Emerging Drug-Device Combinations: A Digitally Enhanced Patient Experience

Kristina J. Lauritsen, PhD
Combination Product Regulatory Policy Advisor
Center for Drug Evaluation and Research
Food and Drug Administration

Topics

- Digital Health
- Devices and Combination Products
- Software as labeling – PDURS framework

mHealth apps category is expected to grow at a compound annual growth rate of 38.9% between 2018 and 2023

Source: P&S Intelligence

The global drug-device combination product market is expected to reach:

$139.2B by 2025

Source: Allied Market Research

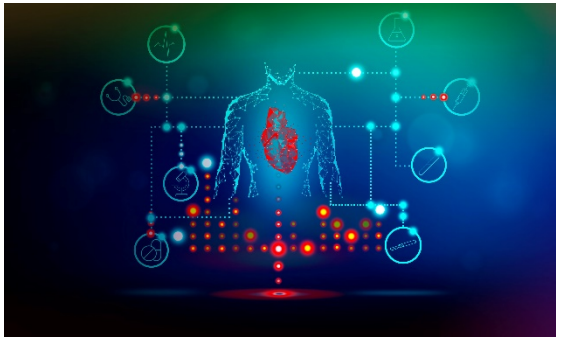
$177.7B by 2024

Source: Grand View Research

Consumers are embracing wearables and other technologies to track their health information. Half of surveyed consumers use this technology and of those 53% share this information with their doctor.

Source: Deloitte 2018 Survey of US Physicians

But…



Only 9% of doctors have implemented technology for remote monitoring and/or integration of data from wearables. Another 27% plan to add the capability in the next 1-2 years.

Source: Deloitte 2018 Survey of US Physicians

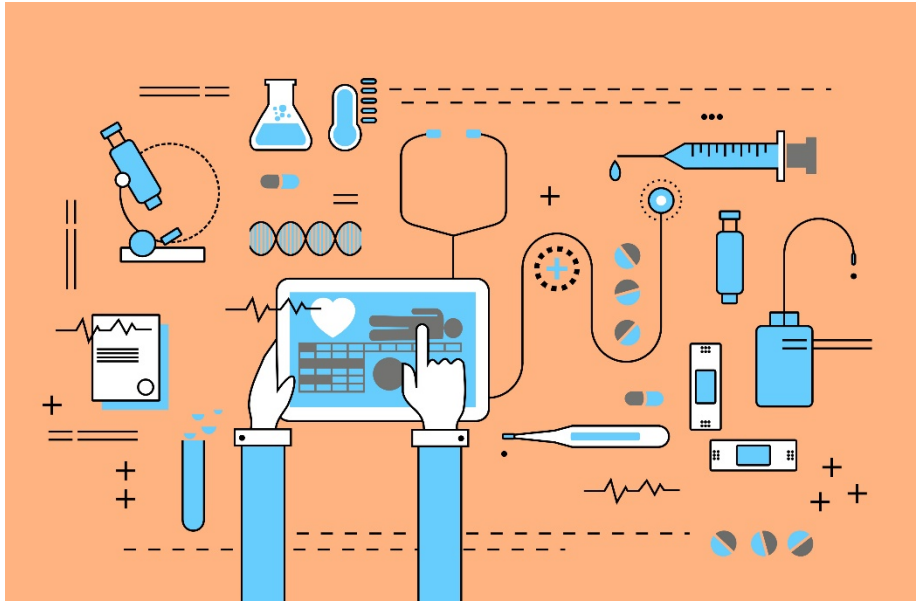
Digital Health

- Mobile Platforms
- Interoperability
- Cybersecurity
- Telemedicine
- Advanced Analytics
- Software
- Wireless
- Machine Learning

Digital Health for Pharmaceuticals

- Potential benefits for providers
  - Improve communication with patients
  - Improve medication adherence
  - Closer in time capture of disease symptoms or drug effects
  - Promote patient independence
- Potential benefits for patients
  - Improve communication with HCPs
  - Information available in real-time
  - Optimized care
  - Monitoring/information for caregivers

Expanding Possibilities



Software can….

