

Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

You may submit comments on any guidance at any time (see 21 CFR 10.115(g)(5)). Submit written requests for single copies of the draft guidance to the Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10001 New Hampshire Ave., Hillandale Building, 4th Floor, Silver Spring, MD 20993-0002; or to the Office of Communication, Outreach, and Development, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, 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 See the **SUPPLEMENTARY INFORMATION** section for electronic access to the draft guidance document.

FOR FURTHER INFORMATION CONTACT: Scott N. Goldie, Office of Biostatistics, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 21, Rm. 3557, Silver Spring, MD 20993-0002, 301-796-2055; or Stephen Ripley, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 7301, Silver Spring, MD 20993-0002, 240-402-7911.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a draft guidance for industry entitled “Meta-Analyses of Randomized Controlled Clinical Trials to Evaluate the Safety of Human Drugs or Biological Products.” Evaluating the safety of drug products, both before approval and after marketing, is a fundamental responsibility of the FDA. This evaluation often requires combining and integrating information from multiple sources, and meta-analysis is a useful tool for this purpose.

This draft guidance describes general principles of design, conduct, and reporting that FDA intends to apply to meta-analyses conducted by the Agency, and to use as benchmarks when evaluating meta-analyses conducted by sponsors or third parties. The focus of the draft guidance is on the evaluation of safety. This draft guidance is not intended to be a reference guide on how to conduct a meta-analysis. Rather, this draft guidance document discusses the important principles underlying best practices for safety meta-analyses and the way that FDA intends to factor

adherence to those principles into its decision-making process.

This draft guidance is being issued to fulfill a commitment made under the Prescription Drug User Fee V agreement (section IX.B.3 of the document entitled “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017”) to promote a better understanding and increased consistency among the Agency, industry and other stakeholders regarding meta-analyses and their role in regulatory decision-making.

This draft guidance is being issued consistent with FDA’s good guidance practices regulation (21 CFR 10.115). The draft guidance, when finalized, will represent the current thinking of FDA on “Meta-Analyses of Randomized Controlled Clinical Trials to Evaluate the Safety of Human Drugs or Biological Products.” 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. This guidance is not subject to Executive Order 12866.

II. Paperwork Reduction Act of 1995

This draft guidance refers to previously approved collections of information that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). The collections of information in 21 CFR parts 312, 314, and 601 have been approved under OMB control numbers 0910-0014, 0910-0001, and 0910-0338 respectively.

III. Electronic Access

Persons with access to the internet may obtain the draft guidance at either <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>, <https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>, or <https://www.regulations.gov>.

Dated: November 1, 2018.

Leslie Kux,

Associate Commissioner for Policy.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2018-N-3758]

Agency Information Collection Activities; Proposed Collection; Comment Request; Individual Patient Expanded Access Applications: Form FDA 3926

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA, Agency, or we) 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, including each proposed extension of an existing collection of information, and to allow 60 days for public comment in response to the notice. This notice solicits comments on individual patient expanded access applications.

DATES: Submit either electronic or written comments on the collection of information by January 7, 2019.

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. Electronic comments must be submitted on or before January 7, 2019. The <https://www.regulations.gov> electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of January 7, 2019. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is 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-2018-N-3758 for “Agency Information Collection Activities; Proposed Collection; Comment Request; Guidance for Industry on Individual Patient Expanded Access Applications: Form FDA 3926.” 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.

- **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.gpo.gov/fdsys/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.

FOR FURTHER INFORMATION CONTACT:

Domini Bean, Office of Operations, Food and Drug Administration, Three White Flint North, 10A-12M, 11601 Landsdown St., North Bethesda, MD 20852, 301-796-5733, PRAStaff@fda.hhs.gov.

SUPPLEMENTARY INFORMATION: Under the PRA (44 U.S.C. 3501-3520), 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, including each proposed extension of an existing 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.

