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Telehealth Policy to Transform Healthcare

October 17, 2025
Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Comments on Draft Guidance for Industry: "Regulatory Considerations for Prescription Drug-Use-Related Software" (Docket No. FDA-2023-D-2482)

Dear Sir or Madam:

On behalf of the American Telemedicine Association] (hereinafter "ATA"), we appreciate the opportunity to submit comments on FDA's 2023 Draft Guidance *Regulatory Considerations for Prescription Drug-Use-Related Software (PDURS)*. ATA represents a broad cross-section of stakeholders engaged in advancing safe, effective, and evidence-based integration of digital health technologies with prescription drug products.

There is considerable enthusiasm for the PDURS framework among ATA members, particularly the FDA-Required Labeling category, which allows drug sponsors to add software outputs to the required drug labeling when they can demonstrate a clinically meaningful benefit to a prescription drug. When the Agency introduced the PDURS framework in 2018, the original intent 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 emphasized that 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." ATA members are aligned with this bold vision of the PDURS framework, and several pharmaceutical manufacturers have already begun developing innovative, clinically validated software solutions that are intended to be paired with prescription drugs and included in their labels, across a range of therapeutic areas.

PDURS will transform healthcare delivery by aligning the interests of all stakeholders around what matters most: patient outcomes. By enabling digital solutions tailored to specific medications, PDURS creates optimized treatment experiences that directly improve patient health and wellbeing. It gives pharmaceutical companies an opportunity for differentiation by pairing their medications with digital tools that boost adherence, strengthen therapeutic outcomes, and deepen patient engagement with their treatment. PDURS also empowers providers to, at their discretion, deploy these solutions to patients who need them most, without adding cost or administrative burden. This is not incremental improvement—it is a fundamental shift toward precision healthcare that serves patients, advances medicine and works within the realities of clinical practice.

This transformation is uniquely positioned to establish American leadership in next-generation therapeutics. The PDURS framework represents a remarkable opportunity for American innovation—

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one that positions U.S. industry to lead from the front, with the ultimate winners being American patients and the broader public. No other country has put forth such a bold vision for the integration of prescription drugs and software, and global policymakers are following this initiative to see how it can be adopted in their healthcare systems. The fact that the Agency has proposed this framework demonstrates clear foresight on how the next generation of therapies can be brought to patients, and we are both excited and grateful that the Agency has been so intentional about putting patients first and allowing industry to drive innovation in a way that can significantly improve healthcare outcomes.

We view the PDURS initiative as both de-regulatory, because it supports the pairing of software and drugs without the constraints of the traditional combination product framework, and deflationary, because it can allow for more effective, integrated solutions without added cost to the healthcare system. This initiative has our full and enthusiastic support.

We commend FDA for continuing to build upon the 2018 PDURS framework and for recognizing the importance of providing clarity to industry regarding the inclusion of software-related information in FDA-required labeling. However, we respectfully submit that several sections of the 2023 draft guidance diverge from the original intent of the 2018 PDURS framework, introduce unnecessary ambiguity, and risk limiting the ability of innovative standalone software solutions to demonstrate and deliver clinically meaningful benefits to patients.

This document provides attached detailed line by line comments that represents consensus from ATA members on specific changes that should be made to the final guidance to better reflect the Agency's original goals for the PDURS framework and that are aligned with the approach that pharmaceutical manufacturers and digital health companies are currently pursuing with PDURS. The detailed comments support the three key themes:

1. **Capture the de-regulatory intent of the 2018 PDURS Framework language in final guidance**: FDA should revert to the more flexible 2018 framework language, particularly in Section II.B., which appropriately focused on whether sponsors provide substantial evidence of a clinically meaningful benefit, rather than suggesting that software be "essential for safe and effective use" or directly tied to a device constituent of a combination product. FDA should also allow greater flexibility in evidence generation. Given the favorable benefit/risk profile of software, sponsors should be permitted to demonstrate clinical benefit through a range of control conditions (per 21 CFR 314.126(b)), as well as through real-world evidence—approaches already recognized by CDRH for digital health.
2. **Reflect the industry consensus that most PDURS required labeling solutions will be standalone software rather than combination software or device-connected software**: Pharmaceutical manufacturers are developing predominately standalone software solutions for PDURS—software that achieves its intended purpose without connection to medical device hardware or to a device constituent of a combination product. Yet, the current draft guidance creates unnecessary ambiguity about how these solutions can be appropriately reviewed by FDA. The final guidance should clearly articulate the approach for standalone software to appear in drug

labeling when supported by adequate evidence of a clinically meaningful benefit and be explicit that software does not need to be connected to a device constituent or classified as a combination product to quality for PDURS designation. The language from Section II.B. of the 2018 PDURS Framework should be restored to support these proposed revisions, and FDA should incorporate examples of standalone software into Appendix A of the final guidance as instances of FDA-required labeling.

