



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2019-N-5973]

Agency Information Collection Activities; Submission for Office of Management and Budget Review; Comment Request; Health Care Providers' Understanding of Opioid Analgesic Abuse Deterrent Formulations

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing that a proposed collection of information has been submitted to the Office of Management and Budget (OMB) for review and clearance under the Paperwork Reduction Act of 1995 (PRA).

DATES: Fax written comments on the collection of information by **[INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]**.

ADDRESSES: To ensure that comments on the information collection are received, OMB recommends that written comments be submitted to <https://www.reginfo.gov/public/do/PRAMain>. Find this particular information collection by selecting "Currently under Review--Open for Public Comments" or by using the search function. The title of this information collection is "Health Care Providers' Understanding of Opioid Analgesic Abuse Deterrent Formulations." Also include the FDA docket number found in brackets in the heading of this document.

FOR FURTHER INFORMATION CONTACT: Ila S. Mizrachi, Office of Operations, Food and Drug Administration, Three White Flint North, 10A-12M, 11601 Landsdown St., North Bethesda, MD 20852, 301-796-7726, PRAStaff@fda.hhs.gov.

SUPPLEMENTARY INFORMATION: In compliance with 44 U.S.C. 3507, FDA has submitted the following proposed collection of information to OMB for review and clearance.

Health Care Providers' Understanding of Opioid Analgesic Abuse Deterrent Formulations

OMB Control Number 0910-NEW

I. Background

Section 1701(a)(4) of the Public Health Service Act (42 U.S.C. 300u(a)(4)) authorizes 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.

Prescription opioids play a significant role in the opioid misuse and abuse epidemic in the United States. Opioid analgesics with properties designed to deter abuse, commonly known as abuse deterrent formulations (ADFs), may play a role in helping to curb this epidemic. Currently available ADFs have been demonstrated to deter some forms of abuse (injection, snorting, or, in some cases, chewing and swallowing). FDA's own research and other evidence suggests considerable variability in health care providers' (HCPs) knowledge of and attitudes toward prescription opioid products and practices (Ref. 1), including understanding of ADFs. ADF prescription practices may present opportunities for HCPs to reduce opioid abuse. Conducting a comprehensive evaluation of opioid prescribers' knowledge, attitudes, perceptions, experiences, and behaviors related to ADFs will help to inform FDA's approaches to ADFs.

Given the significance and far-reaching nature of the opioid crisis, along with FDA concerns about potential misunderstanding among HCPs about ADF terminology and capabilities, FDA determined that systematic research was necessary to provide the detailed and comprehensive evidence on which to base the Agency's ADF-related policy, regulatory, and communication decisions, including potential alternative language that may be necessary to describe and explain these products. This work aligns with Priority 1 of the FDA's Strategic Policy Roadmap (<https://www.fda.gov/about-fda/reports/healthy-innovation-safer-families-fdas-2018-strategic-policy-roadmap>), and the Department of Health and Human Services (HHS) and the Administration have similarly placed high priorities on addressing the epidemic of misuse and abuse of opioid drugs harming U.S. families.

The study's purpose is to explore and assess the ADF-related knowledge, attitudes, and behaviors among opioid prescribers (physicians, nurse practitioners and physician assistants) and dispensers/pharmacists, including the related terms addiction and abuse deterrence, and to explore possible alternative language for describing these products. Phase 1 consisted of focus groups (OMB approval under control number 0910-0695). The research described in this notice represents Phases 2 and 3 of the overall project.

Phase 2 will consist of a survey based on the Phase 1 focus group findings related to: (1) health care provider understanding of addiction, abuse, and abuse deterrent formulations; (2) attitudes toward, perceptions about, and experiences with abuse-deterrent opioid analgesics and abuse deterrence, including prescribing decisions and practices, potential barriers to using ADFs, the quality and understandability of the ADF nomenclature, and the underlying reasons for these perceptions; and (3) HCPs' ideas for minimizing confusion about ADFs, the kinds of ADF training needed, and suggested language/terms they believe would best convey the concept of

abuse deterrence to HCPs. The objective of the survey will be to determine the prevalence of HCP knowledge, attitudes, behaviors, and perceptions identified through the qualitative discussion occurring in the Phase 1 focus groups and to uncover any subgroup differences among opioid prescribers and dispensers. We will conduct one pretest, averaging not longer than 20 minutes, to pilot the main survey procedures among the target HCP populations. The main survey will also average 20 minutes.

