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FDA Draft Guidance Sheds Light on Agency's Evaluation of Prescription Drug Use-Related Software

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The U.S. Food and Drug Administration (FDA) recently published a draft guidance document proposing to regulate end-user output of prescription drug use-related software (PDURS) as labeling.[1] The draft guidance sets forth review pathways that could benefit prescription drug application sponsors, including by allowing sponsors to incorporate information about PDURS in the FDA-approved labeling and to seek premarket review for certain PDURS functions that meet the definition of a medical device. But by proposing to regulate PDURS-related information as labeling, the draft guidance poses potential enforcement risks for sponsors under the Federal Food, Drug, and Cosmetic Act (FDCA), the False Claims Act (FCA), and other laws, including through possible off-label promotion claims. Interested parties should consider submitting comments to FDA on the draft guidance. FDA has invited comments through December 18, 2023.

Introduction

On September 19, 2023, FDA published a new draft guidance document outlining the agency's planned approach for regulating PDURS.[2] Sponsors of new drug applications for prescription drugs have developed PDURS as tools to connect with patients and healthcare providers in various ways, such as providing more information about drugs or their potential side effects and aiding in dosing and medication adherence. For example, sponsors have developed tablets, autoinjectors, and inhalers with integrated sensors that can allow providers to monitor when patients take the drug.[3] They have also created patient diary apps that allow patients to document symptoms they experience, and apps that help patients calculate appropriate doses of products such as insulin.[4]

The PDURS Draft Guidance marks a further step in the agency's evaluation of novel technologies, like mobile apps, that are intended for use with FDA-regulated products. The agency previously has addressed when and how it intends to assert jurisdiction over certain software functions intended for use with medical devices as product components.[5] FDA also has described the types of mobile app functions it views as components of new tobacco products, including those that monitor where a product is located, activated, or used.[6]

FDA first proposed a framework for oversight and review of PDURS in a 2018 *Federal Register* notice.[7] FDA developed the PDURS Draft Guidance in response to comments it received on that 2018 notice.[8]

Under the PDURS Draft Guidance, end-user output produced by PDURS would be considered labeling. End-user output is defined by FDA to include any content that PDURS presents to the end user, including static or dynamic screen displays, sounds, or audio messages created by the software.[9] FDA recommends the inclusion of a description of the end-user output produced by PDURS in the prescribing information (PI) if evidence shows a meaningful effect on clinical outcomes or validated surrogate endpoints. In the PDURS Draft Guidance, FDA also outlines proposed oversight

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processes for device-connected PDURS, including premarket review for software functions regulated as medical devices.

The framework in the PDURS Draft Guidance presents both possibilities and risks for prescription drug sponsors. Sponsors that are able to provide supporting data for the clinical impact of PDURS they develop can utilize FDA's regulatory pathways to augment their FDA-approved labeling and enable additional claims about their products. On the other hand, FDA's regulation of PDURS end-user output as labeling would create another area of enforcement risk under FDCA requirements for prescription drug labeling. Moreover, sponsors might also face potential liability under the FCA if end-user output is not consistent with the FDA-approved label.

FDA Proposed Regulation of PDURS Output as Labeling:

- FDA defines PDURS 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."[10] Accordingly, the PDURS Draft Guidance would not apply to third-party software that is not generated on behalf of a drug sponsor, even if the third-party developer's "intention is for the software to be used with one or more drugs or combination products."[11]

- The PDURS Draft Guidance also makes clear that FDA views the software's end-user output as labeling.[12] Under the FDCA, "labeling" refers to "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article."[13] Under the PDURS Draft Guidance, "end-user output" is broadly defined as "[a]ny material (content) that the [PDURS] presents to the end user (a patient, caregiver, or health care practitioner)."[14] These include static or dynamic screen displays, sounds, or audio messages created by PDURS.[15]

- FDA recognizes two categories of labeling: the FDA-required labeling, which includes the PI and other labeling reviewed and approved by FDA in applications, and promotional labeling.[16] In the PDURS Draft Guidance, FDA views the end-user output associated with a software function as FDA-required labeling if a sponsor of a new drug application submits data from one or more adequate and well-controlled studies demonstrating that use of the software function results in a meaningful improvement on a clinical outcome or validated surrogate endpoint.[17] FDA also recommends that the PI describe such software functions and their end-user output.[18] Under the PDURS Draft Guidance, certain post-approval changes to the end-user output from such a software function would need to be submitted to FDA for review and approval, similar to other changes to the FDA-required labeling.[19]

- In contrast, FDA views all other end-user output from PDURS as promotional labeling.[20] Under the PDURS Draft Guidance, end-user output that constitutes promotional labeling would need to be submitted to FDA on an FDA Form 2253 at the time of initial dissemination. Software updates that do not change the end-user output, such as security patches, would not require submission of an FDA Form 2253.[21] FDA also reminds sponsors in the PDURS Draft Guidance that, in accordance with the FDCA and FDA regulations, promotional labeling must be truthful and non-misleading, convey balanced information about a drug's efficacy and risks, and reveal material facts about the drug, including facts about consequences that can result from use of a drug as suggested in a promotional piece.[22]

FDA Oversight for Device-Connected PDURS Functions

- Under the PDURS Draft Guidance, additional considerations also would apply to

certain PDURS functions that are “device-connected,” in that they receive input data from a device constituent that is part of a combination product.[23] Examples of such functions in the PDURS Draft Guidance include software that connects an app and an inhaler or autoinjector to capture and display data about the patient’s usage, and software that supplies information about a patient’s ingestion of a drug from embedded sensors in the tablet.[24]