3. **Reduce ambiguity:** The current draft guidance leaves critical questions unanswered and creates uncertainty that will slow adoption and discourage investment in PDURS solutions. FDA should better define key terminology—particularly, standalone software, device-connected software, software output, and clinically meaningful benefit. FDA should also provide clearer direction regarding early engagement with the FDA on PDURS, evidence requirements, and submission options for both the software output and the software itself.

We believe the proposed refinements will ensure that the PDURS guidance provides a consistent, predictable, and innovation-friendly regulatory framework while maintaining FDA's high standards for safety and efficacy.

We thank the Agency for its continued engagement with stakeholders and its commitment to developing guidance that reflects the evolving role of digital health technologies in drug development and patient care. ATA welcomes the opportunity to further collaborate with FDA in refining this guidance.

Respectfully submitted,

Attachment: Line-by-Line Comments on Draft Guidance

Line Numbers	Draft Guidance Text	Comment / Proposed Changes
46-53	How the FDA-required labeling, in particular the Prescribing Information (PI), should describe prescription drug use-related software that: - Is determined to be essential for the safe and effective use of the drug product, or - Relies on data directly transferred from the device constituent part of a combination product (see 21 CFR 3.2(e) (defining "combination product") and CFR 4.2 (defining "constituent part"))	1. These two statements are new additions to the 2023 draft guidance and are not reflected in any of the public comments to the 2018 PDURS framework. Further, they contradict the original intent to of the 2018 PDURS framework and are in conflict with many statements in both the 2023 draft guidance and 2018 PDURS framework. The first statement: "Essential for the safe and effective use of the drug product" algins somewhat with the definition of cross-labeled combination product 21 CFR 3.2(e)(3) and (4): "where both are required to achieve the intended use, indication, or effect." The second statement is explicitly reflective of a combination product. However, there are many scenarios, including explicit examples in the 2018 PDURS framework and language in the 2023 draft

		guidance, where standalone software can provide clinically meaningful benefit to a drug. ATA recommends reverting to the language in the 2018 PDURS framework, which more clearly stated that software could be included in FDA-required labeling if the sponsor provides evidence in a marketing application demonstrating "*substantial evidence of an effect on a clinically meaningful outcome as a result of the use of the prescription drug-use-related software*," without suggesting that it be "essential" or "device-connected." Specifically, ATA strongly recommends that FDA reverts to the language of the 2018 PDURS framework, under Section II.B. "Information About Prescription Drug-Use Related Software Output That May Be Included in FDA-Required Labeling."
99-103	Various software functions, including those associated with mobile applications (apps), are currently available to consumers for a variety of health-related uses, such as assisting patients with tracking their own drug ingestion, allowing health care practitioners to monitor patients taking a prescription drug, or providing information on how to use a drug.	2. ATA recommends including additional PDURS examples that are commonly being developed by industry: -Helping patients manage side-effects related to a drug -Improving behavioral health symptoms that may be impacted by a drug -Providing personalized dosing recommendations for patients on a drug -Predicting disease severity or treatment response and personalizing treatment accordingly
140-142	These factors include (1) whether the prescription drug use-related software provides a function that is essential to the safe and effective use of the product	3. See Comment 1
143-145	and (3) whether the prescription drug use-related software relies on data directly transferred from the device constituent part of a combination product.	4. It is unclear why one of the three factors specifically focuses on data directly transferred from the device constituent part of a combination product. If the prescription drug use-related software relies on data from a device constituent part of a combination product, then the software would be expected to be reviewed by FDA as part of a combination product submission. If the software achieves its intended purpose without connection to medical device hardware or to a device constituent of a combination product, it may be considered software as a medical device (SaMD). The SaMD itself would be regulated by FDA under an appropriate CDRH regulatory pathway if the prescription drug use-related software output is not essential to the safe and effective use of the drug product, or alternatively the SaMD would be regulated by FDA under a combination product submission if the criteria per 21 CFR 3.2(e) apply.

