4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2018-N-3138]

Agency Information Collection Activities; Submission for Office of Management and Budget Review; Comment Request; Experimental Study of an Accelerated Approval Disclosure

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 faxed to the Office of Information and Regulatory Affairs, OMB, Attn: FDA Desk Officer, Fax: 202-395-7285, or emailed to oira_submission@omb.eop.gov. All comments should be identified with the OMB control number 0910-NEW and title "Experimental Study of an Accelerated Approval Disclosure." 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.

Experimental Study of an Accelerated Approval Disclosure

OMB Control Number 0910-NEW

I. Background

Section 1701(a)(4) of the Public Health Service Act (PHS 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.

The mission of the Office of Prescription Drug Promotion (OPDP) is to protect the public health by helping to ensure that prescription drug information is truthful, balanced, and accurately communicated so that patients and healthcare providers can make informed decisions about treatment options. The OPDP's research program supports this mission by providing 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 we believe 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 disease and product characteristics 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; and 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 falls under the topic of advertising features (content and format).

Pursuant to section 506(c) of the FD&C Act (21 U.S.C. 356(c)) and 21 CFR part 314, subpart H (or 21 CFR part 601, subpart E for biological products), FDA may grant accelerated approval to a drug product under section 505(c) of the FD&C Act (21 U.S.C. 355(c)) or a biological product under section 351(a) of the PHS Act (42 U.S.C 262(a)). This pathway enables faster approval of prescription drugs intended to treat serious or life-threatening illnesses. Accelerated approval may be based on a determination that a drug product has an effect on a surrogate endpoint (for example, a blood test result) that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit (i.e., an intermediate clinical endpoint). In approving a drug under the accelerated approval pathway, the severity, rarity, or prevalence of a condition, and the availability or lack of alternative treatments, are taken into account.

The accelerated approval pathway is limited to certain products intended to treat serious or life-threatening illnesses as there can be "[u]ncertainty about whether clinical benefit will be verified and the possibility of undiscovered risks" (FDA 2014 guidance for industry entitled "Expedited Programs for Serious Conditions--Drugs and Biologics," available at https://www.fda.gov/files/drugs/published/Expedited-Programs-for-Serious-Conditions-Drugs-and-Biologics.pdf). Sponsors are generally required to conduct post approval studies to verify and describe the predicted clinical benefit, but those confirmatory studies are not complete at the time that the accelerated approval is granted (Ref. 1). In the event that the required post approval

confirmatory studies fail to verify and describe the predicted effect or clinical benefit, a drug's approval can be withdrawn using expedited procedures.

Under FDA's regulations governing physician labeling for prescription drugs, the INDICATIONS AND USAGE section of the FDA-approved prescribing information (PI) for a drug approved under accelerated approval must include a succinct description of the limitations of usefulness of the drug and any uncertainty about anticipated clinical benefits, with reference to the clinical studies section for a discussion of the available evidence (21 CFR 201.57(c)(2)(i)(B)). Therefore, the PI for accelerated approval products typically satisfies this requirement by including a statement in the INDICATIONS AND USAGE section about the product's approval under the accelerated approval pathway. In a guidance, FDA recommended that the INDICATIONS AND USAGE section for drugs approved under accelerated approval should generally describe three elements: indication(s), limitations of usefulness and clinical benefit uncertainty, and continued approval ("Labeling for Human Prescription Drug and Biological Products Approved Under the Accelerated Approval Pathway" (January 2019). Available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM390058.pdf.). As the PI is intended for healthcare professionals, the information related to a drug's accelerated approval generally includes complex concepts and sophisticated wording. For example, PIs for accelerated approval products include language such as:

- This indication is approved under accelerated approval based on [surrogate endpoint]. An improvement in survival or disease-related symptoms has not been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trial; or

- Approval is based on a reduction in [surrogate endpoint]. There are no controlled trials demonstrating a direct treatment benefit such as improvement in disease-related symptoms, functioning, or increased survival.

Despite its complexity, sponsors often use this language from the PI in direct-to-consumer (DTC) promotional materials for drugs approved under accelerated approval. In other cases, DTC promotion of accelerated approval products does not communicate the unique considerations and potential limitations inherent in the accelerated approval process.