- Capture patient-reported outcomes in clinical trial
- Monitor medication adherence
- Enhance patient-HCP interaction
- Support switch from Rx to OTC
- And more to come

Devices and Combination Products

Devices Used with Drugs

- Diagnostic tests
  - Drug levels
  - Phenotyping
  - Biomarkers
- Imaging modalities (CT, PET, MRI)
  - Disease Response
- Activate the drug
  - Photodynamic therapy
- Outcome measuring devices
  - Treadmill / spirometry
  - Body composition
- Patient or home use
  - Dosage cups, spoons
- Software
  - Capture patient-reported outcomes in clinical trial
  - Monitor medication adherence
  - Enhance patient-HCP interaction
  - Support switch from Rx to OTC
- Drug Delivery Devices
  - Metered-dose/Dry Powder Inhalers
  - Transdermal Patches
  - Prefilled syringes
  - Infusion Pumps
  - Autoinjectors
  - Drug-loaded implants

Not All Software is a Device

21st Century Cures – Medical Software

Impact to device definition

The new law amended the definition of “device” in the Food, Drug and Cosmetic Act to exclude certain software functions intended...

- *(A) for administrative support;*
- *(B) for maintaining or encouraging a healthy lifestyle;*
- *(C) to serve as a electronic patient records;*
- *(D) for transferring, storing, converting formats, or displaying clinical laboratory test or other device data and results and certain other related information; and*
- *(E) to provide recommendations to health care professionals for clinical decisions, where the user can independently review the basis of the recommendation.*

Impact to Oversight

- Multiple Functions 
  - Defined by 21 Century Cures as product with:
    - At least one function meets the definition of a device
    - At least one function that does not meet the definition of a device
  - FDA oversight will only focus on device function unless non-device function has an impact on the device function

Policy Impact

- Modifies device definition to embrace technological advances
- Codifies what was typical practice
- Draft Guidance on the impact of 21 Century Cures has been published

General Wellness Products

- A software function with a healthy lifestyle claim is **not a device** as long as its claims are unrelated to the diagnosis, cure, mitigation, prevention, or treatment of a disease or condition.

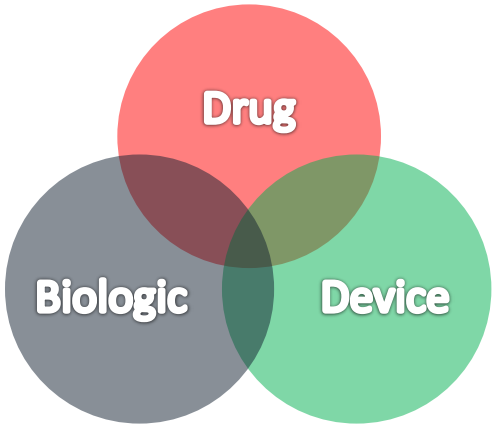
- If the intended use of the software function is related to the diagnosis, cure, mitigation, prevention, or treatment of a disease or condition, then the product is **not excluded** from the definition of the term “device” under section 520(o)(1)(B) of the FD&C Act.

Is it a Combination Product?

What is a Combination Product?

Combinations of 2 or more DIFFERENT medical products:

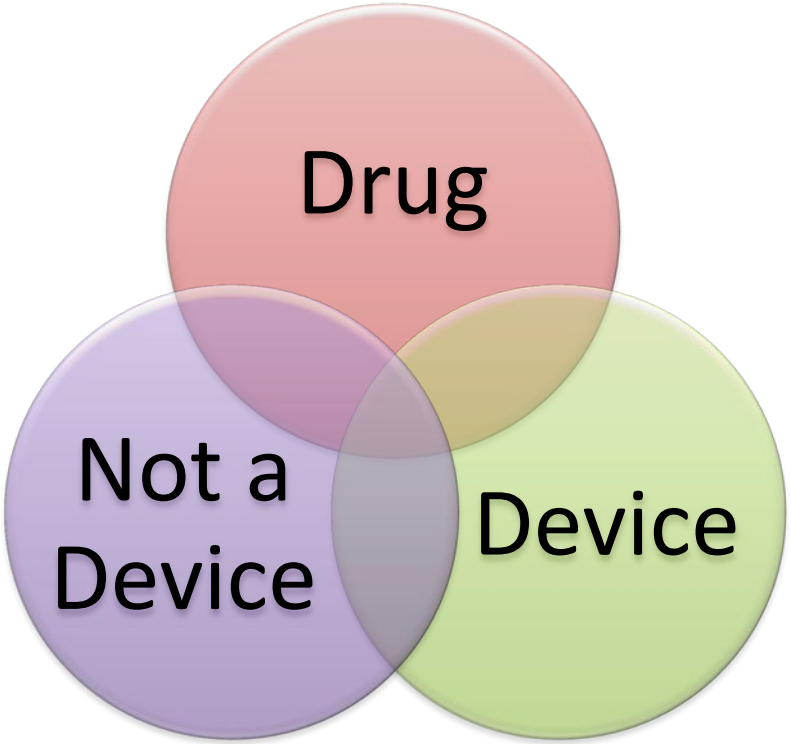
- Drug + Device
- Device + Biologic
- Drug + Biologic
- Drug + Device + Biologic



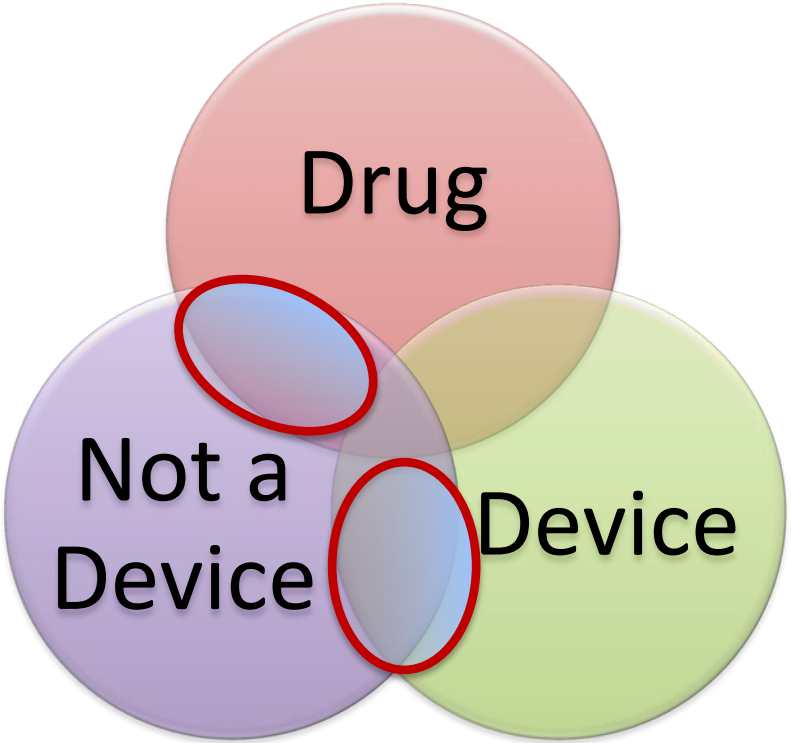
Types of combination products

- Defined by 21 CFR 3.2(e)
- Physically or chemically into a single entity
- Co-packaged / Kit
- Sold separately, but labeled for use together (“cross-labeled”)

