

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**Food and Drug Administration**

[Docket No. FDA-2022-P-1785]

**Determination That LOTENSIN (Benazepril Hydrochloride) Tablets, 5 Milligrams, Were Not Withdrawn From Sale for Reasons of Safety or Effectiveness**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(FDA, Agency, or we) has determined that LOTENSIN (benazepril hydrochloride) tablets, 5 milligrams (mg), were not withdrawn from sale for reasons of safety or effectiveness. This determination means that FDA will not begin procedures to withdraw approval of abbreviated new drug applications (ANDAs) that refer to this drug product, and it will allow FDA to continue to approve ANDAs that refer to the product as long as they meet relevant legal and regulatory requirements.

**FOR FURTHER INFORMATION CONTACT:** Nisha Shah, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6222, Silver Spring, MD 20993-0002, 301-796-4455, [Nisha.Shah@fda.hhs.gov](mailto:Nisha.Shah@fda.hhs.gov).

**SUPPLEMENTARY INFORMATION:** Section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(j)) allows the submission of an ANDA to market a generic version of a previously approved drug product. To obtain approval, the ANDA applicant must show, among other things, that the generic drug product: (1) has the same active ingredient(s), dosage form, route of administration, strength, conditions of use, and (with certain exceptions) labeling as the listed drug, which is a version of the drug that was previously approved and (2) is bioequivalent to the listed drug. ANDA applicants do not have to repeat the extensive clinical testing otherwise necessary to gain approval of a new drug application (NDA).

Section 505(j)(7) of the FD&C Act 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ANDA for reasons of safety or effectiveness or if FDA determines that the listed drug was withdrawn from sale for reasons of safety or effectiveness (21 CFR 314.162).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.

LOTENSIN (benazepril hydrochloride) tablets, 5 mg, are the subject of NDA 019851, held by Validus Pharmaceuticals LLC, and initially approved on June 25, 1991. LOTENSIN is indicated for the treatment of hypertension to lower blood pressure. LOTENSIN (benazepril hydrochloride) tablets, 5 mg, are currently listed in the “Discontinued Drug Product List” section of the Orange Book.

Aurobindo Pharma Ltd. submitted a citizen petition dated August 3, 2022 (Docket No. FDA-2022-P-1785), under 21 CFR 10.30, requesting that the Agency determine whether LOTENSIN (benazepril hydrochloride) tablets, 5 mg, were 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 LOTENSIN (benazepril hydrochloride) tablets, 5 mg, were not withdrawn for reasons of safety or effectiveness. The petitioner has identified no data or other information suggesting that LOTENSIN (benazepril hydrochloride) tablets, 5 mg, were withdrawn for reasons of safety or effectiveness. We have carefully reviewed our files for records concerning the withdrawal of LOTENSIN (benazepril hydrochloride) tablets, 5 mg, from sale. We have also independently evaluated relevant literature and data for possible postmarketing adverse events. We have reviewed the available evidence and determined that this drug product was not withdrawn from sale for reasons of safety or effectiveness.

Accordingly, the Agency will continue to list LOTENSIN (benazepril hydrochloride) tablets, 5 mg, in the “Discontinued Drug Product List” section of the Orange Book. The “Discontinued Drug Product List” delineates, among other items, drug products that have been discontinued

from marketing for reasons other than safety or effectiveness. FDA will not begin procedures to withdraw approval of approved ANDAs that refer to this drug product. Additional ANDAs for this drug product may also be approved by the Agency as long as they meet all other legal and regulatory requirements for the approval of ANDAs. If FDA determines that labeling for this drug product should be revised to meet current standards, the Agency will advise ANDA applicants to submit such labeling.

Dated: January 27, 2023.

