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October 19, 2016

Via ECF

Ms. Patricia S. Connor
Clerk, United States Court of Appeals
for the Fourth Circuit
Lewis F. Powell, Jr. United States
Courthouse Annex
1100 East Main Street, Suite 501
Richmond, VA 23219-3517

RE: *Mallinckrodt Inc. v. U.S. Food and Drug Admin., et al.*,
4th Cir. No. 15-1933, scheduled for oral argument October 26, 2016.

Dear Ms. Connor:

Appellees respectfully file the attached Suggestion of Mootness to inform the Court of the FDA's Notice of Opportunity for Hearing (NOOH) published in the Federal Register yesterday, October 18, 2016, which appears to render moot the above-captioned appeal. The NOOH is also attached for the Court's reference. Counsel for appellant Mallinckrodt has informed us that Mallinckrodt does not believe that the appeal is moot and intends to file a response to the Suggestion of Mootness prior to oral argument.

Sincerely,

/s/ Stephanie R. Marcus

Stephanie R. Marcus
Attorney, Civil Division, Appellate Staff

cc: Counsel of record (via ECF)

IN THE UNITED STATES COURT OF APPEALS
FOR THE FOURTH CIRCUIT

MALLINCKRODT INC.,)	
)	
Plaintiff-Appellant)	
)	
v.)	No. 15-1933
)	
UNITED STATES FOOD AND DRUG)	
ADMINISTRATION AND UNITED STATES)	
OF AMERICA,)	
)	
Defendants-Appellees)	
_____)	

APPELLEES' SUGGESTION OF MOOTNESS

Defendants-appellees the United States Food and Drug Administration (FDA) and the United States are filing this suggestion of mootness to inform the Court of recent developments that appear to render moot the above-captioned appeal, which is scheduled for oral argument on October 26, 2016. We have contacted counsel for appellant Mallinckrodt Inc., and he informed us that Mallinckrodt does not believe that the appeal is moot and intends to file a response to the suggestion of mootness prior to oral argument.

A. On December 28, 2012, FDA approved Mallinckrodt's Abbreviated New Drug Application (ANDA) for its generic version of the reference listed drug Concerta, methylphenidate hydrochloride extended release (ER) tablets, for treatment of

attention-deficit hyperactivity disorder. Compl. ¶¶17, 20, JA 13; op. 7, JA 213. At the time FDA approved the ANDA, it gave Mallinckrodt's drug product a therapeutic equivalence (TE) rating of "AB" in the Orange Book. Compl. ¶21, JA 14; op. 7-8, JA 213-14. An "AB" rating means that "actual or potential bioequivalence problems have been resolved[.]" Orange Book Preface xiii, JA 36.

Soon after the approval, however, FDA began receiving adverse event reports and complaints relating to Mallinckrodt's product's lack of effect. See DE 8-3, JA 110. By September 2013, there were a sufficient number of adverse event reports that the FDA's Office of Generic Drugs/Division of Clinical Review Safety Team (Safety Team) began an investigation. DE 8-4, JA 117.

In response, FDA formed a Tracked Safety Issue Committee to conduct a multi-disciplinary review of plaintiff's drug product. DE 8-3, JA 110. Based on that review, FDA informed Mallinckrodt in November 2014 that it had reason to believe that the company's generic drug product may not be therapeutically equivalent to Concerta, and that the TE rating in the Orange Book for Mallinckrodt's product thus would be updated from "AB" to "BX." See Compl. ¶26, JA 15; op. 8, JA 214; JA 127. A "BX"

rating in the Orange Book means that "data that have been reviewed by the Agency are insufficient to determine therapeutic equivalence." Orange Book Preface xx, JA 43. On November 13, 2014, FDA updated the TE rating for Mallinckrodt's drug product to BX. Compl. ¶29, JA 16. The agency made clear that drugs with BX ratings remain approved and may still be lawfully marketed and that it was continuing its evaluation of the therapeutic equivalence of Mallinckrodt's product to Concerta. See JA 109-112.

