

have been approved under OMB control number 0910-0120; the collections of information in 21 CFR part 812, regarding investigational device exemptions, have been approved under OMB control number 0910-0078; the collections of information in 21 CFR part 814, subparts A through E, regarding premarket approval, have been approved under OMB control number 0910-0231; the collections of information in 21 CFR part 820, regarding quality system regulations, have been approved under OMB control number 0910-0073; the collections of information regarding MedWatch: The Food and Drug Administration Medical Products Reporting Program have been approved under OMB control number 0910-0291; and the collections of information regarding the Adverse Event Program for Medical Devices (Medical Product Safety Network (MedSun)) have been approved under OMB control number 0910-0471.

Dated: November 3, 2016.

Leslie Kux,

Associate Commissioner for Policy.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2010-D-0075]

Non-Inferiority Clinical Trials To Establish Effectiveness; 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 guidance for industry entitled “Non-Inferiority Clinical Trials to Establish Effectiveness.” This document provides guidance to sponsors and applicants submitting investigational new drug applications (INDs), new drug applications (NDAs), biologics licensing applications (BLAs), or supplemental applications on the appropriate use of non-inferiority (NI) study designs to provide evidence of the effectiveness of a drug or biologic. The guidance gives advice on when NI studies demonstrating effectiveness of an investigational drug can provide interpretable results, how to choose the NI margin, and how to test the NI hypothesis.

DATES: Submit either electronic or written comments on Agency guidances at any time.

ADDRESSES: You may submit comments as follows:

Electronic Submissions

Submit electronic comments in the following way:

- *Federal eRulemaking Portal:* <http://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <http://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 <http://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-2010-D-0075 for “Non-Inferiority Clinical Trials to Establish Effectiveness; Guidance for Industry.” Received comments will be placed in the docket and, except for those submitted as “Confidential Submissions,” publicly viewable at <http://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 <http://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 <http://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 this 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 the Office of Communication, Outreach and Development, Center for Biologics Evaluation and Research (CBER), 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 guidance document.

FOR FURTHER INFORMATION CONTACT: Scott Goldie, 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 Robert Temple, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, Rm. 4212, Silver Spring, MD 20993-0002, 301-796-2270; 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 guidance for industry entitled "Non-Inferiority Clinical Trials to Establish Effectiveness." This guidance consists of four parts. The first part is a general discussion of regulatory, study design, scientific, and statistical issues associated with the use of NI studies to establish the effectiveness of a drug or biologic. The second part focuses on some of these issues in more detail, notably the statistical approaches used to determine the NI margin and to test for non-inferiority. The third part addresses commonly asked questions about NI studies. The fourth part includes four examples of successful and unsuccessful efforts to define NI margins and test for non-inferiority.

This guidance finalizes the draft guidance for industry, "Non-Inferiority Clinical Trials," published in 2010. In addition, it supersedes the guidance for industry, "Antibacterial Drug Products: Use of Noninferiority Trials to Support Approval," also published in 2010, which will be withdrawn.

This guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The guidance represents the current thinking of FDA on NI clinical trials to establish effectiveness. 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. Electronic Access

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

Dated: November 3, 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-P-2674]

Determination That CALAN SR (Verapamil Hydrochloride) Extended-Release Oral Tablet, 180 Milligrams, Was Not Withdrawn From Sale for Reasons of Safety or Effectiveness

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA or Agency) has determined that CALAN SR (verapamil hydrochloride) extended-release oral tablet, 180 milligrams (mg), was not withdrawn from sale for reasons of safety or effectiveness. This determination will allow FDA to approve abbreviated new drug applications (ANDAs) for verapamil hydrochloride extended-release oral tablet, 180 mg, if all other legal and regulatory requirements are met.

FOR FURTHER INFORMATION CONTACT:

Stacy Kane, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6236, Silver Spring, MD 20993-0002, 301-796-8363.

SUPPLEMENTARY INFORMATION: In 1984, Congress enacted the Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98-417) (the 1984 amendments), which authorized the approval of duplicate versions of drug products under an ANDA procedure. ANDA applicants must, with certain exceptions, show that the drug for which they are seeking approval contains the same active ingredient in the same strength and dosage form as the "listed drug," which is a version of the drug that was previously approved. ANDA applicants do not have to repeat the extensive clinical testing otherwise necessary to gain approval of a new drug application (NDA).

The 1984 amendments include what is now section 505(j)(7) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)(7)), which requires FDA to publish a list of all approved drugs. FDA publishes this list as part of the "Approved Drug Products With

Therapeutic Equivalence Evaluations," which is known generally as the "Orange Book." Under FDA regulations, drugs are removed from the list if the Agency withdraws or suspends approval of the drug's NDA or ANDA for reasons of safety or effectiveness or if FDA determines that the listed drug was withdrawn from sale for reasons of safety or effectiveness (21 CFR 314.162).

A person may petition the Agency to determine, or the Agency may determine on its own initiative, whether a listed drug was withdrawn from sale for reasons of safety or effectiveness. This determination may be made at any time after the drug has been withdrawn from sale, but must be made prior to approving an ANDA that refers to the listed drug (§ 314.161 (21 CFR 314.161)). FDA may not approve an ANDA that does not refer to a listed drug.

CALAN SR (verapamil hydrochloride) extended-release oral tablet, 180 mg, is the subject of NDA 019152 held by Pfizer Inc. CALAN SR is indicated for the treatment of hypertension, to lower blood pressure. CALAN SR (verapamil hydrochloride) extended-release oral tablet, 180 mg, is currently listed in the "Discontinued Drug Product List" section of the Orange Book.

Heritage Pharma Labs, Inc., submitted a citizen petition dated August 31, 2016 (Docket No. FDA-2016-P-2674), under 21 CFR 10.30, requesting that the Agency determine whether CALAN SR (verapamil hydrochloride) extended-release oral tablet, 180 mg, was withdrawn from sale for reasons of safety or effectiveness.

After considering the citizen petition and reviewing Agency records, and based on the information we have at this time, FDA has determined under § 314.161 that CALAN SR (verapamil hydrochloride) extended-release oral tablet, 180 mg, was not withdrawn for reasons of safety or effectiveness. The petitioner has identified no data or other information suggesting that CALAN SR (verapamil hydrochloride) extended-release oral tablet, 180 mg, was withdrawn for reasons of safety or effectiveness. We have carefully reviewed our files for records concerning the withdrawal of CALAN SR (verapamil hydrochloride) extended-release oral tablet, 180 mg, from sale. We have also independently evaluated relevant literature and data for possible postmarketing adverse events. We have found no information that would indicate that this drug product was withdrawn from sale for reasons of safety or effectiveness.

Accordingly, the Agency will continue to list CALAN SR (verapamil hydrochloride) extended-release oral