Guidance for Industry on Individual Patient Expanded Access Applications: Form FDA 3926

OMB Control Number 0910-0814—Extension

This information collection supports Agency regulations, associated guidance, and Form FDA 3926 concerning individual patient expanded access. Individual patient expanded access allows an individual patient who has a serious or immediately life-threatening disease or condition and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition, the use of an investigational new drug (IND) outside of a clinical investigation, or the use of an approved drug where availability is limited by a risk evaluation and mitigation strategy. When applicable criteria in § 312.305(a) (21 CFR 312.305(a)) (which apply to all types of expanded access) and the criteria in § 312.310(a) (21 CFR 312.310(a)) (which apply specifically to individual patient expanded access, including for emergency use) are met, FDA may permit expanded access.

Section 312.305(b) sets forth the submission requirements for all types of expanded access requests. To assist respondents with requirements in § 312.305 we developed Form FDA 3926 (Individual Patient Expanded Access Investigational New Drug Application) and the guidance document entitled, “Individual Patient Expanded Access Applications: Form FDA 3926.”

The physician may satisfy some of the submission requirements by referring to information in an existing IND, ordinarily the one held by the investigational drug’s manufacturer, if the physician obtains permission from that IND holder. If permission is obtained, the physician should then provide to FDA a letter of authorization (LOA) from the existing IND holder that permits FDA to reference that IND.

One of the requirements under § 312.305(b)(2) is that a “cover sheet” must be included “meeting the requirements of § 312.23(a).” This provision applies to several types of submissions under part 312 (21 CFR part 312), ranging from commercial INDs under § 312.23 that involve large groups of patients enrolled in clinical trials to requests from physicians to use an investigational drug for an individual

patient. Sponsors currently use Form FDA 1571 for all types of IND submissions to meet the requirements in § 312.23(a).

Concerned that physicians requesting expanded access for an individual patient may encounter difficulty in completing Form FDA 1571 and the associated documents because the form is not tailored to requests for individual patient expanded access, we developed Form FDA 3926 to comply with the IND submission requirements in §§ 312.23, 312.305(b), and 312.310(b). Form FDA 3926 provides a streamlined means to request expanded access and is available for licensed physicians. FDA considers a completed Form FDA 3926 with the box in Field 10 checked and the form signed by the physician to be a request in accordance with § 312.10 for a waiver of any additional requirements in part 312 for an IND submission, including additional information currently provided in Form FDA 1571 and Form FDA 1572 (Statement of Investigator, which provides the identity and qualifications of the investigator conducting the clinical investigation).

Under § 312.310(d), in an emergency situation that requires the patient to be treated before a written submission can be made, the request to use the investigational drug for individual patient expanded access may be made by telephone (or other rapid means of communication) to the appropriate FDA review division. Authorization of the emergency use may be given by an FDA official over the telephone, provided the physician explains how the expanded access use will meet the requirements of §§ 312.305 and 312.310 and agrees to submit an expanded access application within 15 working days of FDA's initial authorization of the expanded access use (§ 312.310(d)). The physician may choose to use Form FDA 3926 for the expanded access application.

As explained in the instructions for Form FDA 3926 and discussed in the guidance document, the following information is submitted to FDA:

- Initials for the patient and date of submission.
- Type of submission (initial or follow-up submission).
- Clinical information, including indication, brief clinical history of the patient (age, gender, weight, allergies, diagnosis, prior therapy, response to prior therapy), and the reason for requesting the proposed treatment, including an explanation of why the patient lacks other therapeutic options.
- Treatment information, including the investigational drug's name and the name of the entity supplying the drug (generally the manufacturer), the applicable FDA review division (if known), and the treatment plan. This should include the planned dose, route and schedule of administration, planned duration of treatment, monitoring procedures, and planned modifications to the treatment plan in the event of toxicity.
- LOA, generally obtained from the entity that is the sponsor of the IND (e.g., commercial sponsor/drug manufacturer) being referenced, if applicable.
- Physician's qualification statement. An appropriate statement includes medical school attended, year of graduation, medical specialty, State medical license number, current employment, and job title. Alternatively, the relevant portion of the physician's curriculum vitae may be attached.
- Physician's contact information, including name, physical address, email address, telephone number, facsimile number, and physician's IND number, if previously issued by FDA.
- Contents of submission (for follow-up/additional submissions), including the type of submission being made. FDA

accepts Form FDA 3926 for certain follow-up/additional submissions, which include the following: Initial Written IND Safety Report (§ 312.32(c)); Followup to a Written IND Safety Report (§ 312.32(d)); Annual Report (§ 312.33); Summary of Expanded Access Use (treatment completed) (§ 312.310(c)(2)); Change in Treatment Plan (§ 312.30); General Correspondence or Response to FDA Request for Information (§ 312.41); and Response to Clinical Hold (§ 312.42(e)).

- Request for authorization to use Form FDA 3926 for individual patient expanded access application.
- Signature of the physician certifying that treatment will not begin until 30 days after FDA receives the completed application and all required material unless the submitting physician receives earlier notification from FDA that the treatment may proceed. The physician agrees not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. The physician also certifies that informed consent will be obtained in compliance with Federal requirements (including FDA's regulations in 21 CFR part 50) and that an institutional review board (IRB) that complies with all Federal requirements (including FDA's regulations in 21 CFR part 56) will be responsible for initial and continuing review and approval of the expanded access use. The physician also acknowledges that in the case of an emergency request, treatment may begin without prior IRB approval, provided the IRB is notified of the emergency treatment within 5 working days of treatment. The physician agrees to conduct the investigation in accordance with all other applicable regulatory requirements.

We estimate the burden of this collection of information as follows:

TABLE 1—ESTIMATED ANNUAL REPORTING BURDEN¹

Guidance on Individual Patient Expanded Access Applications: Form FDA 3926	Number of respondents	Number of responses per respondent	Total annual responses	Average burden per response	Total hours
Expanded access submission elements included in Form FDA 3926.	790	3.03	2,394	0.75 (45 mins.)	1,795

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

Based on a review of the information collection, we are retaining the currently approved burden estimate. The estimates for “number of respondents,” “number of responses per respondent,” and “total annual responses” were obtained from reports

and data management systems from the Center for Drug Evaluation and Research (CDER) and from other sources familiar with the number of submissions received for individual patient expanded access use under part 312. The estimates for “average burden per

response” were based on information CDER provided and personnel of the U.S. Department of Health and Human Services familiar with preparing and reviewing expanded access submissions by practicing physicians.

Based on data from the Document Archiving, Reporting and Regulatory Tracking System for the number of submissions to FDA using FDA Form 3926 during fiscal years 2015, 2016, and 2017, we estimate that approximately 790 licensed physicians would use FDA Form 3926 to submit 1.46 requests per physician (respondent) for individual patient expanded access, for a total of 1,153 responses annually. Based on these estimates, FDA calculates the total annual responses to be 2,394 (1,153 requests for individual patient expanded access and 1,241 follow-up submissions) by 790 physicians for an average of 3.03 responses per respondent. FDA estimates the average burden per response to be 45 minutes (0.75 hour). Based on this estimate, FDA calculates the total burden to be 1,795 hours.

Dated: October 31, 2018.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2018-24321 Filed 11-6-18; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2018-N-4130]

Agency Information Collection Activities; Proposed Collection; Comment Request; Recordkeeping Requirements for Microbiological Testing and Corrective Measures for Bottled Water

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, including each proposed extension of an existing collection of information, and to allow 60 days for public comment in response to the notice. This notice solicits comments on the procedure by which both domestic and foreign bottled water manufacturers that sell bottled water in the United States maintain records of microbiological testing and corrective measures, in addition to existing recordkeeping requirements.

DATES: Submit either electronic or written comments on the collection of information by January 7, 2019.

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. Electronic comments must be submitted on or before January 7, 2019. The <https://www.regulations.gov> electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of January 7, 2019. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is 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-2018-N-4130 for "Agency Information

Collection Activities; Proposed Collection; Comment Request; Recordkeeping Requirements for Microbiological Testing and Corrective Measures for Bottled Water." 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.

- **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.gpo.gov/fdsys/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.

FOR FURTHER INFORMATION CONTACT: Domini Bean, Office of Operations, Food and Drug Administration, Three White Flint North, 10A-12M, 11601 Landsdown St., North Bethesda, MD 20852, 301-796-5733, PRASStaff@fda.hhs.gov.