B. FDA has now completed its evaluation of the Mallinckrodt product. Yesterday, October 18, 2016, FDA published a Notice of Opportunity for Hearing (NOOH) in the Federal Register (attached). The NOOH provides public notice that the agency proposes to withdraw approval of Mallinckrodt's ANDA for generic methylphenidate hydrochloride ER tablets. FDA proposed the withdrawal on the grounds that "on the basis of new information, evaluated together with the evidence available when the application was approved, there is a lack of substantial evidence that the drug will have the effect it is represented to have under the conditions of use prescribed, recommended, or suggested in its labeling." 81 Fed. Reg. 71737, 71740 (Oct. 18, 2016); see 21 U.S.C. § 355(e)(3). The notice explained that

Mallinckrodt could request an administrative hearing to show why FDA should not withdraw approval of its ANDA and "to raise, for administrative determination, all issues relating to the legal status of the drug product covered by this application." 81 Fed. Reg. at 71740.

C. At the conclusion of any administrative hearing, if FDA determines that there is "a lack of substantial evidence that the drug will have the effect it purports or is represented to have," it is required to withdraw approval of the ANDA. 21 U.S.C. § 355(e)(3). If, in contrast, FDA determines after the hearing that approval of Mallinckrodt's product should not be withdrawn because any bioequivalence problems have been resolved, it will not withdraw approval of the ANDA, and the Orange Book TE rating would be changed from "BX" back to "AB". In either case, Mallinckrodt's product will cease to have a "BX" TE rating.

D. The present appeal involves a challenge to FDA's November 2014 change in the Orange Book TE rating for Mallinckrodt's drug product. That appeal has now been overtaken by events. We respectfully suggest that FDA's notice moots the appeal.

A case becomes moot "when the issues presented are no longer 'live' or the parties lack a legally cognizable interest in the outcome." *Mellen v. Bunting*, 327 F.3d 355, 363 (4th Cir. 2003) (internal quotations omitted). Here, there is no longer an ongoing case or controversy regarding the TE 2014 rating change. Even if Mallinckrodt were to ultimately prevail in this case, the court could not award Mallinckrodt any meaningful relief. Equitable relief pertaining to the 2014 TE rating update would not (and could not) stop FDA from assigning Mallinckrodt's generic drug product a BX rating based on an augmented administrative record that includes FDA's evaluation of Mallinckrodt's drug product after the November 2014 TE rating change.

Where, as here, FDA initiates withdrawal proceedings for an ANDA product because of lack of therapeutic equivalence to the reference listed drug, the agency generally would change the product's rating to BX in the Orange Book prior to or at the time of issuance of the NOOH. See Orange Book Preface at xxiii, JA 46 ("The publication in the *Federal Register* of a proposal to withdraw approval of a drug product will ordinarily result in a change in a product's code from AB to BX if this action has not already been taken."). Indeed, even if this Court were to

reverse the district court's judgment on subject matter jurisdiction and were to invalidate the 2014 TE rating change to BX as arbitrary and capricious under the Administrative Procedure Act, on remand, FDA has authority to - and would - again change the rating to BX based on the current administrative record, which has been significantly augmented with new information, evaluations and analysis post-November 2014. See 81 Fed. Reg. at 71739-40.

Nor would an injunction or declaration invalidating the 2014 TE rating change preclude FDA from withdrawing Mallinckrodt's ANDA based on the augmented administrative record underlying its October 2016 notice, which may continue to be supplemented during any future administrative proceedings. The current administrative record includes new information, evaluations and analysis that were not in the record at the time of the 2014 TE rating change. The administrative record as supplemented post-November 2014 is not before the Court in this case. Accordingly, any relief afforded Mallinckrodt in the present appeal could not bar FDA from moving forward with the process under the Federal Food, Drug, and Cosmetic Act for withdrawal of an ANDA.

Mallinckrodt thus no longer has a legally cognizable interest in the outcome of its challenge to the 2014 TE rating change. This does not mean that judicial review of FDA's actions is unavailable, however. To the contrary, if, at the conclusion of the administrative process, FDA withdraws approval of Mallinckrodt's ANDA, Mallinckrodt has the statutory right to seek review in the court of appeals. 21 U.S.C. § 355(h). An appeal from an order withdrawing approval of Mallinckrodt's ANDA would challenge a final agency action and would present a live controversy. But that is not this appeal.

The October 2016 notice therefore appears to moot the present appeal and may obviate the need for oral argument.

Respectfully submitted,

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The Department specifically requests comments on: (a) Whether the proposed collection of information is necessary for the proper performance of the functions of the agency, including whether the information shall have practical utility; (b) the accuracy of the agency's estimate of the burden of the proposed collection of information; (c) the quality, utility, and clarity of the information to be collected; and (d) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques or other forms of information technology. Consideration will be given to comments and suggestions submitted within 60 days of this publication.