		In both cases, the software output could support a clinical benefit. ATA recommends that the guidance be updated such that the focus is on the clinical benefit and the mechanism of action provided by the software output, not simply data transfer to hardware.
156-158	***Device-connected prescription drug use-related software functions*** (hereafter referred to as "device-connected software functions") rely on data directly transferred from the device constituent part of a combination product	5. "Device-connected software" is an ambiguous and arbitrary term. There are many examples of device-connected software functions from medical devices that are not device constituent parts of a combination product, with the medical device either being software in a medical device (SiMD) or SaMD. ATA suggests replacing this term with "device constituent-connected software" for precision and clarity.
160-162	All remaining prescription drug use-related software functions (e.g., those functions that rely on user-inputted data) would not be considered device-connected software functions.	6. ATA suggests that FDA provide clear definitions of other relevant prescription drug use-related software functions. This should include "standalone prescription drug use-related software functions", which rely on software to achieve its intended purpose without connection to medical device hardware or to a device constituent of a combination product.
179-181	**IV. DESCRIBING PRESCRIPTION DRUG USE-RELATED SOFTWARE FUNCTIONS AND END-USER OUTPUT IN THE PRESCRIBING INFORMATION**	7. ATA strongly recommends that FDA reverts to the language of the 2018 PDURS framework, under Section II.B. "Information About Prescription Drug-Use Related Software Output That May Be Included in FDA-Required Labeling." This section focuses on two situations that are applicable to PDURS FDA-Required Labeling: (1) Standalone software; and (2) Combination software. The first situation is reflective of industry's current view of how standalone software output can be used to provide clinically meaningful benefit and be included in the prescribing information. Standalone software can achieve its intended purpose without connection to medical device hardware or to a device constituent of a combination product. ATA suggests that FDA includes this language in the final guidance. The language in Section II.B. includes a specific example of standalone software (a "dose tracking or reminder app") in which the standalone software output "would be described in the FDA-required drug labeling". ATA suggests that FDA includes this example in the final guidance. The language in Section II.B. further suggests that the choice to submit evidence of a clinically meaningful benefit is optional, where it states, "if the sponsor chooses to submit such evidence as part of a drug application." ATA suggests that FDA also revert to

		this language in the final guidance, which provides for optionality.
179-181	**IV. DESCRIBING PRESCRIPTION DRUG USE-RELATED SOFTWARE FUNCTIONS AND END-USER OUTPUT IN THE PRESCRIBING**	8. The draft guidance does not provide clarity on marketing submission options, with the potential options varying depending on whether the drug is approved or investigational, and if the software is standalone software or a device constituent of a combination product. ATA recommends that FDA provides clarity on marking submission requirements for each of these scenarios. ATA suggests that this information is included within the reverted language of the 2018 PDURS framework, under Section II.B. "Information About Prescription Drug-Use Related Software Output That May Be Included in FDA-Required Labeling" from Comment 7. Specifically, ATA recommends that FDA include the language from Section II.B., but that the third paragraph of Section II.B.: *"When a sponsor develops clinical evidence from adequate and well-controlled investigations regarding the use of prescription drug-use-related software with a previously approved drug and the sponsor would like to include this information in FDA-required labeling, under this proposed framework, we would expect the sponsor to submit the information to the Agency as a new original application for review. The sponsor should work with the appropriate review division within FDA in developing the submission."* is replaced in the final guidance with the new language below that clarifies that a sponsor can submit evidence as part of a drug application for both previously approved drugs and investigational drugs that have not yet been approved. The current draft guidance focuses on the former. The suggested new language is as follows: *In both situations, when a sponsor develops clinical evidence from adequate and well-controlled investigations regarding the use of prescription drug-use-related software with a drug and the sponsor would like to include this information in FDA-required labeling, we would expect the sponsor to submit the information to the Agency as part of as part of a new drug application (NDA), an abbreviated new drug application (ANDA), a biologics license application (BLA), or supplemental application (21 CFR 314.50(c)(2) and 314.94(a)(8); 21 CFR 601.2(a)), depending on the regulatory pathway of the prescription drug use-related software and whether the drug has been previously approved.*

		With standalone SaMD, the prescription drug use-related software itself is regulated by CDRH and subject to a CDRH marketing submission if it is a non-exempt device; the software output would be reviewed by CDER or CBER, with an NDA, ANDA, or BLA expected for drugs or biologics that have not previously been approved, and a supplemental application expected for drugs or biological that have previously been approved. If the prescription drug use-related software is a device constituent part or an element of a device constituent part of a combination product, both the software and software output would be reviewed by CDER or CBER as a combination product through an NDA, ANDA, BLA, or supplemental application, with CDRH consulted for review of the device constituent technical documentation. The sponsor should work with the appropriate review division within FDA in developing the submission.
193-194	However, to date, the Agency's experience with software functions not considered to be device-connected is that these software functions are more akin to an optional tool	9. ATA suggests that this statement be removed. Since the draft guidance was published, industry has introduced several examples to the Agency of standalone software output that can be used to provide clinically meaningful benefit and be included in the prescribing information. In these examples, the standalone software can achieve its intended purpose without connection to medical device hardware or to a device constituent of a combination product. Instead, ATA suggests FDA provide more clear guidance on standalone software output from prescription drug use-related software that can be used to provide clinically meaningful benefit and be included in the prescribing information.
197-200	Functions such as these that are not directly transferring information from a device constituent part to software, including mobile apps, should not be described in the PI unless there is an additional factor (e.g., the function is necessary for safe and effective use of the drug) that warrants including this information in the PI	10. See Comment 1
224-228	sponsors may propose including information specifying that use of the prescription drug use-related software with the product results in a meaningful improvement in a clinical outcome as compared to use of the product without the prescription drug use-related software (demonstrated by one or more adequate and well-controlled studies)	11. ATA suggests that FDA incorporate specific language from 21 CFR 314.126(b) clarifying that one of several control conditions (placebo concurrent control, dose-comparison concurrent control, no treatment concurrent control, active treatment concurrent control, historical control) may be utilized to demonstrate a clinically meaningful benefit. ATA also suggests that FDA clarify that real world studies can be used to demonstrate a clinically meaningful benefit, in alignment with FDA's draft guidance on Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices (issued December 2023). Further, ATA suggests that FDA state that

