

Clinical pharmacology studies are part of a stepwise approach for developing the data and information needed to support a demonstration of biosimilarity. These studies can reduce the residual uncertainty in assessing the biosimilarity between a proposed biosimilar product and reference product and inform the design of subsequent clinical trials to assess clinically meaningful differences. This guidance is intended to assist sponsors in designing such studies in support of applications submitted under section 351(k) of the Public Health Service Act (42 U.S.C. 262(k)), as added by the BPCI Act.<sup>1</sup> In particular, this guidance discusses certain critical considerations for using clinical pharmacology testing to support biosimilarity, approaches for developing the appropriate clinical pharmacology database to support a demonstration of biosimilarity, and the utility of modeling and simulation for designing and analyzing clinical trials. Scientific principles described in the guidance may also be informative for the development of certain biological products under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(b)(2)).

On May 14, 2014, FDA issued a notice announcing the availability of a draft guidance with the same name as the current guidance to solicit comments from the public (79 FR 27622). After carefully reviewing received comments and in light of increased regulatory experience and the evolution of the science in biosimilar product development and evaluation, FDA has finalized that guidance with certain changes. These changes are for clarity, however, and are not substantive.

This guidance is one in a series that FDA is developing to implement the BPCI Act and is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The guidance represents the current thinking of FDA on conducting clinical pharmacology studies in support of proposed biosimilar 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.

## II. The Paperwork Reduction Act of 1995

The 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 collection of information submitted under section 351(k) applications for biosimilars is approved under OMB control number 0910–0719. The collection of information submitted under 21 CFR part 312 is approved under OMB control number 0910–0014.

## III. Electronic Access

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

Dated: December 22, 2016.

**Leslie Kux,**

*Associate Commissioner for Policy.*

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## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

[Docket No. FDA–2016–D–4318]

#### Compounding and Repackaging of Radiopharmaceuticals by State-Licensed Nuclear Pharmacies and Federal Facilities; Draft Guidance for Industry; Availability

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

**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA or Agency) is announcing the availability of a draft guidance for industry entitled “Compounding and Repackaging of Radiopharmaceuticals by State-Licensed Nuclear Pharmacies and Federal Facilities.” This guidance sets forth FDA's policy regarding compounding and repackaging of radiopharmaceuticals for human use by State-licensed nuclear pharmacies and Federal facilities that are not registered as outsourcing facilities. Because such radiopharmaceuticals are not eligible for exemptions from provisions of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) related to the production of drugs, FDA is issuing this guidance to describe the conditions under which it does not intend to take action for violations of certain provisions of the FD&C Act when a State-licensed nuclear pharmacy or Federal facility compounds or repackages radiopharmaceuticals.

**DATES:** Although you can comment on any guidance at any time (see 21 CFR 10.115(g)(5)), to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance, submit either electronic or written comments on the draft guidance by February 27, 2017. Submit either electronic or written comments concerning the collection of information proposed in the draft guidance by February 27, 2017.

**ADDRESSES:** You may submit comments as follows:

#### 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):** Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

- For written/paper comments submitted to the Division of Dockets Management, 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–2016–D–4318 for “Compounding and Repackaging of Radiopharmaceuticals by State-Licensed Nuclear Pharmacies and Federal Facilities.” Received

<sup>1</sup> The BPCI Act was enacted as part of the Patient Protection and Affordable Care Act (Pub. L. 111–148) on March 23, 2010.

comments will be placed in the docket and, except for those submitted as “Confidential Submissions,” publicly viewable at <https://www.regulations.gov> or at the Division of Dockets Management 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 Division of Dockets Management. 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: <http://www.fda.gov/regulatoryinformation/dockets/default.htm>.

*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 Division of Dockets Management, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

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. 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:** Edisa Gozun, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 5197, Silver Spring, MD 20993, 301–796–3110.

**SUPPLEMENTARY INFORMATION:**

**I. Background**

Under current law, radiopharmaceuticals that are compounded by entities that are not registered with FDA as outsourcing facilities, and radiopharmaceuticals that are repackaged, are subject to all applicable provisions of the FD&C Act related to the production of drugs. Because Congress explicitly excluded radiopharmaceuticals from section 503A of the FD&C Act (21 U.S.C. 353a) (see section 503A(d)(2)),<sup>1</sup> compounded radiopharmaceuticals are not eligible for the exemptions under section 503A from section 505 of the FD&C Act (21 U.S.C. 355) (concerning new drug approval requirements), section 502(f)(1) of the FD&C Act (21 U.S.C. 352(f)(1)) (concerning labeling with adequate directions for use), and section 501(a)(2)(B) of the FD&C Act (21 U.S.C. 351(a)(2)(B)) (concerning current good manufacturing practice (CGMP) requirements). In addition, Congress did not exempt repackaged radiopharmaceuticals from any provisions of the FD&C Act.