Disclosures may be used to communicate information such as this to consumers. Disclosures can include information about scientific and clinical data, any residual uncertainty about clinical benefit, and the practical utility of scientific and clinical data. These disclosures may influence consumer comprehension and affect perception of drug risks and benefits. This study will examine the presence, wording, and prominence of a disclosure communicating information related to the drug's accelerated approval in DTC promotional materials. This information includes the use of surrogate or intermediate clinical endpoints to support approval, the uncertainty about the relationship of the surrogate or intermediate clinical endpoint to the predicted clinical benefit, and the need for confirmatory trials.

We plan to conduct one pretest not longer than 20 minutes, administered via internet panel, to test the experimental manipulations and pilot the main study procedures. After implementing any lessons learned from the pilot, we plan to conduct one main study not longer than 20 minutes, administered via internet panel. For the pretest and main study, we will randomly assign the participants to one of the test conditions (see table 1 for the study design). We have chosen to focus on oncology products because cancer is a life-threatening illness, and many oncology products are granted accelerated approval. Moreover, DTC promotion of

oncology drugs is common. In the study, participants will view a website for a fictional oncology prescription drug. After viewing the website, participants will complete a questionnaire that assesses whether participants noticed the disclosure and their interpretation of it, as well as perceptions of the drug's risks and benefits. We will also measure covariates such as demographics and literacy. The questionnaire is available upon request from DTCresearch@fda.hhs.gov.

We will vary the presence and prominence of the disclosure (e.g., size, color, and location). We hypothesize that participants will be more likely to notice the disclosure when it is presented more, rather than less, prominently. In turn, we expect that participants' perceptions of the drug are more likely to be affected by the disclosure in the high prominence condition. We also will vary whether the disclosure is written in consumer-friendly language or uses language, in use by many sponsors, which is the same as or similar to that directed at healthcare professionals in FDA-approved prescription drug labeling for accelerated approval products. The consumer-friendly version of the accelerated approval disclosure will be based on consumer feedback elicited in focus groups conducted prior to the pretest (approved under OMB control number 0910-0695). The physician labeling version of the accelerated approval disclosure will be drawn from FDA-approved physician labeling. We hypothesize that participants will be more likely to notice and understand the disclosure and use it to form their perceptions of the drug if they view the consumer-friendly language. To test these hypotheses, we will conduct inferential statistical tests such as logistic regression and analysis of variance.

Table 1.--Study Design

	High prominence	Low prominence	Absent
Physician Labeling version			

Consumer-friendly version			

We will recruit a general population sample of adult volunteers 18 years of age or older. We will exclude individuals who work for the U.S. Department of Health and Human Services or work in the healthcare, marketing, advertising, or pharmaceutical industries. We will use health literacy quotas to ensure that our sample includes participants with a range of health literacy skills. With the sample sizes described below, we will have sufficient power to detect small-sized effects in the main study (table 2).

In the *Federal Register* of October 17, 2018 (83 FR 52478), FDA published a 60-day notice requesting public comment on the proposed collection of information. FDA received four submissions that were PRA-related. Within those submissions, FDA received multiple comments, which the Agency has addressed below.

(Comment 1) One comment suggested that the study does not evaluate the extent to which patients understand accelerated approval, "including the serious and life-threatening nature of the disease, the fact that FDA determined that the product is likely to provide a meaningful advantage over available therapy, the fact that the product likely addresses a significant unmet medical need, and that the accelerated approval has yet to be confirmed with additional data." The comment suggests updating Q12, Q13, and Q18 to reflect this context.

(Response) We will begin the study by giving participants information about acute lymphoblastic leukemia, which includes its serious and life-threatening nature, to put the accelerated approval of the drug product in the appropriate context. Questions 3-9 assess participants' understanding of the accelerated approval concepts conveyed in the disclosure. The concepts in the disclosure align with the elements recommended by FDA to describe accelerated

approval products and information currently seen in DTC promotion (Ref. 2). Questions 12, 13, and 18 are designed to measure participants' perceptions of the drug's risks.