Robert Sargis,

Reports Clearance Officer.

[FR Doc. 2016-25120 Filed 10-17-16; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2016-N-3118]

Mallinckrodt Pharmaceuticals; Proposal To Withdraw Approval of an Abbreviated New Drug Application for Extended-Release Methylphenidate 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 methylphenidate hydrochloride (HCl) extended-release (ER) tablets and is announcing an opportunity for the holder of the ANDA to request a hearing on this proposal.

DATES: Mallinckrodt Pharmaceuticals may submit a request for a hearing by November 17, 2016. Submit all data, information, and analyses upon which the request for a hearing relies by December 19, 2016. Submit written or electronic comments by December 19, 2016.

ADDRESSES: The request for a hearing may be submitted by Mallinckrodt Pharmaceuticals by either of the following methods:

Electronic Submissions

Submit electronic comments in the following way:

- **Federal eRulemaking Portal:** <http://www.regulations.gov>. Follow the instructions for submitting comments to submit your request for a hearing. Comments submitted electronically to <http://www.regulations.gov>, including any attachments to the request for 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):** Division of Dockets Management (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 may not wish to be publicly posted, such as confidential business information, *e.g.*, a manufacturing process. The request for a hearing must include the Docket No. FDA-2016-N-3118 for "Mallinckrodt Pharmaceuticals; Proposal to Withdraw Approval of an Abbreviated New Drug Application for Extended-Release Methylphenidate Tablets; Opportunity for a Hearing." The request for a hearing will be placed in the docket and 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.

Mallinckrodt Pharmaceuticals may submit all data and analysis 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 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 <http://www.regulations.gov> or available at the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday. Submit both copies to the Division of Dockets Management. 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:** <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-2016-N-3118 for "Mallinckrodt Pharmaceuticals; Proposal to Withdraw Approval of an Abbreviated New Drug Application for Extended-Release Methylphenidate Tablets; Opportunity for a Hearing." 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.

FOR FURTHER INFORMATION CONTACT: Maryll W. Toufanian, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 75, Rm. 1716, Silver Spring, MD 20993–0002, 240–402–7944.

SUPPLEMENTARY INFORMATION:

I. Background

A. Approval of ANDAs Referencing CONCERTA

CONCERTA (methylphenidate HCl) ER tablet is the subject of new drug application (NDA) 021121, held by Janssen Pharmaceuticals, Inc., and was approved on August 1, 2000. CONCERTA is a central nervous system

stimulant intended for the treatment of attention deficit hyperactivity disorder in children 6 years of age and older, adolescents, and adults up to the age of 65. CONCERTA is a multiphasic modified-release product that is formulated to release a bolus of methylphenidate, resulting in an initial rapid rise in plasma concentration comparable to the effect of an immediate-release (IR) methylphenidate formulation, followed by sustained delivery later in the day, thereby allowing for once daily dosing. The relative bioavailability of CONCERTA in adults is comparable to IR methylphenidate administered three times daily, but the CONCERTA formulation minimizes the fluctuations between peak and trough concentrations associated with IR methylphenidate administered three times daily. CONCERTA is approved for the following strengths: 18 milligrams (mg), 27 mg, 36 mg, and 54 mg. CONCERTA was approved based on, among other things, safety studies and adequate and well-controlled clinical efficacy studies showing that the product is safe for its intended uses and has the effects claimed for it.

FDA’s Office of Generic Drugs (OGD) approved ANDA 202608, held by Mallinckrodt Pharmaceuticals (Mallinckrodt), for a generic version of CONCERTA under the requirements of section 505(j) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 355(j)) and FDA’s implementing regulations. OGD approved ANDA 202608 on December 28, 2012, for the 27-mg, 36-mg, and 54-mg strengths.

At the time of approval, FDA determined that the ANDA included data sufficient to demonstrate the bioequivalence of the Mallinckrodt product to CONCERTA. The bioequivalence (BE) testing and data submitted in the ANDA conformed to recommendations provided in a draft guidance for industry on “Methylphenidate hydrochloride.” The draft guidance was issued on September 14, 2012 (77 FR 56851), and provided information and recommendations for establishing bioequivalence to CONCERTA that reflected FDA’s understanding, at that time, of how to evaluate the pharmacokinetic (PK) properties of CONCERTA to support a demonstration of bioequivalence. The demonstration of bioequivalence was necessary to the approval of Mallinckrodt’s product. Unlike CONCERTA, Mallinckrodt was not required to submit clinical studies to demonstrate the safety and effectiveness of its product. Instead, Mallinckrodt’s ANDA was approved based on a finding

that the product was bioequivalent to CONCERTA and met the other requirements for ANDA approval in section 505(j) of the FD&C Act.