Because State-licensed nuclear pharmacies and Federal facilities sometimes compound or repackage radiopharmaceuticals for patients, but radiopharmaceuticals are not eligible for the exemptions in section 503A of the FD&C Act, FDA is issuing this guidance to describe the conditions under which the Agency does not intend to take action for violations of sections 505, 502(f)(1), and 501(a)(2)(B) of the FD&C Act when a State-licensed nuclear pharmacy or a Federal facility that is not an outsourcing facility compounds or repackages radiopharmaceuticals for human use.

Elsewhere in this issue of the **Federal Register**, FDA is announcing the availability of a separate draft guidance document concerning compounding and repackaging of radiopharmaceuticals by outsourcing facilities entitled “Compounding and Repackaging of

Radiopharmaceuticals by Outsourcing Facilities.”

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 “Compounding and Repackaging of Radiopharmaceuticals by State-Licensed Nuclear Pharmacies and Federal Facilities.” 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**

Under the Paperwork Reduction Act of 1995 (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 that 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 collection of information associated with this document, FDA invites comments on the following 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.

One of the conditions of the draft guidance is that the compounded radiopharmaceutical is not essentially a copy of an approved radiopharmaceutical. If a compounder intends to rely on a determination from a prescriber that there is a change between the compounded radiopharmaceutical and the

<sup>1</sup> Section 503A of the FD&C Act describes the conditions that must be met for drug products compounded by a licensed pharmacist in a State-licensed pharmacy or Federal facility, or by a licensed physician, to qualify for exemptions from sections 505, 502(f)(1), and 501(a)(2)(B) of the FD&C Act. Section 503A(d)(2) of the FD&C Act states that “this section shall not apply to . . . radiopharmaceuticals.”

comparable approved radiopharmaceutical that produces for an identified individual patient a clinical difference, the determination is documented on the prescription or order in writing by either (1) the prescribing practitioner, or (2) the compounder, reflecting a conversation with the prescribing practitioner. The compounder maintains records of the prescription or order documenting this determination.

We estimate that annually a total of approximately 10 compounders (“No. of Respondents” in table 1, line 1) will consult a prescriber to determine whether he or she has made a determination that the compounded

radiopharmaceutical has a change that produces a clinical difference for an identified individual patient as compared to the comparable approved radiopharmaceutical. We estimate that compounders will document this determination on approximately 250 prescriptions or orders for compounded radiopharmaceuticals (“Total Annual Disclosures” in table 1, line 1). We estimate that the consultation between the compounder and the prescriber and noting this determination on each prescription or order that does not already document this determination will take approximately 3 minutes per prescription or order.

A compounder also maintains records of prescriptions or orders noting the determination that a prescriber has determined that the compounded radiopharmaceutical has a change that produces a clinical difference for an identified individual patient. We estimate that the compounder will take approximately 2.1 hours to maintain the records of 250 prescriptions or orders documenting the prescriber’s determination of clinical difference (“Total Hours” in table 2). We estimate that maintaining such records will take approximately 30 seconds per prescription or order.

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

TABLE 1—ESTIMATED ANNUAL THIRD-PARTY DISCLOSURE BURDEN <sup>1</sup>

| Type of reporting  | Number of respondents | Number of disclosures per respondent | Total annual disclosures | Average burden per disclosure | Total hours |
|--|-----------------------|--------------------------------------|--------------------------|-------------------------------|-------------|
| Consultation between the compounder and prescriber or health care facility, and the notation on the prescription or order documenting the prescriber’s determination of clinical difference. | 10                    | 25                                   | 250                      | 3 minutes ....                | 12.5        |

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

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

| Type of reporting  | Number of recordkeepers | Number of records per recordkeeper | Total annual records | Average burden per record-keeping | Total hours |
|--|-------------------------|------------------------------------|----------------------|-----------------------------------|-------------|
| Maintenance of records of prescriptions or orders documenting the prescriber’s determination of clinical difference. | 10                      | 25                                 | 250                  | 30 seconds ..                     | 2.1         |

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

**III. Electronic Access**

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

Dated: December 22, 2016.

**Leslie Kux,**

*Associate Commissioner for Policy.*

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**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**Food and Drug Administration**

[Docket No. FDA–2014–D–1953]

**Providing Regulatory Submissions in Electronic Format—Submission of Manufacturing Establishment Information; Draft Guidance for Industry; Availability**

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

**ACTION:** Notice of availability.

**SUMMARY:** The Food and Drug Administration (FDA or Agency) is announcing the availability of a draft guidance for industry entitled “Providing Regulatory Submissions in Electronic Format—Submission of Manufacturing Establishment Information.” This guidance discusses the requirements for a valid electronic

submission of manufacturing establishment information (MEI) under the Federal Food, Drug, and Cosmetic Act (the FD&C Act). This action will streamline the review of all manufacturing establishments involved in the preparation of a drug or biological product by consolidating information in one location and eliminating the inclusion of erroneous and/or outdated information from other Agency files.

**DATES:** Although you can comment on any guidance at any time (see 21 CFR 10.115(g)(5)), to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance, submit either electronic or written comments on the draft guidance by February 27, 2017.

**ADDRESSES:** You may submit comments as follows: