4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2019-N-3723]

Watson Laboratories, Inc.; Proposal to Withdraw Approval of an Abbreviated New Drug Application for Oxycodone Hydrochloride and Ibuprofen Tablets; Opportunity for a Hearing

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration's (FDA or Agency) Center for Drug Evaluation and Research (CDER) is proposing to withdraw approval of an abbreviated new drug application (ANDA) for oxycodone hydrochloride and ibuprofen tablets and is announcing an opportunity for the holder of the ANDA to request a hearing on this proposal. The basis for the proposal is that the holder of the ANDA has repeatedly failed to submit the required data to support a finding of bioequivalence for this ANDA.

DATES: Watson Laboratories, Inc. may submit a request for a hearing by [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. Submit all data, information, and analyses upon which the request for a hearing relies by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. Submit electronic or written comments by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

ADDRESSES: The request for a hearing may be submitted by Watson Laboratories, Inc. by either of the following methods:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: https://www.regulations.gov. Follow the instructions for submitting comments to submit your request for a hearing. Comments submitted electronically to https://www.regulations.gov, including any attachments to the request for a hearing, will be posted to the docket unchanged.

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.
- Because your request for a hearing will be made public, you are solely responsible for ensuring that your request 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. The request for a hearing must include the Docket No. FDA-2019-N-3723 for "Watson Laboratories, Inc.; Proposal to Withdraw Approval of an Abbreviated New Drug Application for Oxycodone Hydrochloride and Ibuprofen Tablets; Opportunity for a Hearing." The request for a hearing will be placed in the docket and publicly viewable at https://www.regulations.gov or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday.

Watson Laboratories, Inc., may submit all data and analyses upon which the request for a hearing relies in the same manner as the request for a hearing except as follows:

- Confidential Submissions--To submit any data and analyses with confidential information that you do not wish to be made publicly available, submit your data and analyses only as a written/paper submission. You should submit two copies total of all data and analyses. 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 any decisions on this matter. 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 or available at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday. Submit both copies to the Dockets Management Staff. Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law.

Comments Submitted by Other Interested Parties: For all comments submitted by other interested parties 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): 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-2019-N-3723 for "Watson Laboratories, Inc.; Proposal to Withdraw Approval of an Abbreviated New Drug Application for Oxycodone Hydrochloride and Ibuprofen Tablets; Opportunity for a Hearing." 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: Maryll W. Toufanian, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 75, Rm. 1720, Silver Spring, MD 20993-0002, 240-402-7944.

SUPPLEMENTARY INFORMATION:

I. Background

A. Approval of ANDA 078394 for Oxycodone Hydrochloride and Ibuprofen Tablets

FDA's Office of Generic Drugs (OGD) approved ANDA 078394, held by Watson Laboratories, Inc. (Watson),[1] for a generic version of oxycodone hydrochloride and ibuprofen tablets, 5 milligrams (mg)/400 mg, under the requirements of section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(j)) and FDA's implementing regulations. OGD approved ANDA 078394 on November 26, 2007.

In seeking approval of its ANDA 078394, Watson relied on the reference listed drug (RLD) product, COMBUNOX (oxycodone hydrochloride and ibuprofen) tablets, 5 mg/400 mg, approved under new drug application (NDA) 021378 (see § 314.94 (21 CFR 314.94)). As an applicant under section 505(j) of the FD&C Act, Watson was not required to conduct clinical studies to demonstrate the safety and effectiveness of its drug product. Rather, in addition to meeting the other requirements for ANDA approval enumerated in section 505(j) of the FD&C Act and applicable FDA regulations, Watson was required to demonstrate that its product was bioequivalent to the RLD, COMBUNOX (see section 505(j)(2)(A)(iv) and (j)(4)(F) of the FD&C Act; § 314.94(a)(7); 21 CFR 314.127(a)(6)(i)). The information that Watson submitted to show that its ANDA 078394 was bioequivalent to the RLD included bioequivalence studies, with the bioanalytical analysis conducted by Cetero Research at the Houston, TX site during 2006.

[1] In correspondence dated February 23, 2017, Watson notified FDA that Watson is an indirect, wholly-owned subsidiary of Teva Pharmaceuticals USA, Inc.