B. Concerns About Insufficient Therapeutic Effect

1. ANDA 202608

Mallinckrodt began marketing its generic version of CONCERTA in March 2013. OGD routinely monitors all newly approved ANDA products for safety and efficacy concerns as they penetrate the marketplace, including the monitoring of adverse events reported to the Agency. In May 2013, the FDA Adverse Event Reporting System (FAERS) began receiving reports that described insufficient therapeutic effect of the Mallinckrodt product, particularly reports describing insufficient effect later in the day.¹ These reports indicated potential therapeutic inequivalence of the Mallinckrodt product as compared to CONCERTA. In light of the reports received, CDER began an investigation of the Mallinckrodt product.²

2. CDER’s Investigations

a. Tracked safety issue (TSI). CDER began its investigation of the Mallinckrodt product with a reevaluation of the data and information submitted in the application to demonstrate bioequivalence; an assessment of FAERS data; and a comparative analysis of the design, composition, dissolution, and active pharmaceutical ingredient (API) degradation of the generic product as compared to CONCERTA. The findings of these investigations led to the initiation of a TSI. In general, when CDER staff suspect that a potential safety issue could be significant, a TSI is opened and an interdisciplinary team assesses the safety issue, reevaluates the risk-benefit profile of the drug, and determines the need for further action. CDER considers postmarketing safety issues to be significant for tracking purposes if these issues have the potential to lead to, among other things, withdrawal of FDA approval of a drug application.

The initial meeting of the TSI Committee occurred in December 2013.

¹ In addition to reports submitted to FAERS, FDA received complaints related to therapeutic failure from multiple other sources, including FDA’s Detroit District Office and a director of anesthesia support at a children’s hospital.

² FDA investigated ANDA 202608 concurrently with ANDA 091695, which is another generic product referencing CONCERTA, held by Kremers Urban Pharmaceuticals Inc. Elsewhere in this issue of the **Federal Register**, FDA is proposing to withdraw approval of ANDA 091695.

The TSI Committee was composed of CDER physicians, pharmacists, and chemists, as well as other CDER scientists and experts, who carefully reviewed all of the data and information related to the Mallinckrodt product. Key information reviewed and discussed by the TSI Committee is summarized as follows:

- *Adverse event reports.* An analysis was conducted of FAERS reports, along with additional data regarding therapeutic failure provided by Mallinckrodt and Janssen (CONCERTA's NDA holder), to assess, among other things, the reporting rate for therapeutic failure for the Mallinckrodt product as compared to the reporting rate for therapeutic failure for the authorized generic version of CONCERTA marketed by Actavis plc.³ The reporting rate for therapeutic failure was found to be 88 per 100,000 person-years of exposure for the Mallinckrodt product and 7.0 per 100,000 person-years of exposure for the authorized generic drug product.

- *Product composition.* The Mallinckrodt product and CONCERTA were tested in FDA laboratories to evaluate differences in drug design, composition, stability, and dissolution. The testing identified concerns with API degradation and in vivo dissolution, which could result in differences in drug release. These differences could, in turn, result in differences in therapeutic effect of the generic product compared to CONCERTA.

- *BE data.* A review and reanalysis were conducted of the data that were submitted in the ANDA to establish bioequivalence to CONCERTA. In particular, an outlier analysis was

performed on the BE data to evaluate the difference in product absorption between the Mallinckrodt product and CONCERTA across various PK sampling time points. The analysis showed that the greatest difference in product absorption between the Mallinckrodt product and CONCERTA occurred at 10 hours post-dosing under fasting conditions.

- *Modeling of potential clinical impact.* In light of the close relationship between the PK profile and clinical effect of methylphenidate products (Ref. 1), modeling was done based on the BE data submitted in the ANDA to predict the potential clinical significance of the difference in PK profile, *i.e.*, product absorption, of the Mallinckrodt product compared to CONCERTA. The modeling suggested some potential clinical inequivalence between the generic product and CONCERTA after 6 hours post-dosing. The greatest mean percent reduction in clinical efficacy for the Mallinckrodt product is predicted to be approximately 21 percent at 10 hours post-dosing under fasting condition.