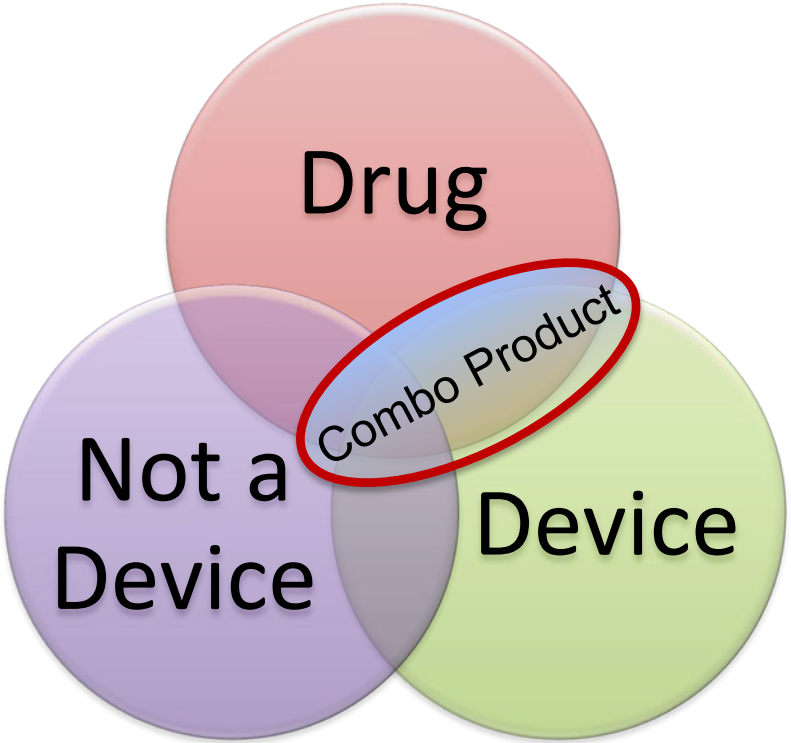
Software + Drug



Software + Drug ≠ Combination Product

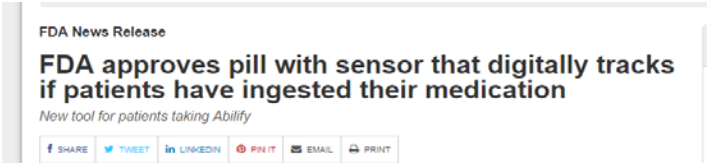


Software + Drug May Be Combination Product



Drugs and Digital Health

- Growing experience with drugs + software


FDA News Release

FDA approves pill with sensor that digitally tracks if patients have ingested their medication

New tool for patients taking Abilify

SHARE TWEET LINKEDIN PIN IT EMAIL PRINT

- CDER established an internal WG on digital health
  - Representation from across CDER and including CDRH
  - Addressing policy issues for software used with drugs
  - Resource for review teams with application-specific questions
  - Goal is risk-based approach that also considers existing CDRH policies on software as a medical device

Prescription Drug Use Related Software

Proposed PDURS Framework

PDURS

What: Proposed framework for Prescription Drug Use Related Software (PDURS) disseminated by or on behalf of drug sponsors for use with one or more of their prescription drug products.

Why: Provide prescription drug sponsors the flexibility to develop and disseminate innovative software, while maintaining appropriate Agency oversight over the sponsors' communications about their products.

Goal: Development of guidance based on feedback

When: Open for comments until April 29 (Docket No. FDA-2018-N-3017)

PDURS Highlights

- Risk-based approach
- Independent of device status
- Output of software is labeling

Docket No. FDA-2018-N-3017, Closes April 29, 2019

Risk-based

The proposed framework is designed to take a risk-based approach to PDURS.

It is anticipated that in most cases, the output of such software will not require review by FDA prior to dissemination.

Device Status

- Whether software is a device is determined by CDRH and may depend upon the software's functions.
- The focus of this proposed framework is not on whether the software is a device. While FDA anticipates that some PDURS will meet the definition of a device, other PDURS will not meet this definition.
- This proposed framework does not alter the regulatory framework for devices, but focuses on the output of software disseminated by or on behalf of a drug sponsor for use with one or more of its prescription drug(s).