- FDA recommends that sponsors briefly describe device-connected software functions in the appropriate section of the FDA-approved labeling for the prescription drug, such as the “How Supplied/Storage and Handling” section.[25] In contrast, FDA does not generally expect the approved labeling to describe end-user output from PDURS that does not include device-connected software functions, unless the PDURS is considered essential to a safe and effective use of the drug, or the sponsor has submitted evidence that use of the PDURS leads to a clinically meaningful benefit.[26]

- According to the PDURS Draft Guidance, device-connected functions could meet the definition of “medical device” under the FDCA and be subject to regulation by the Center for Devices and Radiological Health (CDRH). They also may require premarket device submissions, such as a 510(k) notification, de novo classification request, or premarket application (PMA).[27] When it reviews a premarket submission for a device-connected function, CDRH would consult with the Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER), as applicable, to evaluate any considerations related to representations within the PDURS function. For PDURS functions that are medical devices cleared or approved by FDA, changes may require a new premarket submission or supplement.[28]

- Postmarket changes to end-user output of PDURS functions that constitute promotional labeling and do not require a CDRH marketing submission should be submitted to FDA at the time of initial dissemination on Form FDA 2253.[29]

- Consistent with FDA’s enforcement approach to device software functions, FDA intends to focus its device regulatory oversight on PDURS functions which are devices and whose functionality could pose a risk to patient safety if they fail to function as intended.[30]

FDA encourages interested parties to submit comments on the PDURS Draft Guidance to Docket No. FDA-2023-D-2482.[31] FDA requests the submission of comments by December 18, 2023, to allow for agency review before it begins work on the final version of the draft guidance.

Sponsors who currently use, or are considering using or developing, PDURS should consider submitting comments on the PDURS Draft Guidance to help shape the FDA’s development of final guidance. In particular, sponsors should seek to identify costs and complications not identified as considerations by FDA, such as those related to delays in development and FDA clearance or approval of PDURS, where required; challenges that may stem from necessary updates to end-user output from PDURS associated with the FDA-approved labeling; the discrepancy between the approaches in the PDURS Draft Guidance to sponsor-developed PDURS and to third-party-developed PDURS; and potential alternatives or modifications to the PDURS Draft Guidance’s approach that FDA should consider. Sponsors should also consider whether FDA’s proposed framework and review processes, particularly for PDURS described in the FDA-approved labeling, could impact their ability to timely develop and update software to help patients who use their products. Sponsors also should consider potential enforcement and compliance risks and costs that would stem from implementation of the PDURS Draft Guidance, including expansion of possible off-label promotion liability, which remains an active enforcement area for FDA and the U.S. Department of Justice[32] and a frequent claim in class actions.

Gibson Dunn is prepared to help sponsors and other interested entities consider potential effects of the PDURS Draft Guidance and submit comments to FDA recommending modifications to the PDURS Draft Guidance.

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[1] 88 Fed. Reg. 64443 (Sept. 19, 2023); FDA, Draft Guidance for Industry: Regulatory Considerations for Prescription Drug Use-Related Software (Sept. 2023) ("PDURS Draft Guidance").

[2] PDURS Draft Guidance.

[3] *See, e.g.*, *id.* at 11; Office of Inspector Gen., Dep't of Health & Hum. Serv. ("HHS OIG"), Advisory Opinion No. 19-02 (Jan. 24, 2019).

[4] *See, e.g.*, PDURS Draft Guidance at 11-12, 14.

[5] *See, e.g.*, FDA, Guidance for Industry and Food and Drug Administration Staff: Policy for Device Software Functions and Mobile Medical Applications (Sept. 2022) ("Device Software Functions Guidance").

[6] 21 C.F.R. § 1114.7(i)(1)(i); *see also* 86 Fed. Reg. 55300, 55332 (Oct. 5, 2021).

[7] 83 Fed. Reg. 58574 (Nov. 20, 2018).

[8] PDURS Draft Guidance at 1; *see* Docket No. FDA-2018-N-3017.

[9] PDURS Draft Guidance at 6, 16.

[10] *Id.* at 16.

[11] *Id.* at 2.

[12] *Id.*

[13] 21 U.S.C. § 321(m).

[14] PDURS Draft Guidance at 16.

[15] *Id.* at 6.

[16] *Id.* at 2.

[17] *Id.* at 7.

[18] *Id.* at 7-8.

[19] *Id.*; *see, e.g.*, 21 C.F.R. §§ 314.70, 601.12.

[20] PDURS Draft Guidance at 2.

[21] *Id.* at 9.

[22] *Id.* at 4-5; *see, e.g.*, 21 U.S.C. §§ 321(n), 352(a)(1), (f)(1); 21 C.F.R. §§ 201.5, 201.6, 202.1.

[23] PDURS Draft Guidance at 5.

[24] *Id.* at 8, 11

[25] *Id.* at 8-9.

[26] *Id.* at 9.

[27] *Id.* at 3.

[28] *Id.* at 9-10.

[29] *Id.* at 9, 14-15.

[30] *Id.* at 3.

[31] *See* Docket No. FDA-2023-D-2482.

[32] *See, e.g.* U.S. Dep't of Justice, Press Release, "Jet Medical and Related Companies Agree to Pay More Than $700,000 to Resolve Medical Device Allegations" (Jan. 4, 2023).

Gibson Dunn's lawyers are available to assist in addressing any questions you may have regarding the issues discussed in this update. Please contact the Gibson Dunn lawyer with whom you usually work, any leader or member of the firm's FDA and Health Care practice group, or the following authors:

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