The TSI was concluded in June 2014. Based on the information considered, the TSI Committee determined that the Mallinckrodt product may deliver methylphenidate into the body at a slower rate than CONCERTA during the time period of 7 to 12 hours post-dosing, and therefore, the product may not be bioequivalent or therapeutically equivalent to CONCERTA. Following the TSI Committee's investigation, CDER concluded that the therapeutic equivalence (TE) rating for the Mallinckrodt product in FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (commonly referred to as the "Orange Book") should be changed from AB to BX to indicate that the data are insufficient to determine that the Mallinckrodt product is therapeutically equivalent to CONCERTA.⁴

⁴ In the Orange Book, FDA "classifies as therapeutically equivalent those products that meet the following general criteria: (1) [T]hey are approved as safe and effective; (2) they are pharmaceutical equivalents in that they (a) contain identical amounts of the same active drug ingredient in the same dosage form and route of administration, and (b) meet compendial or other applicable standards of strength, quality, purity, and identity; (3) they are bioequivalent in that (a) they do not present a known or potential bioequivalence problem, and they meet an acceptable in vitro standard, or (b) if they do present such a known or potential problem, they are shown to meet an appropriate bioequivalence standard; (4) they are adequately labeled; (5) they are manufactured in compliance with Current Good Manufacturing Practice regulations" (Orange Book Preface at vii, available at <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/UCM071436.pdf>). (FDA has verified the Web site addresses, as of the date this document publishes

On November 6, 2014 (79 FR 65978), CDER issued a revised draft guidance for industry on "Bioequivalence Recommendations for CONCERTA (Methylphenidate Hydrochloride) Extended-Release Tablets" (revised draft BE guidance) (Ref. 2), with recommendations for establishing bioequivalence to CONCERTA that reflect CDER's refined understanding of the relationship between the PK profile of CONCERTA and its therapeutic effect. The revised draft BE guidance is available on FDA's Web site and will be placed in Docket No. FDA-2016-N-3118.

On November 12, 2014, representatives from OGD and other CDER offices notified Mallinckrodt by telephone of CDER's concerns regarding its generic product. OGD explained that the TE rating for the product would be changed from AB to BX immediately. OGD requested that Mallinckrodt: (1) Voluntarily withdraw its product from the market under 21 CFR 314.150(d) and request that FDA withdraw approval of the ANDA or (2) confirm bioequivalence of its product within 6 months, consistent with the recommendations in the revised draft BE guidance issued on November 6, 2014. Mallinckrodt declined to voluntarily withdraw its product from the market, and it has not submitted data or information that confirms bioequivalence of its product to CONCERTA.

b. *Post-TSI investigation.* After communicating CDER's concerns to Mallinckrodt about its methylphenidate product and changing the TE rating for the product to BX, CDER continued to evaluate data and information related to the bioequivalence of Mallinckrodt's product to CONCERTA. CDER reanalyzed the BE data originally submitted in Mallinckrodt's ANDA in accordance with the recommendations provided in the November 6, 2014, revised draft BE guidance. The reanalysis showed that the 54-mg Mallinckrodt product on which the in vivo BE testing was conducted does not provide the same extent of methylphenidate exposure as CONCERTA during the 7- to 12-hour time period after administration. Specifically, the 90 percent confidence interval (CI) of the geometric mean ratio of the test product (Mallinckrodt's) to reference product (CONCERTA) for AUC_{7-12} ⁵ (at 64.41 percent to 72.49

in the Federal Register, but Web sites are subject to change over time.)).

⁵ The area under the plasma concentration-time curve (AUC) is used to evaluate the "extent" of absorption of a drug. See section 505(j)(7)(B) of the FD&C Act. AUC_{7-12} captures the extent of

³ Authorized generic drug is defined in section 505(t) of the FD&C Act and in § 314.3(b) (21 CFR 314.3(b)) (Authorized generic drug means a listed drug, as defined in § 314.3(b), that has been approved under section 505(c) of the FD&C Act and is marketed, sold, or distributed directly or indirectly to retail class of trade with labeling, packaging (other than repackaging as the listed drug in blister packs, unit doses, or similar packaging for use in institutions), product code, labeler code, trade name, or trademark that differs from that of the listed drug.). A listed drug is a new drug product that has an effective approval under section 505(c) of the FD&C Act for safety and effectiveness, or under section 505(j), that has not been withdrawn or suspended under section 505(e)(1) through (e)(5) or (j)(5) of the FD&C Act, and that has not been withdrawn from sale for what FDA determines are reasons of safety or effectiveness (§ 314.3(b)). Listed drugs are identified as drugs with an effective approval in FDA's current edition of "Approved Drug Products With Therapeutic Equivalence Evaluations" (commonly referred to as the "Orange Book") (*Id.*). A list of currently available authorized generics is available at <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm126391.htm>. (FDA has verified the Web site addresses, as of the date this document publishes in the Federal Register, but Web sites are subject to change over time.)

percent) falls outside of the 80 percent to 125 percent BE acceptance criteria (Ref. 4). The lower level of methylphenidate exposure compared to CONCERTA 7 to 12 hours after administration is consistent with the reports received describing lack of therapeutic effect later in the day.

In addition to the reanalysis described above, FDA performed further clinical trial simulations based on the BE data originally submitted in the ANDA to assess the potential clinical significance of the difference in PK profile, *i.e.*, methylphenidate absorption, of the Mallinckrodt product compared to CONCERTA (Ref. 5). The simulation suggested some potential difference in effect between Mallinckrodt's product and CONCERTA after 6 hours post-dosing. Consistent with the evaluation presented during the TSI, the greatest mean percent reduction in efficacy was predicted to be 21.17 percent at 10 hours post-dosing, with individual changes ranging from a 44.09 percent decrease and a 9.04 percent increase in efficacy compared to CONCERTA.

Along with a reanalysis of data submitted in the original ANDA, in March 2015, CDER sponsored its own study to evaluate bioequivalence of the 27-mg Mallinckrodt product as compared to CONCERTA. The CDER-sponsored study was a single-dose, 4-treatment, fully replicated, crossover, randomized BE study (consistent with the study design recommended in the revised draft BE guidance) in healthy subjects under fasting conditions. The study compared: (1) The test product—Mallinckrodt's methylphenidate HCl ER tablets, 27 mg; and (2) the reference product—CONCERTA ER tablets, 27 mg. A total of 28 subjects were enrolled in the study, and 24 subjects completed all 4 periods. Plasma samples were collected for up to 24 hours following each treatment. The mean methylphenidate plasma concentration profiles for both the test and reference products exhibited PK properties consistent with those observed in the 54-mg fasting BE study submitted by Mallinckrodt in its ANDA. In particular, decreased plasma concentrations were observed with administration of the Mallinckrodt product as compared to CONCERTA after 6 to 7 hours. The 90 percent CI of the geometric mean test-to-reference ratio for AUC_{7-12} was below the 80 percent to 125 percent BE acceptance range (at 60.99 percent to 70.50 percent). All other metrics were

absorption from 7 to 12 hours post-dosing. See, *e.g.*, the draft guidance for industry entitled "Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted under an ANDA" (Ref. 3).

found to be within the BE acceptance range of 80 percent to 125 percent. The observed lower level of methylphenidate exposure compared to CONCERTA 7 to 12 hours after administration is consistent with that observed in the reanalysis of the 54-mg BE study submitted in Mallinckrodt's ANDA.

Finally, FDA analyzed FAERS reports from February 2014 to May 2015. The types and quality of reports received by FDA during that time period were very similar to the reports received before FDA changed the TE rating. The reports continued to contain specific complaints describing the failure of therapeutic effect during the latter part of the day.

The applicant has not submitted data that confirms bioequivalence of its product to CONCERTA. A memorandum describing in detail the information considered following the TSI and explaining CDER's determination will be placed in Docket No. FDA-2016-N-3118 (Ref. 6).

II. Conclusions and Proposed Action

An NDA (or reference listed drug) 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, reference listed drugs 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). A reference listed drug 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 the reference listed drug and is required to meet other requirements such as demonstrating bioequivalence to the reference listed drug to support approval. In the absence of information showing bioequivalence between the generic drug at issue and the reference listed drug, there is no basis for concluding that the Agency's finding of safety and efficacy (or substantial evidence of effectiveness) supporting approval of the reference listed drug likewise supports approval of the generic drug.

Therefore, based on all available data and information, notice is given to Mallinckrodt and to all other interested persons that the Director of CDER proposes to issue an order, under

section 505(e)(3) of the FD&C Act and § 314.150(a)(2)(iii), withdrawing approval of ANDA 202608 and all amendments and supplements to it on the grounds that, on the basis of new information, evaluated together with the evidence available when the application was approved, there is a lack of substantial evidence that the drug will have the effect it is represented to have under the conditions of use prescribed, recommended, or suggested in its labeling.

III. Hearing Procedures

In accordance with section 505(e) of the FD&C Act, the applicant is hereby provided an opportunity to request a hearing to show why approval of ANDA 202608 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 hearing (see **DATES**), 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 to resolve (see **DATES**). 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.

All 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 in the Division of Dockets Management (see **ADDRESSES**) between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at <http://www.regulations.gov>.

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

IV. References

The following references are on display in the Division of Dockets Management (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 <http://www.regulations.gov>. FDA has verified the Web site addresses, as of the date this document publishes in the **Federal Register**, but Web sites are subject to change over time.

- Swanson, J.M., et al., "A Comparison of Once-Daily Extended-Release Methylphenidate Formulations in Children With Attention-Deficit/Hyperactivity Disorder in the Laboratory School (The Comacs Study)," *Pediatrics*, vol. 113, pp. 206–216, 2004.
- FDA, draft guidance for industry, "Bioequivalence Recommendations for CONCERTA (Methylphenidate Hydrochloride) Extended-Release Tablets," November 2014 (available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM320007.pdf>).
- FDA, draft guidance for industry, "Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA," December 2013 (available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM377465>).
- Dighe, S.V. and W.P. Adams. "Bioequivalence: A United States Regulatory Perspective." In Welling, P.G., L.S. Tse, and S.V. Dighe, eds., *Pharmaceutical Bioequivalence*. New York: Marcel Dekker, Inc., pp. 347–380, 1991.
- Kimko, H., et al., "Population Pharmacodynamic Modeling of Various Extended-Release Formulations of Methylphenidate in Children With Attention Deficit Hyperactivity Disorder Via Meta-Analysis," *Journal of Pharmacokinetics and Pharmacodynamics*, vol. 39(2), pp. 161–176, 2012.

6. Memorandum to Janet Woodcock, Director, Center for Drug Evaluation and Research, in Support of Beginning Approval Withdrawal Proceedings for ANDA 202608 (October 1, 2016, Peters).

Dated: October 12, 2016.

Janet Woodcock,

Director, Center for Drug Evaluation and Research.

[FR Doc. 2016–25093 Filed 10–17–16; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2016–N–3120]

Kremers Urban Pharmaceuticals Inc.; Proposal To Withdraw Approval of an Abbreviated New Drug Application for Extended-Release Methylphenidate 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 methylphenidate hydrochloride (HCl) extended-release (ER) tablets and is announcing an opportunity for the holder of the ANDA to request a hearing on this proposal.

DATES: Kremers Urban Pharmaceuticals Inc., may submit a request for a hearing by November 17, 2016. Submit all data, information, and analyses upon which the request for a hearing relies by December 19, 2016. Submit written or electronic comments by December 19, 2016.

ADDRESSES: The request for a hearing may be submitted by Kremers Urban Pharmaceuticals Inc., by either of the following methods:

Electronic Submissions

Submit electronic comments in the following way:

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

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper request for a hearing):** Division of Dockets Management (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 may not wish to be publicly posted, such as confidential business information, *e.g.*, a manufacturing process. The request for a hearing must include the Docket No. FDA–2016–N–3120 for "Kremers Urban Pharmaceuticals Inc.; Proposal to Withdraw Approval of an Abbreviated New Drug Application for Extended-Release Methylphenidate Tablets; Opportunity for a Hearing." The request for a hearing will be placed in the docket and 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.

Kremers Urban Pharmaceutical Inc., may submit all data and analysis 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 analysis. 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 information redacted/blacked out, will be available for public viewing and posted on <http://www.regulations.gov> or available at the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday. Submit both copies to the Division of Dockets Management. 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 you may submit comments as follows:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal:** <http://www.regulations.gov>. Follow the

CERTIFICATE OF SERVICE

I hereby certify that on this 19th day of October, 2016, I electronically filed the foregoing Suggestion of Mootness with the Clerk of the Court for the U.S. Court of Appeals for the Fourth Circuit by using the CM/ECF system. I further certify that on this 19th day of October, 2016, I served the foregoing Suggestion of Mootness on counsel of record for plaintiff-appellant by electronic service via the CM/ECF system.

s/ Stephanie R. Marcus
Stephanie R. Marcus