Phase 3 will build on findings from the Phase 1 focus groups and Phase 2 survey and will consist of an experimental study examining variations in descriptive terminology for abuse deterrent formulation products. We will conduct two pretests, each averaging not longer than 20 minutes, to test the experimental manipulations and pilot the main study procedures. The main study procedure will also average 20 minutes in length. Participants will be randomly assigned to read a description of abuse deterrent formulation opioids that contains one of four terms that could be used to refer to these products (ADF will function as the control term) and then complete a questionnaire that assesses their comprehension and perceptions of the information, including terminology, as well as their attitudes, behavioral intentions, and experience related to these types of opioid products.

For all phases of this research, we will recruit adult health care professional volunteers 18 years of age or older. We will exclude individuals who work for HHS or work in the health care, marketing, or pharmaceutical industries. The sample will consist of 10 percent pharmacists, at least half of whom dispense ADF opioids. The other 90 percent will be prescribers who, at the time they are recruited, spend at least 50 percent of their time seeing patients and who have prescribed opioids to at least five different patients in the last 30 days, with at least half of the opioids they prescribe being for chronic non-cancer pain. The prescriber sample will be

segmented to include 70 percent primary care providers (i.e., those practicing in family practice, or internal or general medicine) and 30 percent a mix of specialists practicing in a variety of fields such as rheumatology, neurology, anesthesiology, pain management, emergency medicine, surgery, orthopedics, and physical medicine and rehabilitation. In each of these groups, 60 to 70 percent will consist of physicians, 15 percent nurse practitioners, and 15 percent physician assistants. A minimum of 30 percent must have experience prescribing an ADF opioid.

We will use soft quotas to ensure that our sample includes a diversity of participants, including related to age, race/ethnicity, gender, years and location of practice, and opioid prescribing levels. We will also exclude pretest participants from the main studies, and participants will not be able to participate in more than one phase of the project. With the sample sizes described below, we will have sufficient power to detect primarily small-sized effects for Phases 2 and 3.

In the *Federal Register* of February 5, 2020 (85 FR 6562), FDA published a 60-day notice requesting public comment on the proposed collection of information. FDA received three submissions that were PRA-related. Within those submissions, FDA received multiple comments, which the Agency has addressed below.

(Comment 1) I believe Phase 2 should include more pharmacists than 10 percent ratio.

(Response 1) We have carefully planned the sample for the study to ensure sufficient numbers of prescribers, including primary care providers and several types of specialists (including neurologists, pain management specialists, rheumatologists, neurologists, surgeons, orthopedists, physical medicine and rehabilitation specialists), physician assistants and nurse practitioners, as well as including a group of pharmacists for analysis. Expanding the sample further is beyond the scope of what we have planned for the project. Our power analysis

suggests we will have sufficient power to ensure comparisons between groups in the sample. In addition, in the earlier focus group phase, pharmacists said they rarely talk with patients about ADFs and never talk with health care professionals about them, suggesting the feedback we would receive from them would likely be limited.

(Comment 2) Practitioners chosen should be based on greater prescribing habits. Those practitioners who are the larger rate of treating chronic non-cancer pain with ADF opioid should be the target of information gathering.

(Response 2) One of our screening criteria is that at least half of a provider's prescriptions must be for chronic, non-cancer pain. We plan to include approximately equal numbers of low, medium, and high prescribers across each prescriber type and field of practice so that comparisons can be made between groups. In addition, in the earlier focus group phase, current prescribers of ADFs were already aware of and had significant knowledge about ADFs, so their feedback likely would not provide the kind of insight needed about the misunderstanding and confusion we previously observed among other prescribers.

(Comment 3) We support FDA's decision to conduct a comprehensive evaluation of opioid prescribers' knowledge, attitudes, perceptions, experiences, and behaviors related to ADFs and agree with the FDA that new language is needed to better describe and explain ADFs.

(Response 3) Thank you for this comment.

(Comment 4) We strongly encourage testing the impact of terminology that more accurately describes the product's abuse-deterrent properties. For example, if a pill is formulated to be difficult to crush, it should be labeled "crush-resistant."

(Response 4) The survey, in part, will provide HCPs an opportunity to propose terms they think best describe these opioids and will test both objectively and subjectively numerous

alternative terms that were commonly cited as appropriate by HCP participants in the earlier focus group phase of this study. This includes terms that relate to physical manipulation such as “alteration-resistant opioids” and “tamper-resistant opioids.”

(Comment 5) We support FDA’s efforts to ensure the diversity of the sample populations for the three proposed studies. It is important to study health care providers with varying opioid prescribing levels, and years and locations of practice. We particularly commend the efforts to additionally account for diverse ages, ethnicities, and gender of the health care providers, as all of these factors can affect knowledge, attitudes, and the patients they serve.

(Response 5) Thank you for this comment.

(Comment 6) The proposed study plans to include a wide range of health care providers, including primary care providers; specialists from various fields such as rheumatology, neurology, anesthesiology, pain management, emergency medicine, surgery, orthopedics, and physical medicine and rehabilitation; nurse practitioners; physician assistants; as well as dispensers/pharmacists. However, there is clear evidence that dentists, periodontists, and oral surgeons should also be included, since research has shown that they often overprescribe opioids.

(Response 6) While the reviewers raises an important consideration, the inclusion of dentists and oral surgeons is beyond the scope of the current study. Dentists do not typically prescribe for long-term pain and are therefore less likely to prescribe an abuse-deterrent formulation opioid or ADF, which is the main focus of this study. For a similar reason, based on what we heard in the earlier focus group phase of this study, we chose to exclude emergency medicine physicians from the sample survey populations.

(Comment 7) The proposed study should explore providers' knowledge of how ADF opioids are used and abused once they are on the market. Opioids considered to be abuse-deterrent are still widely abused through the most common oral route.

(Response 7) Our survey questions will include items about provider knowledge of ADFs, including specific questions to test whether they are aware that ADFs can still be abused, as well as related to their experiences with use, misuse, and abuse of opioids.

(Comment 8) We applaud the effort to gather information about HCPs' understanding of these products. This effort is consistent with the Agency's history of extensive and diverse efforts to balance the needs of people seeking relief from severe acute and chronic pain and the simultaneous need to avoid worsening of the abuse, addiction, and diversion of opioid medications in these times of the opioid overdose epidemic.

(Response 8) Thank you for this comment.

(Comment 9) We believe that the proposed sample design adequately accounts for current ADF product prescribers for chronic non-cancer pain. It is not clear, however, whether the proposed sample design would adequately capture the second relevant population, i.e. appropriate potential prescribers of ADF products for chronic non-cancer pain. Commenter recommends that FDA focus on those HCPs who specialize in chronic non-cancer pain management, because these relatively few HCPs manage a disproportionate volume of patients with chronic non-cancer pain and, therefore, manage a disproportionate volume of current and appropriate potential prescriptions of ADF products for chronic non-cancer pain.

Suggestions:

- The proposed threshold of 5 patients treated with opioids for chronic non-cancer pain in a typical month is too low. A low threshold does not ensure that pain specialists will be

included, and evidence has shown that the treatment of chronic non-cancer pain with opioids has consolidated under such pain specialists in recent years.

- Study should focus on HCPs who specialize in chronic non-cancer pain management. This small subset of HCPs manage a disproportionate volume of patients with chronic non-cancer pain, and therefore, they manage a disproportionate volume of current and appropriate potential ADF prescriptions.
- Study can capture both intended populations (current and “appropriate potential” prescribers) by recruiting only pain specialists and imposing a threshold for experience prescribing ADF products.