(Comment 2) One comment suggested that the proposed disclosure language, "we currently do not know if Drug X helps people live longer or feel better" should be replaced with "we currently do not know if Drug X helps to minimize progression of disease and improve quality of life." The comment noted that the proposed language may be simplistic and inaccurate because "feel better" is subjective and may be irrelevant for cancer treatments.

(Response) In many cases, the available data for accelerated approval products do provide information about disease progression, without providing information on overall survival (i.e., living longer). Therefore, we do not believe that replacing "live longer" with "minimizing progression of disease" makes the disclosure more accurate or consumer-friendly. In addition, based on our focus group testing, we believe that "feel better" is a consumer-friendly way to discuss improvements in symptoms or quality of life. We disagree that this is an irrelevant outcome for cancer patients.

(Comment 3) One comment stated that Q26 (Perspective Taking Scale) does not appear necessary.

(Response) We included the Perspective Taking Scale as a potential moderator. Participants will be drawn from the general public, and we will ask them to imagine that someone close to them was recently diagnosed with the relevant medical condition. Participants' ability to identify with a different perspective might affect how well they are able to do this. We will evaluate the usefulness of this measure in the pretest and drop it from the main study if it does not apply.

(Comment 4) One comment recommended studying another consumer-friendly disclosure in place of the physician labeling version of the disclosure. In addition, this comment recommended that the consumer-friendly disclosure not mention unknown outcomes (i.e., "we currently do not know if Drug X helps people live longer or feel better.").

(Response) We plan to study the physician labeling version of the disclosure because sponsors currently use this language to explain accelerated approval in DTC promotion (Ref. 2). We plan to include a statement about unknown outcomes in the disclosure because it is one of the elements recommended by FDA to describe accelerated approval products, and it is present in currently used accelerated approval disclosures (Ref. 2). We are in support of additional research that would study alternate consumer-friendly versions.

(Comment 5) One comment requested clarification on the execution of the prominence conditions, in particular regarding its proximity to the indication.

(Response) The disclosure will be presented in direct conjunction with the indication in both prominence conditions. In the high prominence condition, the disclosure will also be presented along with the largest claim.

(Comment 6) Three comments requested access to the study stimuli.

(Response) We have described the purpose of the study, the design, the population of interest, and have provided the questionnaire to numerous individuals upon request. We provided the disclosure language in the questionnaire. Our full stimuli are under development during the PRA process. We do not make draft stimuli public during this time because of concerns that this may contaminate our participant pool and compromise the research.

(Comment 7) One comment requested that we clarify the primary measure of the study.

(Response) Our hypotheses are based on noticing the disclosure (Q20), understanding the disclosure (Q3-Q9), and perceptions (Q10-Q17).

(Comment 8) One comment asked why items Q20 and Q21 come after items Q7-Q19.

(Response) Items Q7-Q19 are designed to measure participants' reaction to the experimental condition to which they were assigned. Items Q20 and Q21 show the disclosure to all participants (regardless of experimental condition) and ask them to respond to it.

(Comment 9) One comment questioned the utility of Q19-B.

(Response) We agree with this concern and have deleted this item.

(Comment 10) One comment stated a concern that an accelerated approval disclosure could cause undue apprehension and deter people who might otherwise benefit from seeking treatment advice about accelerated approval products. Based on this concern, the comment suggested adding questions about whether participants would seek information regarding potential risks or discuss the accelerated approval status with a healthcare professional.

(Response) The current study is intended to gather data that will help us understand how accelerated approval disclosures may impact consumer perception of an accelerated approval drug product. In a content analysis of accelerated approval product websites, we found that 73 percent currently include some form of a disclosure already (Ref. 2). Therefore, it is important to study what effect these disclosures may have. We will measure participants' perceptions of the drug's benefits and risks. In addition, we have expanded our intention question to also measure intentions to suggest a loved one ask their doctor about the drug's risks, benefits, and FDA approval.

(Comment 11) One comment suggested that promotional materials are not the best venue for providing information about prescription drugs, given the role of healthcare professionals in

discussing and prescribing treatments. Based on this, the comment suggested modifying the study to focus on prescriber-patient interactions rather than DTC promotion.

(Response) Consumers often wish to participate in shared decision-making with healthcare professionals when selecting prescription drugs and may request specific prescription drugs from their healthcare professionals based on promotions they have seen in the marketplace. Because information consumers receive through DTC prescription drug promotion can impact these requests, it is important to investigate how the information in prescription drug promotional pieces impacts consumer attention, understanding, and perceptions.

(Comment 12) One comment noted that, in real-world conditions, consumers do not choose an accelerated approval product in a vacuum. This comment requested that we provide participants with information on the limited availability and/or effectiveness of alternative treatments.

(Response) We acknowledge that accelerated approval products often constitute the only treatment option or one of a limited number of treatment options available to patients. We revised the questionnaire to include information for participants in this study about the treatment landscape for the disease.

(Comment 13) One comment recommends enrolling a diversity of participants across demographic categories and geographic locations. They suggest screening for pretest participants, individuals who have recently participated in prescription drug research, and individuals with prior use of oncology products or accelerated approval products.

(Response) Participants will be internet panel members. We will use soft quotas to ensure recruitment of a low health literacy population as well as a demographically diverse set of participants. Pretest participants will not be allowed to participate in the main study. We added

questionnaire items asking participants whether they have been diagnosed with cancer, and if so whether they have ever taken prescription drugs, and specifically accelerated approval products, for cancer.

(Comment 14) One comment noted that participants may pay more attention to information presented in a study, including claims designed to be intentionally misleading, and asked what efforts we will take to avoid response bias.

(Response) The study design does not include intentionally misleading claims. Based on previous research with DTC prescription drug websites, we expect the median time spent on the study stimuli to be under a minute to 2 minutes (Ref. 3). In general, we attempt to minimize response bias by following best practices, such as keeping the survey length short and cognitive-testing and pretesting the questions to make sure they are clearly written.

(Comment 15) One comment requested that the screener and consent form be made available.

(Response) The screener and consent form are available as part of the information collection submission to the OMB.

(Comment 16) One comment noted that the wording of Q4 and Q9 could lead participants toward a specific response.

(Response) These questions are designed to measure whether participants processed the information in the disclosure. Thus, Q4 asks about the unknown outcome information from the disclosure, and Q9 asks about the continuing research information from the disclosure. Because these are not meant to be questions about perceptions, we have changed the wording of Q4 to clarify that we are asking about what the website said, rather than what they might think. We will evaluate these items in cognitive interview and pretesting.

(Comment 17) One comment recommended adding intermediate response values for Q10-Q17 and Q24-Q26.

(Response) We have added intermediate response values for these items, with the exception of Q26, the Perspective Taking Scale, to be consistent with its previous use.

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

Table 2.--Estimated Annual Reporting Burden[1]

Activity	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
Pretest screener	916	1	1	0.08 (5 minutes)	73.28
Study screener	1,507	1	1	0.08 (5 minutes)	120.56
Pretest	385	1	1	0.33 (20 minutes)	127.05
Main Study	633	1	1	0.33 (20 minutes)	208.89
Total					529.78

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

II. References

The following references are on display with 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; these are not available electronically at https://www.regulations.gov as these references are copyright protected. Some may be available at the website address, if listed. 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. Beaver J.A., L.J. Howie, L. Pelosof, et al., "A 25-Year Experience of U.S. Food and Drug Administration Accelerated Approval of Malignant Hematology and Oncology Drugs

and Biologics: A Review." *JAMA Oncology*, 4(6):849-856, 2018. doi:10.1001/jamaoncol.2017.5618.

2. Sullivan H.W., A.C. O'Donoghue, K.T. David, et al., "Disclosing Accelerated Approval on Direct-to-Consumer Prescription Drug Websites." *Pharmacoepidemiology and Drug Safety*, 27:1277-1280, 2018. https://doi.org/10.1002/pds.4664.

3. Sullivan H.W., A.C. O'Donoghue, D.J. Rupert, et al., "Placement and Format of Risk Information on Direct-to-Consumer Prescription Drug Websites." *Journal of Health Communication*, 22:171-181, 2017.

Dated: May 2, 2019.

Lowell J. Schiller,

Principal Associate Commissioner for Policy.

[FR Doc. 2019-09418 Filed: 5/7/2019 8:45 am; Publication Date: 5/8/2019]