DIGITAL THERAPEUTICS ALLIANCE

December 11, 2024

Dockets Management
Food and Drug Administration
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

RE: Docket FDA-2023-D-2482 Regulatory Considerations for Prescription Drug Use-Related Software

The Digital Therapeutics Alliance ("DTA") is a 501(c)(6) non-profit association of industry leaders and stakeholders dedicated to broadening the understanding and adoption of digital therapeutics into healthcare. DTA is the leading international organization on digital therapeutics through leadership and education with the mission of enabling expanded access to high-quality, evidence-based digital therapeutics for patients, qualified health care professionals, and payors in order to improve clinical and health economic outcomes. With over 100 member companies across 17 countries, DTA champions the advancement of high-quality, evidence-based digital therapeutics.

DTA and its member companies, including both pharmaceutical manufacturers and digital health companies, are energized by the Food and Drug Administration's (referred to below as "FDA" or the "Agency") proposed prescription drug use-related software ("PDURS") framework. In requesting comments on the creation of a PDURS framework in 2018 ("2018 Proposal") the Agency's stated goal was "to promote the development of digital technologies that can…help guide the safe and effective use of medicines, to help patients improve their health" and "to modernize our approach to overseeing software products that are designed to be used in conjunction with prescription drugs." The Agency also indicated the framework was intended to "provide prescription drug sponsors the flexibility to develop and disseminate innovative software while maintaining appropriate Agency oversight over the sponsors' communications about their products."

DTA and its members are enthusiastic about achieving these goals and excited about the proposed PDURS framework, particularly the PDURS FDA-required labeling category. This part of the framework allows drug sponsors to add software outputs to

the required drug labeling if they can demonstrate a clinically meaningful benefit to a prescription drug.

DTA has recently initiated a PDURS Working Group, bringing together members actively pursuing PDURS FDA-required labeling solutions for prescription drugs. Through this effort, DTA has identified PDURS FDA-required labeling scenarios that the Agency has not addressed in its 2023 draft guidance on PDURS ("Draft Guidance"). DTA hopes to ensure that these scenarios are considered by the Agency as the Draft Guidance is finalized and recommends including them as additional examples in Appendix A of the final guidance.

Notably, the 2018 Proposal focused heavily on standalone software paired with prescription drugs, whereas the Draft Guidance focuses more on device-connected software that is paired with these drugs. As further discussed below, DTA is concerned about this shift in focus because most of the scenarios under consideration by DTA members for PDURS FDA-required labeling focus on software that achieves its intended purpose without connection to medical device hardware or to a device constituent of a combination product ("Software Products").

Additionally, the Draft Guidance states:

> "The end-user output from prescription drug use-related software with no device-connected software functions generally would be considered promotional labeling and would not be described in the PI, unless the prescription drug use-related software is considered essential to the safe and effective use of a product or the drug sponsor submits evidence demonstrating that the use of prescription drug use-related software leads to a clinically meaningful benefit."

This language coupled with the overall shift in focus from the 2018 Proposal suggests to us that FDA may not have fully contemplated scenarios in which Software Products could indeed play a critical role in the clinical efficacy or safety profile of a prescription drug. There are many such examples under development today, and thus **it is imperative that FDA recognize Software Products' potential to deliver significant clinical benefits and adjust its guidance to accommodate such instances where Software Products meet the evidentiary standard for inclusion in labeling.**

For example, the 2018 Proposal stated:

> "...evidence might be developed that shows that use of prescription drug-use-related software with a drug improves patient compliance and thus improves blood levels of the validated endpoint hemoglobin A1c (HbA1c)

compared to drug use alone. Reductions in HbA1c directly reflect improvement in glycemic control. Therefore, if there is substantial evidence that the use of a dose-tracking or reminder app with an antidiabetic drug results in a reduction in HbA1c compared to taking the drug without using the app, such evidence would be sufficient to support a labeling claim and the prescription drug-use-related software and its output would be described in the FDA-required drug labeling, if the sponsor chooses to submit such evidence as part of a drug application."

This case exemplifies how Software Products can lead to a clinically meaningful benefit with a prescription drug, underscoring its potential significance in enhancing drug efficacy or safety. DTA therefore strongly recommends that this example be included in the final guidance.

Furthermore, there are several additional examples that are known to DTA members where Software Products can provide a clinically meaningful benefit to a prescription drug, including:

- **Personalized Dosing Support Software**: A software function can be integrated with a drug to optimize drug dosing based on active and/or passive inputs from the patient, leading to improved therapeutic or safety outcomes.
- **Behavioral Support Software**: Computerized behavioral therapy or related approaches can be paired with a drug, leading to meaningful and quantifiable enhancements to clinical efficacy. The software may contribute directly to the primary endpoint of an associated drug, or it may complement the drug's primary action with a distinct efficacy endpoint.
- **Symptom Tracking Software**: Software can provide real-time monitoring and systematic tracking of side effects of patients on a drug therapy, leading to a clinically meaningful enhancement to patient safety outcomes. Such software can offer timely and precise data on adverse reactions, allowing for swift intervention and adjustments in treatment protocols that are tailored to individual patient needs. This early detection capability is particularly essential for drugs with significant risk profiles, where delays in managing adverse events could lead to severe or irreversible patient harm.
- **Prognostic Software**: Software can be used to predict disease severity or the likelihood of disease flares in patients on pharmacotherapy, leading to improved efficacy and safety outcomes. The software can provide actionable insights into

disease trajectories, enhancing patient safety and optimizing efficacy outcomes through individualized risk management and tailored treatment plans.

- **Biofeedback Software:** A digital intervention can incorporate stress reduction techniques such as biofeedback to reduce systemic inflammation, enabling better receptiveness to a drug, and leading to improved safety or efficacy outcomes. Examples include cardiovascular disease and pain management.

DTA respectfully requests that these examples be incorporated into Appendix A of the final guidance as instances of FDA-required labeling. Including these cases will provide clear, practical illustrations of scenarios where Software Products achieve a clinically meaningful benefit, thereby enhancing the guidance's relevance and applicability.

Thank you for considering our feedback, and we look forward to continued collaboration in advancing digital health innovation.

Sincerely,

Andy Molnar
Chief Executive Officer
Digital Therapeutics Alliance