**Lauren K. Roth,**

*Associate Commissioner for Policy.*

[FR Doc. 2023-02101 Filed 1-31-23; 8:45 am]

**BILLING CODE 4164-01-P**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**Food and Drug Administration**

[Docket No. FDA-2022-D-2983]

**Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products; 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 “Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products.” FDA is issuing this draft guidance as part of a series of guidance documents under its Real-World Evidence (RWE) Program and to satisfy, in part, a mandate under the Federal Food, Drug, and Cosmetic Act (FD&C Act) to issue guidance about the use of RWE in regulatory decision-making. This draft guidance includes recommendations to sponsors and investigators considering the use of externally controlled trials to provide evidence of the safety and effectiveness of a drug product. The draft guidance also describes considerations related to communicating with FDA and ensuring access by the Agency to data from an externally controlled trial.

**DATES:** Submit either electronic or written comments on the draft guidance by May 2, 2023 to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance.

**ADDRESSES:** You may submit comments on any guidance at any time 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):** 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-2022-D-2983 for "Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products." Received 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 Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240-402-7500.

- **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.govinfo.gov/content/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, 240-402-7500.

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:** John Concato, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6346, Silver Spring, MD 20993-0002, 301-796-2500, [john.concato@fda.hhs.gov](mailto:john.concato@fda.hhs.gov); or Diane

Maloney, 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 "Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products." This draft guidance provides recommendations to sponsors and investigators considering the use of externally controlled trials to provide evidence of the safety and effectiveness of a drug product. In an externally controlled trial, outcomes in participants receiving the test treatment according to a protocol are compared to outcomes in a group of people external to the trial who had not received the same treatment.

The draft guidance addresses considerations for the design and analysis of externally controlled trials to study the effectiveness and safety of drugs, including discussion of threats to the validity of trial results from potential bias. Although various sources of data can serve as the control arm in an externally controlled trial, this draft guidance focuses on the use of patient-level data from other clinical trials or from real-world data (RWD) sources, such as registries as well as electronic health records and medical claims. The draft guidance also describes considerations related to communicating with FDA and ensuring access by the Agency to data from an externally controlled trial.

This draft guidance does not address other types of external controls, such as using summary-level estimates instead of patient-level data. This draft guidance does not discuss details of the design and analysis of a natural history study, nor the reliability and relevance of various sources of RWD that could be used in an externally controlled trial. Finally, this draft guidance also does not discuss considerations for using external control data to supplement a control arm in a traditional randomized controlled clinical trial.

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 "Considerations for the Design and Conduct of Externally Controlled Trials for Drug and 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.

## II. Paperwork Reduction Act of 1995

While this guidance contains no collection of information, it does refer to previously approved FDA collections of information. Therefore, clearance by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (PRA) (44 U.S.C. 3501–3521) is not required for this guidance. The previously approved collections of information are subject to review by OMB under the PRA. The collections of information in 21 CFR part 312 have been approved under OMB control number 0910–0014; the collections of information in 21 CFR part 314 have been approved under OMB control number 0910–0001; and the collections of information in 21 CFR part 601 have been approved under OMB control number 0910–0338.

## III. Electronic Access

Persons with access to the internet may obtain an electronic version of the draft guidance at <https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs>, <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>, or <https://www.regulations.gov>.

Dated: January 27, 2023.

**Lauren K. Roth,**

*Associate Commissioner for Policy.*

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## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

[Docket No. FDA–2023–D–0093]

### M13A Bioequivalence for Immediate-Release Solid Oral Dosage Forms; International Council for Harmonisation; 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 “M13A Bioequivalence for Immediate-Release Solid Oral Dosage Forms.” The draft guidance was prepared under the auspices of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for

Human Use (ICH). The draft guidance describes the scientific and technical aspects of study design and data analysis to support bioequivalence (BE) assessment for orally administered immediate-release solid oral dosage forms, such as tablets, capsules, and granules/powders for oral suspension. The draft guidance is intended to provide globally harmonized scientific recommendations for conducting BE studies during both development and postapproval phases for these products.

**DATES:** Submit either electronic or written comments on the draft guidance by April 3, 2023 to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance.

**ADDRESSES:** You may submit comments on any guidance at any time 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):* 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–2023–D–0093 for “M13A Bioequivalence for Immediate-Release Solid Oral Dosage Forms.” Received 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 Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240–402–7500.

- *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.govinfo.gov/content/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, 240–402–7500.

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–