Impact to Stand-Alone Software?

No change to FDA's regulation of a stand-alone software function that does not accompany a prescription drug (e.g., a software function that uses complex algorithms to analyze a skin lesion to determine whether it contains cancerous cells or blood establishment computer software and accessories used in the manufacture of blood and blood components).

If, however, software that is a device is disseminated by or on behalf of a sponsor of a prescription drug for use with that drug, it may be subject to regulation under drug, biologic, and device authorities, as appropriate. For example, when PDURS meets the definition of a device because of its function, it would be subject to regulation as a device and its output may also constitute drug labeling.

Focus on Output of Software

Regardless of whether a software function meets the definition of a device, or is a device that falls within an FDA enforcement discretion policy related to software as a device, under this proposed framework, only the **output** of the software disseminated **by or on behalf of a drug sponsor** for use with one or more of the drug sponsor's prescription drugs would be treated as drug labeling.

What is Output?

The material presented to the end user of the PDURS (including a patient, caregiver, or healthcare professional) constitutes the output.

- screen displays (static or dynamic)
- sounds
- audio messages

Docket No. FDA-2018-N-3017, Closes April 29, 2019

Drug Labeling

FDA generally recognizes two broad categories of labeling for drugs:

(1) FDA required labeling 

(2) Promotional labeling 

Required Labeling

For prescription drugs and biological products, FDA-required labeling is the labeling, drafted by the manufacturer, that is **reviewed and approved by FDA**

It includes the information that is **essential for a provider to make an informed decision** about the risks and benefits of prescribing the drug for a patient and **the information needed to safely and effectively use the drug.**

Promotional Labeling

Promotional labeling is generally **any labeling other than FDA required labeling that is devised for promotion** of the product.

Promotional labeling may have other functions in addition to promotion.

Promotional labeling can include **printed, audio, or visual matter descriptive of a drug** that is disseminated by or on behalf of a drug's manufacturer, packer, or distributor.

(21 CFR 202.1(l)(2))

Promotional Labeling, cont.

Promotional labeling is not approved by FDA in advance of dissemination.

Applicants submit to FDA's Office of Prescription Drug Promotion (OPDP) or Advertising and Promotional Labeling Branch (APLB), as appropriate, ‘‘labeling or advertising devised for promotion’’ of a drug product at the time of initial dissemination or publication of such promotional labeling or advertisement.

(21 CFR 314.81(b)(3)(i) and 601.12(f)))

Promotional Labeling, cont.

Submission of promotional materials to OPDP or APLB is a longstanding requirement applicable to all communications that are considered promotional labeling, regardless of the content of those communications or the medium used for distribution.

PDURS output would be subject to the same regulations as other promotional materials disseminated by or on behalf of the drug sponsor, such as patient brochures.

Docket No. FDA-2018-N-3017, Closes April 29, 2019

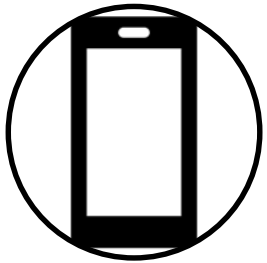
PDURS in Labeling

Drug Tracking Software Continuum

Ingestion of Drug with Device Enables Tracking and Results in Clinically Meaningful Benefit

Ingestion of Drug with Device Enables Tracking

Use of Device Enables Tracking but Drug Product Unchanged



Patient-input Required Tracking (via mobile app)

Required Labeling ⟵ ⟶ Promotional Labeling

PDURS in FDA-Required Labeling

Docket No. FDA-2018-N-3017, Closes April 29, 2019

When is PDURS Required in labeling?

(1) Where the drug sponsor demonstrates to FDA that there is substantial evidence of an effect on a clinically meaningful outcome as a result of the use of the PDURS, or

(2) 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 of which such software is a device constituent part or an element of a device constituent part.