B. Investigations Regarding Bioequivalence Studies Conducted by Cetero Research

In May 2010 and December 2010, FDA conducted comprehensive inspections of bioequivalence studies conducted by Cetero Research at the Houston, TX site. The inspections were part of FDA's Bioresearch Monitoring Program, which includes inspections to evaluate the conduct of research, to confirm that data intended for submission to FDA are reliable as a basis for FDA approval and regulatory decisions, and to verify compliance with the bioavailability and bioequivalence requirements in section 505 of the FD&C and Act 21 CFR part 320. The findings of these inspections of bioequivalence studies conducted by Cetero Research raised significant concerns about the validity of the reported results of analytical studies conducted between April 1, 2005, and June 15, 2010, in support of drug applications (see Ref. 1). The inspections and a third-party audit identified significant instances of misconduct and violations of Federal regulations, including document falsification and sample manipulation. The pattern of misconduct was serious enough to raise concerns about the integrity of the data that Cetero Research generated during the 5-year time frame between 2005 and 2010. On July 26, 2011, FDA notified pharmaceutical companies that bioanalytical studies conducted at Cetero Research between April 1, 2005, and June 15, 2010, in support of marketing applications may need to be repeated or confirmed (see Ref. 2).

On August 9, 2011, FDA issued a letter to Watson regarding ANDA 078394 because this drug product application was supported by bioequivalence studies with the bioanalytical analysis conducted by Cetero Research at the Houston, TX site between April 1, 2005, and June 15, 2010 (see Ref. 3). As FDA noted in its August 9, 2011, correspondence, inspection findings regarding Cetero Research's bioequivalence studies raised significant concerns about the validity of the reported results of the analytical studies conducted between April 2005 and June 2010 in support of drug applications, and as such, steps needed to be taken to demonstrate the bioequivalence of

Watson's drug product approved under ANDA 078394. FDA informed Watson that ANDA 078394 needed to be supplemented by conducting new bioequivalence studies or re-assaying the samples from the original bioequivalence study. FDA recommended to Watson that the results of the requested bioequivalence studies, or re-assays, be submitted to ANDA 078394 within 6 months of the date of the August 9, 2011, letter. As noted in the August 9, 2011 correspondence, if the necessary information was not submitted within the recommended timeframe, FDA would consider downgrading the therapeutic equivalence evaluation of approved applications in the Agency's "Approved Drug Products With Therapeutic Equivalence Evaluations" (Orange Book) from an "AB" to a "BX" rating because of new information raising a significant question as to bioequivalence. FDA did not receive a response from Watson to this August 9, 2011, correspondence.

On August 19, 2016, FDA issued another letter to Watson requesting that, within 30 calendar days, Watson either: (1) supplement ANDA 078394 with the requested bioequivalence data or (2) voluntarily seek withdrawal of ANDA 078394 under § 314.150 (21 CFR 314.150(d)) and waive the opportunity for a hearing under § 314.150(a) (see Ref. 4). As noted in the August 19, 2016, correspondence, if Watson did not submit new bioequivalence data within 30 calendar days, if the new data did not support a finding of bioequivalence, or if Watson did not agree to voluntarily seek withdrawal of ANDA 078394 within 30 calendar days, FDA would commence downgrading the therapeutic equivalence evaluation of approved applications in the Orange Book from an "AB" to a "BX" rating. FDA also stated that if the aforementioned conditions were not met, FDA would consider all other appropriate regulatory action, including commencing steps to withdraw approval of ANDA 078394 under section 505(e) of the FD&C

Act and § 314.150. FDA did not receive a response from Watson to this August 19, 2016, correspondence.

On April 24, 2017, FDA issued Watson a third letter notifying them that FDA had changed the therapeutic equivalence evaluation of ANDA 078394 in the Orange Book from an "AB" to a "BX" rating (see Ref. 5). Further, in the April 24, 2017, correspondence, FDA requested that Watson voluntarily seek withdrawal for ANDA 078394 under § 314.150(d) and waive the opportunity for a hearing under § 314.150(a). FDA requested that Watson provide such a withdrawal request or a letter stating that Watson would not voluntarily seek withdrawal of the approval of ANDA 078394 no later than May 24, 2017. As noted in the April 24, 2017, correspondence, FDA advised Watson that if Watson did not agree to voluntarily seek withdrawal of the approval of ANDA 078394 under § 314.150(d), FDA would plan to commence steps to withdraw approval of this ANDA under 505(e) of the FD&C Act and § 314.150. FDA did not receive a response from Watson to this April 24, 2017, correspondence.

In the June 2017 Cumulative Supplement to the 37th Edition of the Orange Book, ANDA 078394 was moved to the Discontinued Section of the Orange Book based on notification by Watson to the Agency that Watson was no longer marketing its drug product approved under ANDA 078394. Because drug products that are in the Discontinued Section of the Orange Book do not have therapeutic equivalence codes and because ANDA 078394 is currently in the Discontinued Section of the Orange Book, ANDA 078394 is not currently assigned a therapeutic equivalence code.

II. Conclusions and Proposed Action

An NDA applicant must submit "full reports of investigations" to show that the drug for which the applicant is seeking approval is safe and effective. In other words, NDAs must meet

the safety and substantial evidence of effectiveness standard (see section 505(b)(1) and (2), (c), and (d) of the FD&C Act). An NDA applicant can meet the standard by conducting its own clinical studies (stand-alone application) or relying, in part, on the Agency's previous finding of safety and/or effectiveness or literature (a 505(b)(2) application). An ANDA applicant does not submit independent clinical studies to demonstrate safety and effectiveness. Rather, an ANDA applicant relies on the Agency's previous finding of safety and effectiveness for its RLD and is required to meet other requirements, such as demonstrating bioequivalence to the RLD to support approval. In the absence of information showing bioequivalence between the generic drug at issue and the RLD, there is no basis for concluding that the Agency's finding of safety and efficacy supporting approval of the RLD can be used as a basis to support approval of the generic drug. Section 505(e) of the FD&C Act provides FDA the authority to withdraw approval of an ANDA in these circumstances. While the Watson application was approved on the basis of a bioequivalence study, new information about the facility that conducted the bioanalytical analysis for that study leads CDER to conclude that the results of that study are not credible.

Therefore, based on all available data and information, notice is given to Watson Laboratories, Inc. and to all other interested persons that the Director of CDER proposes to issue an order, under section 505(e) of the FD&C Act and § 314.150, withdrawing approval of ANDA 078394 and all amendments and supplements to it on the grounds that Watson has failed to submit the required bioequivalence data necessary to demonstrate the bioequivalence of its drug product.

III. Hearing Procedures

In accordance with section 505(e) of the FD&C Act, Watson Laboratories, Inc. is hereby provided an opportunity to request a hearing to show why approval of ANDA 078394 should not

be withdrawn and an opportunity to raise, for administrative determination, all issues relating to the legal status of the drug product covered by this application.

An applicant who decides to seek a hearing must file the following: (1) a written notice of participation and request for a hearing (see DATES and ADDRESSES) and (2) the data, information, and analyses relied on to demonstrate that there is a genuine and substantial issue of fact that requires a hearing (see DATES and ADDRESSES). Any other interested person may also submit comments on this notice. The procedures and requirements governing this notice of opportunity for a hearing, notice of participation and request for a hearing, the information and analyses to justify a hearing, other comments, and a grant or denial of a hearing are contained in § 314.200 (21 CFR 314.200) and in 21 CFR part 12.

The failure of an applicant to file a timely written notice of participation and request for a hearing, as required by § 314.200, constitutes an election by that applicant not to avail itself of the opportunity for a hearing concerning CDER's proposal to withdraw approval of the application and constitutes a waiver of any contentions concerning the legal status of the drug product. FDA will then withdraw approval of the application, and the drug product may not thereafter be lawfully introduced or delivered for introduction into interstate commerce. Any new drug product introduced or delivered for introduction into interstate commerce without an approved application is subject to regulatory action at any time.

A request for a hearing may not rest upon mere allegations or denials but must present specific facts showing that there is a genuine and substantial issue of fact that requires a hearing. If a request for a hearing is not complete or is not supported, the Commissioner of Food and Drugs will enter summary judgment against the person who requests the hearing, making findings and conclusions, and denying a hearing.

Paper submissions under this notice of opportunity for a hearing must be filed in two copies. Except for data and information prohibited from public disclosure under 21 U.S.C. 331(j) or 18 U.S.C. 1905, the submissions may be seen at the Dockets Management Staff (see ADDRESSES) between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at https://www.regulations.gov.

This notice is issued under section 505(e) of the FD&C Act and under authority delegated to the Director of CDER by the Commissioner of Food and Drugs.

IV. References

The following references are on display at the Dockets Management Staff (see ADDRESSES) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they are also available electronically at https://www.regulations.gov. FDA has verified the website address, as of the date this document publishes in the *Federal Register*, but websites are subject to change over time.

1. Letter from Leslie Ball, FDA, to Roger Hayes, Cetero Research, July 26, 2011.

2. FDA, "Notification to Pharmaceutical Companies: Acceptance of third-party data integrity audit for Cetero studies conducted from March 1, 2008, to August 31, 2009" (https://wayback.archive-it.org/7993/20170113203457/http:/www.fda.gov/Drugs/DrugSafety/ucm265559.htm), accessed September 10, 2019.

3. Letter from Keith Webber, FDA, to Watson Laboratories, Inc., August 9, 2011.

4. Letter from Carol A. Holquist, FDA, to Watson Laboratories, Inc., August 19, 2016.

5. Letter from Carol A. Holquist, FDA, to Watson Laboratories, Inc., April 24, 2017.

Dated: October 21, 2019.

Janet Woodcock,

Director,

Center for Drug Evaluation and Research.

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