

Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500.

You may submit comments on any guidance at any time (see 21 CFR 10.115(g)(5)).

Submit written requests for single copies of this guidance to the Division of Drug Information, Center for Drug Evaluation and Research (CDER), Food and Drug Administration, 10001 New Hampshire Ave., Hillandale Building, 4th Floor, Silver Spring, MD 20993-0002. Send one self-addressed adhesive label to assist that office in processing your requests. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the guidance document.

**FOR FURTHER INFORMATION CONTACT:** Elizabeth Pepinsky, CDER/Office of Compliance, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 4258, Silver Spring, MD 20993-0002, 301-796-8763.

#### **SUPPLEMENTARY INFORMATION:**

##### **I. Background**

FDA is announcing the availability of a final guidance for industry entitled “Exemption and Exclusion from Certain Requirements of the Drug Supply Chain Security Act for the Distribution of FDA-Approved Naloxone Products During the Opioid Public Health Emergency.” We are issuing this guidance consistent with our good guidance practices (GGP) regulation (§ 10.115 (21 CFR 10.115)). We are implementing this guidance without prior public comment because we have determined that prior public participation is not feasible or appropriate (§ 10.115(g)(2)). The Agency made this determination because the guidance requires immediate implementation for public health reasons. Although this guidance document is immediately in effect, it remains subject to comment in accordance with FDA’s GGP regulation.

Combating the opioid overdose epidemic is an urgent public health priority for FDA. Naloxone is a medication that rapidly reverses the effects of opioid overdose and is the standard treatment for opioid overdose. FDA understands that naloxone is being made available to underserved communities through entities such as harm reduction programs. FDA is aware of concerns that harm reduction programs are having difficulty acquiring naloxone. The Agency is aware that some stakeholders have viewed as a contributing factor the current availability of approved naloxone products only as prescription drugs and FDA has recently become aware that some stakeholders have viewed as a

contributing factor certain requirements under the Drug Supply Chain Security Act (DSCSA) for distribution of FDA-approved prescription drug products., e.g., being an authorized trading partner. FDA is issuing this guidance to clarify the scope of the public health emergency exclusion and exemption under the DSCSA as they apply to the distribution of FDA-approved naloxone products indicated for the emergency treatment of opioid overdose to harm reduction programs during the opioid public health emergency.

The guidance represents the current thinking of FDA on “Exemption and Exclusion from Certain Requirements of the Drug Supply Chain Security Act for the Distribution of FDA-Approved Naloxone Products During the Opioid Public Health Emergency.” It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations.

##### **II. Paperwork Reduction Act of 1995**

This guidance contains no collection of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

##### **III. Electronic Access**

Persons with access to the internet may obtain the guidance at <https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs>, <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>, or <https://www.regulations.gov>.

Dated: September 19, 2022.

**Lauren K. Roth,**

*Associate Commissioner for Policy.*

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#### **DEPARTMENT OF HEALTH AND HUMAN SERVICES**

##### **Food and Drug Administration**

**[Docket No. FDA-2022-N-1874]**

##### **Agency Information Collection Activities; Proposed Collection; Comment Request; Perceptions of Prescription Drug Products With Medication Tracking Capabilities**

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA or Agency) is announcing an opportunity for public

comment on the proposed collection of certain information by the Agency. Under the Paperwork Reduction Act of 1995 (PRA), Federal Agencies are required to publish notice in the **Federal Register** concerning each proposed collection of information and to allow 60 days for public comment in response to the notice. This notice solicits comments on a proposed study entitled “Perceptions of Prescription Drug Products With Medication Tracking Capabilities.”

**DATES:** Either electronic or written comments on the collection of information must be submitted by November 22, 2022.

**ADDRESSES:** You may submit comments as follows. Please note that late, untimely filed comments will not be considered. The <https://www.regulations.gov> electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of November 22, 2022. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are received on or before that date.

##### *Electronic Submissions*

Submit electronic comments in the following way:

- **Federal eRulemaking Portal:** <https://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <https://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else’s Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on <https://www.regulations.gov>.

- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see “Written/Paper Submissions” and “Instructions”).

##### *Written/Paper Submissions*

Submit written/paper submissions as follows:

- **Mail/Hand Delivery/Courier (for written/paper submissions):** Dockets Management Staff (HFA-305), Food and

Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in “Instructions.”

*Instructions:* All submissions received must include the Docket No. FDA–2022–N–1874 for “Agency Information Collection Activities; Proposed Collection; Comment Request; Perceptions of Prescription Drug Products With Medication Tracking Capabilities.” Received comments, those filed in a timely manner (see **ADDRESSES**), will be placed in the docket and, except for those submitted as “Confidential Submissions,” publicly viewable at <https://www.regulations.gov> or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240–402–7500.

- **Confidential Submissions**—To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states “THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.” The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <https://www.regulations.gov>. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as “confidential.” Any information marked as “confidential” will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA’s posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: <https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf>.

*Docket:* For access to the docket to read background documents or the electronic and written/paper comments received, go to <https://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the “Search” box and follow the prompts

and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240–402–7500.

**FOR FURTHER INFORMATION CONTACT:**

*Regarding the collection of information:* JonnaLynn Capezzuto, Office of Operations, Food and Drug Administration, Three White Flint North, 10A–12M, 11601 Landsdown St., North Bethesda, MD 20852, 301–796–3794, [PRAStaff@fda.hhs.gov](mailto:PRAStaff@fda.hhs.gov).

*For copies of the questionnaire:* Amie O’Donoghue, Office of Prescription Drug Promotion (OPDP) Research Team, 301–796–0754, [DTCresearch@fda.hhs.gov](mailto:DTCresearch@fda.hhs.gov).

**SUPPLEMENTARY INFORMATION:** Under the PRA (44 U.S.C. 3501–3521), Federal Agencies must obtain approval from the Office of Management and Budget (OMB) for each collection of information they conduct or sponsor. “Collection of information” is defined in 44 U.S.C. 3502(3) and 5 CFR 1320.3(c) and includes Agency requests or requirements that members of the public submit reports, keep records, or provide information to a third party. Section 3506(c)(2)(A) of the PRA (44 U.S.C. 3506(c)(2)(A)) requires Federal Agencies to provide a 60-day notice in the **Federal Register** concerning each proposed collection of information before submitting the collection to OMB for approval. To comply with this requirement, FDA is publishing notice of the proposed collection of information set forth in this document.

With respect to the following collection of information, FDA invites comments on these topics: (1) whether the proposed collection of information is necessary for the proper performance of FDA’s functions, including whether the information will have practical utility; (2) the accuracy of FDA’s estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

**Perceptions of Prescription Drug Products With Medication Tracking Capabilities**

*OMB Control Number 0910—NEW*

Section 1701(a)(4) of the Public Health Service Act (42 U.S.C. 300u(a)(4)) authorizes the FDA to conduct research relating to health information. Section 1003(d)(2)(C) of the Federal Food, Drug, and Cosmetic Act

(FD&C Act) (21 U.S.C. 393(d)(2)(C)) authorizes FDA to conduct research relating to drugs and other FDA-regulated products in carrying out the provisions of the FD&C Act.

The mission of the Office of Prescription Drug Promotion (OPDP) is to protect the public health by helping to ensure that prescription drug promotional material is truthful, balanced, and accurately communicated so that patients and health care providers can make informed decisions about treatment options. OPDP’s research program provides scientific evidence to help ensure that our policies related to prescription drug promotion will have the greatest benefit to public health. Toward that end, we have consistently conducted research to evaluate the aspects of prescription drug promotion that are most central to our mission, focusing in particular on three main topic areas: advertising features, including content and format; target populations; and research quality. Through the evaluation of advertising features, we assess how elements such as graphics, format, and the characteristics of the disease and product impact the communication and understanding of prescription drug risks and benefits. Focusing on target populations allows us to evaluate how understanding of prescription drug risks and benefits may vary as a function of audience. Our focus on research quality aims at maximizing the quality of research data through analytical methodology development and investigation of sampling and response issues. This study will inform the first topic area, advertising features.

Because we recognize that the strength of data and the confidence in the robust nature of the findings are improved through the results of multiple converging studies, we continue to develop evidence to inform our thinking. We evaluate the results from our studies within the broader context of research and findings from other sources, and this larger body of knowledge collectively informs our policies as well as our research program. Our research is documented on our home page at <https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/office-prescription-drug-promotion-opdp-research>, which includes links to the latest **Federal Register** notices and peer-reviewed publications produced by our office.

Patient non-adherence to medication regimens is a well-known challenge in health care. The World Health Organization defines adherence as the extent to which a person’s behavior—taking medication, following a diet,

and/or executing lifestyle changes—corresponds with agreed recommendations from a health care provider (Ref. 1). It is estimated that only half of all patients with chronic health conditions take their medications as prescribed (Ref. 2), leading to as many as 100,000 preventable deaths and \$100 billion in additional medical costs every year (Ref. 3). Numerous solutions have been tried to improve adherence, including resource-intensive approaches such as directly observed therapy, which entails a trained observer watching as the patient takes their medications (Ref. 4), and technology-supported tools for patients (e.g., smartphone apps) (Ref. 5). As attention to the public health issue of medication adherence has grown, OPDP has noted a corresponding increase in the number of claims and presentations in prescription drug promotion that focus, either directly or through implication, on a product's potential to improve adherence to treatment regimens. Many of these presentations include information about options and capabilities available to help patients track their medication usage.

One avenue that prescription drug sponsors have begun exploring to track medication use includes the development of software that is disseminated by or on behalf of the drug sponsor and accompanies one or more of the sponsor's prescription drugs. This software is called prescription drug use-related software.<sup>1</sup> Studies exploring drug products with prescription drug

use-related software have been conducted with medications to treat an array of chronic disorders, including psychiatric disorders (Ref. 6), uncontrolled type 2 diabetes (Ref. 7), end-stage renal disease requiring transplants (Ref. 8), and opioid use among patients with acute fractures (Ref. 9).

In recent years, new technologies that capture data on medication-taking behavior and drug administration have been employed. The SureClick 2.0 autoinjector for the prescription medication ENBREL, for example, has Bluetooth built into the white cap that covers the needle. The autoinjector records initial removal of the cap and can send this data via Bluetooth to a paired smartphone using a mobile app (Ref. 10). Technology can also now support the use of ingestible sensors embedded in pills that will emit a weak signal to a receiver (patch or lanyard) worn by the patient after the pill has been swallowed (Ref. 11). This data can then be transmitted to a paired mobile device and viewed by the patient through a smartphone app (Ref. 12). Whether these new technologies will have an impact on adherence is currently unknown.

Very little is known about patient and health care provider perceptions of products that track medication use or that work in tandem with software to track medication use, with most commentaries having been largely theoretical (Refs. 13, 14). The focus of the present study is to explore patient

and health care provider perceptions of a fictitious prescription drug product that is accompanied by software that is intended to track medication use.

We have the following specific questions:

*Research questions:*

1. When prescription drug promotional communications include claims about a product's ability to track medication use, do these claims influence perceptions about the product's risks and/or benefits (including its effect on medication adherence)?

2. If the promotional claims about the product's ability to track medication use are accompanied by a disclosure that describes what is known about the effect of medication tracking on medication adherence, does this have an influence on perceptions of the product's risks and/or benefits (including its effect on medication adherence)?

To complete this research, we propose the design in table 1, which varies based on:

- Whether the fictitious prescription drug product includes technology that tracks medication use;
- Whether the prescription drug promotional communication includes a disclosure describing what is known about the tracking technology's effect on medication adherence; and
- What the disclosure communicates about the tracking technology's effect on medication adherence (positive effect shown, no effect shown, or unknown effect).

TABLE 1—PROPOSED ONE-WAY, FIVE-LEVEL DESIGN (1 × 5)

Experimental condition	Claims about existence of medication tracking technology	Disclosure about technology's effect on adherence	Content of disclosure
1. Drug .....	No	No.	
2. Drug + medication tracking technology .....	Yes	No.	
3. Drug + medication tracking technology + no adherence data collected.	Yes	Yes	No data is available on the technology's effect on adherence.
4. Drug + medication tracking technology + data show no effect on adherence.	Yes	Yes	Data show the technology has no effect on adherence.
5. Drug + medication tracking technology + data show a positive effect on adherence.	Yes	Yes	Data show the technology has a positive effect on adherence.

**Note:** Condition 5 is the only condition in which an adherence benefit has been demonstrated for the fictitious product. The evidence required to support a medication adherence claim is not the focus of this study, and the evidence will not be described in the disclosure.

Condition 2 is a control because the drug product does include medication tracking technology, but the promotional communication does not include a disclosure about the technology's effect on medication adherence. Condition 1 is a true control because the drug product does not include medication tracking technology. Comparisons between conditions 1 and 2 will show us the baseline of this issue, *i.e.*, will indicate whether the fact that the drug product contains a tracking technology will alter perceptions of risks and benefits (including adherence).

We will conduct pretests with 50 consumers who self-identify as having

been diagnosed with diabetes and 50 primary care physicians who treat

diabetes (both obtained from a web-based research vendor) to ensure that

<sup>1</sup> In 2018, FDA established a public docket to solicit public comment on a proposed framework for regulating software applications disseminated

by or on behalf of drug sponsors for use with one or more of their prescription drug products. See [https://www.federalregister.gov/documents/2018/](https://www.federalregister.gov/documents/2018/11/20/2018-25206/prescription-drug-use-related-software-establishment-of-a-public-docket-request-for-comments)

[11/20/2018-25206/prescription-drug-use-related-software-establishment-of-a-public-docket-request-for-comments](https://www.federalregister.gov/documents/2018/11/20/2018-25206/prescription-drug-use-related-software-establishment-of-a-public-docket-request-for-comments).

the questionnaire programming works as expected. For the main study, we will then recruit 350 consumers who self-identify as having been diagnosed with diabetes and 350 primary care physicians who treat diabetes. Each

participant will see one of five versions of a consumer web page for a fictitious prescription diabetes treatment, as reflected in table 1. They will answer a questionnaire designed to take no more than 20 minutes regarding their

perception of the product's benefits, risks, and effect on adherence.

FDA estimates the burden of this collection of information as follows:

TABLE 2—ESTIMATED ANNUAL REPORTING BURDEN<sup>1 2</sup>

Activity	Number of respondents	Number of responses per respondent	Total annual respondents	Average burden per response	Total hours
Screener Consumers .....	680	1	680	.08 (5 minutes) ....	54.4
Screener Primary Care Physicians .....	680	1	680	.08 (5 minutes) ....	54.4
Pretest Consumers .....	50	1	50	.33 (20 minutes) ..	16.5
Pretest Primary Care Physicians .....	50	1	50	.33 (20 minutes) ..	16.5
Main Study Consumers .....	350	1	350	.33 (20 minutes) ..	115.5
Main Study Primary Care Physicians .....	350	1	350	.33 (20 minutes) ..	115.5
Total .....					372.8

<sup>1</sup> There are no capital costs or operating and maintenance costs associated with this collection of information.

<sup>2</sup> Burden estimates of less than 1 hour are expressed as a fraction of an hour in decimal format.

## References

The following references marked with an asterisk (\*) are on display at the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they also are available electronically at <https://www.regulations.gov>. References without asterisks are not on public display at <https://www.regulations.gov> because they have copyright restriction. Some may be available at the website address, if listed. References without asterisks are available for viewing only at the Dockets Management Staff. FDA has verified the website addresses, as of the date this document publishes in the **Federal Register**, but websites are subject to change over time.