(Response 9) Pain management is one of the specialties included on our recruitment screener (in addition to rheumatology, neurology, anesthesiology, surgery, orthopedics, and physical medicine and rehabilitation). Our screening criteria will ensure an approximately equal number of low, medium, and high-volume prescribers across each provider group. We also have included a requirement that at least 50 percent of prescriptions must be for chronic, non-cancer pain. A key objective of this study is to gain insight into misunderstandings about ADF opioids and the terminology and how to best address the confusion and misunderstandings that we found in the earlier focus group phase of the study as well as in prior research FDA conducted. These data indicated pain management specialists already tend to have considerable knowledge about and experience with ADFs, suggesting their feedback would likely be of limited usefulness with respect to the study’s key objectives. This is similarly the case for ADF prescribers, which is the reason the study populations were purposely inclusive of a broad cross-section of opioid prescribers.

(Comment 10) Include a screening question with a list of ADF products to account for respondents' lack of knowledge about which products are and are not ADF.

(Response 10) Thank you for the suggestion. Our recruitment screener includes such a question, which asks respondents to identify which of 17 different listed opioids they have prescribed, including six abuse-deterrent formulations that will not be identified as such. The survey questionnaire itself also asks prescribers to specifically cite in an open-ended question the ADF opioids they have prescribed, which will be used, in part, to assess ADF knowledge.

(Comment 11) Set quotas to ensure recruitment of representative sample sizes for both non-specialists and pain specialists.

(Response 11) Early in the protocol development we identified the need for samples of prescribers working in primary care fields and among those in specific specialties, which research has shown generally prescribe the most opioids overall, and the sample populations included in the study will reflect this necessary diversity.

(Comment 12) Lower Ns for Phase 2 and 3 to ensure timely completion. In the company's experience, a survey of 200 HCPs takes 5 weeks to complete.

(Response 12) We identified current sample sizes based on power calculations. Any reduction in sample size would reduce our power to find effects. We have planned a timeline for the project to complete both phases 2 and 3 based on experience collecting data using these methods but will be adjusting as necessary given the COVID-19 pandemic and any other unforeseen factors. This project is an FDA priority, and we will prioritize rigorous methodology that ensures representativeness and robust data and evidence even if it means taking a little more time.

(Comment 13) Implement appropriate honoraria to ensure feasibility and timely results.

(Response 13) The financial incentive rates were based on going rates for incentives in provider panel surveys and on recent research on incentives for physician surveys. These will also comport with those allowable by OMB. In addition, our experience has shown that the topic of this study--opioids and the national crisis--and the fact that the research is being undertaken by FDA, the Federal agency responsible for regulating these products, are additional incentives for participation.

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

Table 1.--Estimated Annual Reporting Burden^{1,2,4}

Activity	No. of Respondents ³	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
Phase 2					
Pretest screener	470	1	470	0.17 (10 minutes)	79.90
Pretest	235	1	235	0.33 (20 minutes)	77.55
Survey screener	2,120	1	2,120	0.17 (10 minutes)	360.40
Survey	1,060	1	1,060	0.33 (20 minutes)	349.80
Phase 3					
Pretests screener	732	1	732	0.17 (10 minutes)	124.44
Pretests	366	1	366	0.33 (20 minutes)	120.78
Main study screener	2,120	1	2,120	0.17 (10 minutes)	360.40
Main study	1,060	1	1,060	0.33 (20 minutes)	349.80
Total					1,823.07

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

² Includes total burden for project phases 2 and 3.

³ Includes 10 percent overage.

⁴ With online surveys, several participants may be in the process of completing the survey at the time that the total target sample is reached. Those participants will be allowed to complete the survey, which can result in the number of valid completes exceeding the target number. With this in mind, we have included an additional 10 percent over our target number of valid completes to account for some overage.

II. Reference

The following reference is on display with the Dockets Management Staff (see ADDRESSES) and is available for viewing by interested persons between 9 a.m. and 4 p.m.,

Monday through Friday; it is not available electronically at <https://www.regulations.gov> as this reference is copyright protected.

1. Hwang, C. S., L. W. Turner, S. P. Kruszewski, et al. "Primary Care Physicians' Knowledge and Attitudes Regarding Prescription Opioid Abuse and Diversion." *The Clinical Journal of Pain*, 32(4), 279-284, 2016.

Dated: June 30, 2020.

Lowell J. Schiller,

Principal Associate Commissioner for Policy.

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