		clinical study design and evidence decisions are risk-based, and that industry may engage with FDA for alignment on these decisions in a pre-submission.
228	For example, the evidence may demonstrate that a combination product with device-connected prescription drug use-related software (e.g., a dose-tracking app that relies on data on drug use directly transferred from a device constituent part within the product) leads to a meaningful change in a clinical outcome or validated surrogate endpoint compared to using the combination product without the device-connected prescription drug use-related software.	12. ATA suggests that FDA revert to the original version of this example, from Section II.B. of the 2018 PDURS framework that states: *"For example, 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 example specifically describes standalone software that can achieve its intended purpose without connection to medical device hardware or to a device constituent of a combination product.
238-240	…post-approval changes to such output (e.g., end-user output from a mobile app specific to the software function) should be reviewed and approved by FDA as is required for other changes[25] to FDA-required labeling. 25. Applicants must notify FDA about changes to an existing NDA consistent with 21 CFR 314.70. Certain prescription drug use-related software function information may be submitted in an annual report if the information is consistent with 21 CFR 314.70(d)(2).	13. ATA recommends that FDA clarify the regulatory pathway required for approving changes to FDA-required labeling that include prescription drug use-related software output. This may vary whether a drug is approved or investigational. When adding prescription drug use-related software to the PI of an approved drug, ATA recommends that FDA clarity what kind of supplemental application would be required [Prior Approval Supplement (PAS), Changes Being Effected in 30 Days (CBE-30), Changes Being Effected (CBE-0), Annual Report], or whether the type of supplement is a risk-based decision.
240-245	When a sponsor is considering developing clinical evidence to support the use of prescription drug use-related software and the sponsor would like to include this information in FDA-required labeling, the sponsor	14. ATA suggests that FDA provide clarity on how industry can work with the appropriate review division, depending on the status of the drug. The appropriate type of interaction can vary greatly depending on whether the drug is approved or investigational, and if it is investigational, the type of interaction could depend on the stage (e.g., phase I, prior to phase II, end of

	should work with the appropriate FDA review division early in the development process to discuss the types of data and information that would support inclusion of the prescription drug use-related software-related information in the PI.	phase II). In some cases, sponsors may also want to engage with the Agency on PDURS FDA-Required Labeling before a specific drug has been identified. There are many possible interaction mechanisms [Type B (pre-IND, end of phase II), Type C, INTERACT] that may be appropriate depending on drug approval status and stage.
254-255	The following examples describe software with such device-connected software functions:	15. These examples are very narrow in scope, only focusing on data transfer for device constituent-connected software. ATA suggest that FDA rename the section header to be specific to this type of product, or that it expand this section to give additional examples, including examples with standalone software.
315-316	**APPENDIX A: EXAMPLES OF PRESCRIPTION DRUG USE-RELATED SOFTWARE FUNCTIONS AND END-USER OUTPUT**	16. ATA suggests that additional examples are provided with standalone software functions, such as those given in the December 11, 2024 public comment by Digital Therapeutics Alliance (comment ID: FDA-2023-D-2482-0016). The examples are as follows: · *Personalized Dosing Support Software that 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 through computerized behavioral therapy or related approaches, leading to an additive clinical efficacy benefit that is directly related to the primary endpoint of the drug or additional clinical efficacy benefit in an endpoint that is distinct from the primary endpoint of the drug.* · *Symptom Tracking Software to improve side effect management for patients on a drug with a serious risk profile, leading to a clinically meaningful improvement in safety outcomes.* · *Prognostic Software that can predict disease severity or disease flares, supporting disease management, side effect management, or dosing, and leading to improved efficacy or safety outcomes.* · *Biofeedback Software that 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.*
457	**GLOSSARY**	17. See Comment 6.