- \*1. World Health Organization, "Adherence to Long-Term Therapies: Evidence for Action," p. 3, 2003, available at <https://apps.who.int/iris/handle/10665/42682>, accessed May 16, 2022.
2. Frias, J., N. Virdi, P. Raja, et al., "Effectiveness of Digital Medicines to Improve Clinical Outcomes in Patients with Uncontrolled Hypertension and Type 2 Diabetes: Prospective, Open-Label, Cluster-Randomized Pilot Clinical Trial," *Journal of Medical Internet Research*, vol. 19, Issue 7, Article e246, 2017, doi:10.2196/jmir.7833.
3. Kleinsinger, F., "The Unmet Challenge of Medication Nonadherence," *The Permanente Journal*, vol. 22, Issue 3, Article 18-033, 2018, doi:10.7812/TPP/18-033.
4. Karumbi, J. and P. Garner, "Directly Observed Therapy for Treating Tuberculosis," *Cochrane Database of Systematic Reviews*, Issue 5, Article CD003343, 2015, doi:10.1002/14651858.CD003343.pub4.

5. Dayer, L., S. Heldenbrand, P.O. Gubbins, et al., "Smartphone Medication Adherence Apps: Potential Benefits to Patients and Providers," *Journal of the American Pharmacy Association* (2003), vol. 53, Issue 2, pp. 172–181, 2013, doi:10.1331/JAPhA.2013.12202.
- \*6. FDA, "FDA Approves Pill with Sensor That Digitally Tracks If Patients Have Ingested Their Medication," FDA News Release, November 13, 2017, available at <https://www.fda.gov/news-events/press-announcements/fda-approves-pill-sensor-digitally-tracks-if-patients-have-ingested-their-medication>, accessed May 16, 2022.
7. Browne, S.H., Y. Behzadi, and G. Littlewort, "Let Visuals Tell the Story: Medication Adherence in Patients with Type II Diabetes Captured by a Novel Ingestion Sensor Platform," *JMIR mHealth uHealth*, vol. 3, Issue 4, Article e108, 2015, doi:10.2196/mhealth.4292.
8. Eisenberger, U., R.P. Wüthrich, A. Bock, et al., "Medication Adherence Assessment: High Accuracy of the New Ingestible Sensor System in Kidney Transplants," *Transplantation*, vol. 96, Issue 3, pp. 245–250, 2013, doi:10.1097/TP.0b013e31829b7571.
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- \*10. Amgen Inc., "Enbrel (etanercept): Highlights of Prescribing Information," revised April 2021, available at [https://www.pi.amgen.com/-/media/amgen/repositories/pi-amgen-com/enbrel/enbrel\\_pi.pdf](https://www.pi.amgen.com/-/media/amgen/repositories/pi-amgen-com/enbrel/enbrel_pi.pdf), accessed May 16, 2022.
- \*11. Reuter, E., "Smart Pill' Startup EctRx Strikes Partnership with Pear Therapeutics," *Med City News*, January 14, 2021, available at <https://medcitynews.com/2021/01/smart-pill-startup-ectrx-strikes-partnership-with-pear-therapeutics>, accessed May 16, 2022.

12. The Medical Futurist, "The Present and Future of Digital Pills," July 21, 2020, available at <https://medicalfuturist.com/the-present-and-future-of-digital-pills>, accessed May 16, 2022.
13. George, C.E., "Should a Psychiatrist Prescribe a Nanodrug to Help Parents Monitor a Teen's Adherence?," *AMA Journal of Ethics*, vol. 21, issue 4, article e317–323, 2019, doi:10.1001/amajethics.2019.317.
- \*14. Yang, M., "A Psychiatrist's Perspective on the Digital Pill," *KevinMD.com*, December 2, 2017, available at <https://www.kevinmd.com/blog/2017/12/psychiatrists-perspective-digital-pill.html>, accessed May 16, 2022.

Dated: September 19, 2022.

**Lauren K. Roth,**

*Associate Commissioner for Policy.*

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## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

[Docket No. FDA–2022–N–1894]

### Agency Information Collection Activities; Proposed Collection; Comment Request; Yale-Mayo Clinic Centers of Excellence in Regulatory Science and Innovation B12 Pediatric Device Survey

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA or Agency) is announcing an opportunity for public comment on the proposed collection of certain information by the Agency. Under the Paperwork Reduction Act of