1. Clinically Meaningful Outcome

IF: A sponsor demonstrates through substantial evidence (from one or more adequate and well-controlled investigations) that the use of software with a drug results in a clinically meaningful improvement compared to using the drug alone, and the sponsor chooses to submit such evidence as part of a drug application.

THEN: Information about the PDURS output would be included in FDA required labeling (e.g., prescribing information, medication guide, or instructions for use).

HOW: FDA generally would expect the sponsor to submit the information to the Agency as a new original application for review.

2. Essential To Combo Product

IF: The PDURS is software that is part of a system comprising a device constituent part **or** is itself a device constituent part of a drug-device combination product, **and** such software provides a function or information that is essential to one or more intended uses of that product.

THEN: Information about that function of the software is included in the FDA-required drug labeling because that function is essential for the combination product to achieve one of its intended uses—for example, tracking ingestion of the drug.

For example, CDER recently approved Abilify MyCite, a combination product comprised of aripiprazole tablets embedded with an ingestible event marker (IEM) designed to communicate a time-stamped confirmation of IEM device ingestion with an external patch. Software is used to interact with the external patch to organize and display the information about ingestion for a patient, provider, or both.

Docket No. FDA-2018-N-3017, Closes April 29, 2019

PDURS as Promotional Labeling

Docket No. FDA-2018-N-3017, Closes April 29, 2019

When is PDURS Promotional?

PDURS output that is not included in FDA-required labeling is **devised, at least in part, to promote use of a sponsor's prescription drug.**

For example, such output would likely display the name of the drug and may be marketed as part of an integrated system to encourage use of the drug over a competing product.

While PDURS output that promotes a prescription drug may also serve additional purposes, such as providing electronic reminders or other information about the prescription drug or the disease it is intended to treat, it is nonetheless devised, at least in part, to promote the use of the sponsor's prescription drug.

Submit PDURS Like Other Promotional Materials

In the same way that drug sponsors currently submit their other promotional materials, PDURS also submitted to FDA by drug sponsors at the time of initial dissemination using Form FDA 2253 (‘‘Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use’’).

- Include screenshots or other appropriate representations of what the user will experience
- Updates should be submitted to FDA at the time of initial dissemination only when an update to such software results in changes to the output experienced by the user
- Software updates, such as security patches and other software updates that do not alter the output, would not need to be resubmitted.

Docket No. FDA-2018-N-3017, Closes April 29, 2019

Is PDURS Output Consistent with Required Labeling?

In order to help evaluate whether a sponsor's communication is consistent with FDA required labeling, FDA recently published a guidance entitled ''Medical Product Communications That Are Consistent With the FDA-Required Labeling—Questions and Answers.''

That guidance explains that, in evaluating whether a product communication is consistent with the FDA-required labeling for that product, among other factors, FDA will evaluate whether product communications ''increase the potential for harm to health relative to the information reflected in the FDA-required labeling.''

Docket No. FDA-2018-N-3017, Closes April 29, 2019

Reliability of Software

Unlike other types of promotional labeling, such as patient brochures and booklets, PDURS output could change if, for example, the software does not function as intended.

Whether PDURS output is consistent with the FDA-required labeling may be dependent upon reliability of the underlying software to produce its output as intended.

Expect PDURS output would be reliably produced by the software.

It is the responsibility of the drug sponsor to ensure the reliability of the PDURS it disseminates; FDA's labeling oversight described in this proposed framework focuses only on the output, not the software.

Most PDURS Will Not Increase Risk

For example, an app that a sponsor makes available that allows **patients** to track signs and symptoms or reminds patients to take an upcoming dose, but does not instruct them to alter their dose or intake of a drug, would not be expected to increase risks associated with use of the drug provided it functions as intended.

- The user interface is also an important component and expect sponsors to consider how the design of the user interface could affect the use of the PDURS output with their drugs.

PDURS output directed to **healthcare providers** is generally not expected to pose additional risk (e.g., an app made available by a sponsor that gives healthcare providers information on when dosing adjustments consistent with the labeling for that sponsor's drug might be warranted based on clinical data) because of the healthcare providers' training and expertise in properly evaluating treatment options.

Examples

- App that reminds providers to obtain a blood test before prescribing or renewing a drug prescription as recommended in the FDA-required labeling.
- App that provides patients with information about their prescribed drug that is also found in the FDA required labeling directed to patients (i.e., instructions for use or patient labeling or both).
- App that allows a patient to record the incidence or severity of symptoms of their condition.
- App that allows a patient to enter a regimen for a drug and then reminds the patient to take a dose if the patient fails to record taking a dose at the scheduled time of administration.

Docket No. FDA-2018-N-3017, Closes April 29, 2019

Voluntary Advisory Comment

Where an app processes symptom-related information and provides recommendations on when the patient should or should not contact a healthcare provider, the use of such recommendations could increase potential for harm to health by making implicit recommendations on when it is not necessary to seek medical attention.

- For example, PDURS that communicates with a scale in a patient's home to allow the tracking of weight in patients with heart failure and uses the information to generate output with a recommendation of when to contact a healthcare provider is implicitly making a recommendation that it is not necessary to contact the provider if weight gain has not reached a certain threshold.

- The potential for harm to health stems from the use of any recommendation, explicit or implicit, that the patient's signs and symptoms, as entered into the app, do not require attention from a healthcare provider.

Docket No. FDA-2018-N-3017, Closes April 29, 2019

PDURS With Multiple Functions

Docket No. FDA-2018-N-3017, Closes April 29, 2019

Multiple Functions, Example 1

Some prescription combination products may have PDURS that includes within a single app a function that is required for use of the combination product and functions that are not required for use of the product.

- Required function to track drug ingestion through an IEM
- Non-required functions to record symptoms like pain or fatigue
  - not required to achieve the intended effect of the combination product
  - may not be considered a device constituent of thecombination product.

In such situations, FDA may require a drug sponsor to provide users of PDURS with adequate disclosure(s) that certain functions have not been evaluated by FDA.

Multiple Functions, Example 2

PDURS where clinical studies are done to show an effect on a clinical endpoint.

- Required labeling describes use of a dose-tracking app with an antidiabetic medication that led to an improvement in serum HbA1c,

- Non-required functions such as an electronic carbohydrate counter

If there are no clinical studies to show the electronic carbohydrate counter software function improves HbA1c, the PDURS output from this function would be treated as promotional labeling.

Output of PDURS That Has Also Been Cleared or Approved by CDRH

Docket No. FDA-2018-N-3017, Closes April 29, 2019

PDURS within CDRH Device

If PDURS is cleared or approved by CDRH as a device (and is not a constituent of an approved prescription drug-device combination product), drug sponsors would only need to submit the PDURS output to CDER or CBER (as appropriate) at the time of first dissemination.

Because such software was reviewed by CDRH, and CDRH would have consulted with CDER or CBER during the premarket review, FDA would not expect that the use of such software would result in an increased potential for harm to patients.

FDA would not recommend that a drug sponsor submit the PDURS output for voluntary advisory comment prior to first use, but would still expect such output to be promotional labeling and must submit on Form FDA 2253 at the time of first use.

Concluding Thoughts

- The digital health product market will continue to expand.
- Developers of PDURS and/or drug-device combination products should:
  - Consider relevant regulatory approaches early
  - Take advantage of pre-submission meeting opportunities to gain Agency input
- FDA will continue to:
  - Foster collaboration (within the Agency and with stakeholders)
  - Improve efficiency and transparency in the approach to digital health technologies

Acknowledgements

- Linda Ricci, CDRH
- Jonas Santiago, CDER
- Evan Wearne, CDER
- Andrew Nguyen, CDER
- Ashley Boam, CDER
- PDURS working group


FDA
U.S. FOOD & DRUG
ADMINISTRATION