DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2017–D–5961]

Clinical Drug Interaction Studies—Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions and In Vitro Drug Interaction Studies—Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions; 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 two final guidances for industry entitled ''Clinical Drug Interaction Studies—Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions'' and ''In Vitro Drug Interaction Studies—Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions.'' These guidances finalize the draft guidances entitled ''Clinical Drug Interaction Studies—Study Design, Data Analysis, and Clinical Implications'' and ''In Vitro Metabolism- and Transporter-Mediated Drug-Drug Interaction Studies'' published in October 2017. The final guidances are intended to assist drug developers in the planning and evaluation of drug-drug interaction (DDI) potential during drug development and describe a systematic, risk-based approach to the assessment of DDIs.

DATES: The announcement of the guidance is published in the **Federal Register** on January 23, 2020.

ADDRESSES: You may submit either electronic or written comments on Agency guidances 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–2017–D–5961 for ''Clinical Drug Interaction Studies—Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions'' and ''In Vitro Drug Interaction Studies—Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions.'' 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.

- 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.

You may submit comments on any guidance at any time (see 21 CFR 10.115(g)(5)).

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. 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: Lauren Milligan, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 3159, Silver Spring, MD 20903–0002, 301–796–5008, or *OCP@fda.hhs.gov.*

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of two final guidances for industry entitled ''Clinical Drug Interaction Studies—Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions'' and ''In Vitro Drug Interaction Studies—Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions.'' The concomitant use of more than one medication in a patient is common. Unanticipated, unrecognized, or mismanaged DDIs are an important cause of morbidity and mortality associated with prescription drug use and have occasionally been the basis for withdrawal of approved drugs from the market. In some instances, understanding how to safely manage a DDI can allow approval of a drug that

would otherwise have an unacceptable level of risk.

Clinically relevant DDIs between an investigational drug and other drugs should therefore: (1) Be defined during drug development as part of an adequate assessment of the drug's overall benefit/risk profile; (2) be known at the time of the drug's approval; and (3) be communicated in labeling. These two final guidances are intended to assist drug developers in the planning and evaluation of DDI potential during drug development. The in vitro DDI guidance focuses on in vitro experimental approaches for evaluating metabolizing enzyme- and transporter-based drug interaction potential and how to extrapolate in vitro data to decide on the need for clinical DDI studies. The clinical DDI guidance focuses on clinical studies that evaluate DDIs that alter a drug's pharmacokinetics by modulating the effects of drug metabolizing enzymes and/or transporters and advises sponsors on the timing and design of the clinical studies, interpretation of the results, and options for DDI management in patients.

Revisions to the draft guidances include clarification on the scope of the guidances, additional considerations for prospective drug interaction studies, and when DDI studies are needed for drugs identified as transporter substrates from in vitro studies. Together, the two final guidances describe a systematic, risk-based approach to evaluation and communication of DDIs.

These guidances are being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The guidances represent the current thinking of FDA on the topics they address. They do not establish any rights for any person and are 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

These guidances refer to previously approved collections of information found in FDA regulations. These collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3521). The collections of information in 21 CFR 314.50(d) have been approved under OMB control number 0910–0001.

III. Electronic Access

Persons with access to the internet may obtain the guidance at either *https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs* or *https://www.regulations.gov.*

Dated: January 16, 2020.

Lowell J. Schiller,

Principal Associate Commissioner for Policy.

[FR Doc. 2020–01064 Filed 1–22–20; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2019–P–1525]

Determination That CARDENE (Nicardipine Hydrochloride) Injection, 25 Milligrams/10 Milliliters, 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 CARDENE (nicardipine hydrochloride) injection, 25 milligrams (mg)/10 milliliters (mL), was not withdrawn from sale for reasons of safety or effectiveness. This determination will allow FDA to approve abbreviated new drug applications (ANDAs) for nicardipine hydrochloride injection, 25 mg/10 mL, if all other legal and regulatory requirements are met.

FOR FURTHER INFORMATION CONTACT: Daniel Gottlieb, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6210, Silver Spring, MD 20993–0002, 301–796–6650, *daniel.gottlieb@fda.hhs.gov.*

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.

CARDENE (nicardipine hydrochloride) injection, 25 mg/10 mL, is the subject of NDA 019734, held by Chiesi USA, Inc., and initially approved on January 30, 1992. CARDENE is indicated for short-term treatment of hypertension when oral therapy is not feasible or not desirable.

In a letter dated February 13, 2018, Chiesi USA, Inc. notified FDA that CARDENE (nicardipine hydrochloride) injection, 25 mg/10 mL, was being discontinued, and FDA moved the drug product to the ''Discontinued Drug Product List'' section of the Orange Book.

Baxter Healthcare Corporation submitted a citizen petition on May 6, 2019 (Docket No. FDA–2019–P–1525), under 21 CFR 10.30, requesting that the Agency determine whether CARDENE (nicardipine hydrochloride) injection, 25 mg/10 mL, 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 CARDENE (nicardipine hydrochloride) injection, 25 mg/10 mL, was not withdrawn for reasons of safety or effectiveness. The petitioner has identified no data or other information suggesting that this drug product was withdrawn for reasons of safety or effectiveness. We have carefully reviewed our files for records concerning the withdrawal of CARDENE (nicardipine hydrochloride) injection, 25 mg/10 mL, from sale. We have also independently evaluated relevant literature and data for possible postmarketing adverse events. We have found no information that would