvement compared to use of the drug alone, as demonstrated through substantial evidence, and the sponsor submits such evidence as part of an application (*e.g.*, software that improves patient compliance and improves outcomes of the relevant clinical endpoint compared to drug use alone), or
- ii. where the PDURS provides a function or information that is essential to one or more intended uses of a drug-led drug-device combination product (*e.g.* software that displays tracking information for a drug product with an ingestible event marker).

Software output information included in the approved product label would be subject to heightened controls under the FDA-required drug labeling regulations. Although FDA does not squarely address this issue, any post-approval changes to the PDURS output in these scenarios, such as changes in displays or sounds, could potentially require changes to the approved labeling and therefore trigger the need for FDA approval of a supplemental new drug application or the submission of a CBE-30 supplement prior to implementing the changes.

PDURS Output As Promotional Labeling and Associated Obligations. FDA proposes that if PDURS output information is not included in FDA-required labeling as described above, then the PDURS output would be considered promotional labeling subject to FDA's postmarket reporting regulations under 21 C.F.R. § 314.81(b)(3)(i) and 601.12(f). Specifically, sponsors would be required to submit such output to FDA at the time of initial dissemination using Form 2253, the same form sponsors currently use to submit other promotional materials. Such submissions would include, among other things, screenshots or other appropriate representations of the user experience for the PDURS. Additionally, FDA proposes that sponsors would be required to submit updates whenever a software update results in changes to the user experience. FDA does not specify how significant a change must be to trigger a new submission requirement.

FDA also explains that, like other promotional labeling, PDURS output should be consistent with the FDA-required labeling based on the factors described in FDA's recent guidance document on this topic (see prior Ropes & Gray [alert](#)). FDA anticipates that most uses of PDURS output would not pose an increased risk compared to other promotional labeling currently in use. FDA asserts, however, that certain software output may provide recommendations that could "direct patients to make decisions about their drug or disease that would normally be made in consultation with a healthcare provider," such as software output that provides recommendations on when to contact their healthcare provider or how to adjust their dose based on their symptoms and other related information. For these software outputs, FDA recommends the sponsor submit the software output through FDA's voluntary, pre dissemination advisory comment process so that the sponsor can obtain feedback from FDA on whether the output is consistent with the FDA-required labeling. PDURS that has received clearance or approval as a medical device does not need to be submitted through the advisory comment process; however, the sponsor is still required to comply with the 2253 submission requirements for the PDURS output at the time of dissemination.

Points for Consideration and Practical Implications

FDA is soliciting comments regarding the proposed framework on a variety of specific issues, including, among others:

- Whether the proposed approach adequately fosters innovation;
- Recommendations for how to appropriately address the balancing of benefit information and risk information when PDURS output includes a benefit claim about the drug;

- The appropriate types of software output for which the pre-dissemination, voluntary advisory comment process is recommended;
- Actions to ensure end users have access to PDURS appropriate to the specific drug dispensed (*e.g.*, in cases of generic substitution); and
- Issues to consider to facilitate timely generic competition for prescription drugs that are approved with PDURS output included in the FDA-required labeling.

If implemented, the proposed framework could have a significant impact on both drug product sponsors looking to innovate with the use of digital health software and the developers of such software. Of particular importance, the requirement to submit PDURS output on Form 2253 may come as a surprise to some sponsors who previously did not consider such software to be labeling. More generally, pharmaceutical companies likely would need to exert heightened control over any software applications that are branded with the company's drug product name because such applications would be considered PDURS if disseminated by or on behalf of the company. Companies likely would also need to become more involved in the process for software updates, as any update to the user experience could trigger the need for a Form 2253 or CBE-30 submission to FDA or potentially even prior FDA approval (if the update is a major change affecting PDURS output information included in the FDA-required labeling). Furthermore, given ambiguity in the proposed framework regarding when software disseminated by or on behalf of the sponsor "accompanies" a prescription drug, companies would need to consider whether the framework would apply to third-party software in which the company has purchased ad space or has otherwise paid for the inclusion of branded product communications.

Other questions raised by FDA could have broader implications that should be carefully considered. For example, determining the appropriate balancing of benefit and risk information in PDURS output could impact the balancing of information in other digital media communications. Additionally, the expanded use of PDURS by branded drug sponsors could raise complex issues related to generic competition.

FDA will be accepting comments until January 22, 2019. Ropes & Gray will continue to monitor these and other developments in the digital health space. If you have any questions about how these issues may affect your interests, please contact any member of Ropes & Gray's [FDA regulatory](#) practice or your usual Ropes & Gray advisor.