DEPARTMENT OF HEALTH & HUMAN SERVICES

DEC 11 2014

Food and Drug Administration
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Re: Docket No. FDA-2013-P-0127

Dear Ms. Bedoya-Toro:

This letter responds to your citizen petition dated February 1, 2013 (Petition). The Petition requests that the Food and Drug Administration (FDA or the Agency):

(1) develop and publish an individual bioequivalence recommendation for budesonide extended-release tablets, and

(2) refrain from approving any abbreviated new drug application (ANDA) that identifies Uceris (budesonide) extended-release tablets (Uceris) as the reference listed drug (RLD) unless the generic product is shown to be bioequivalent based on appropriate data from a clinical efficacy endpoint study, comparative pharmacokinetic (PK) testing, in vitro dissolution testing, and pharmacoscintigraphy studies.

FDA has carefully considered the information submitted in your Petition and the comment submitted to the docket. For the reasons set forth below, the Petition is granted in part and denied in part.[1]

I. BACKGROUND

A. Uceris (Budesonide) Extended-Release Tablets

FDA approved new drug application (NDA) 20-3634 for Uceris (budesonide) extended-release tablets, 9 milligrams (mg), on January 14, 2013. Uceris is indicated for the induction of remission in patients with active, mild to moderate ulcerative colitis (UC). UC is an idiopathic, chronic, inflammatory disease of the colon and rectum. Uceris is formulated as a delayed- and extended-release tablet to deliver budesonide directly into the colon and then slowly disperse the budesonide throughout the colon. Specifically, the tablet, coated with an acid-resistant polymer film, breaks down at or above pH 7.0, which is the normal pH in the terminal ileum. The acid-resistant coating allows the tablet to pass through the acidic condition of the stomach without

[1] This response addresses the Petition's requests generally. The response should not be construed as addressing specific issues raised by any pending application submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(j)), nor does it purport to make any final decision with respect to any such pending application. Those decisions would be made in the normal course as part of the review process applicable to any application.

significant decomposition. In the ileum, budesonide is released from the tablet core. The tablet core contains budesonide with specific polymers that provide for the extended release of budesonide throughout the colon.

B. Entocort and Mesalamine Products

Budesonide has been approved in various formulations, including powder for inhalation, suspension for inhalation, aerosol, nasal spray, oral capsules, and extended-release oral tablets, for various indications, including asthma, noninfectious rhinitis, and inflammatory bowel disease. In particular, Entocort EC (budesonide) oral capsules, NDA 21-324, was approved on October 2, 2001 and also was designed to release budesonide in the GI tract. Entocort EC capsules are indicated for the treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon and the maintenance of clinical remission of mild to moderate Crohn's disease involving the ileum and/or the ascending colon for up to 3 months. FDA has published a draft bioequivalence recommendation for budesonide capsules.[2]

FDA also has approved a number of mesalamine products to treat UC. Mesalamine is an anti-inflammatory agent. Although its mechanism of action is not fully understood, data suggest that mesalamine primarily acts locally rather than systemically. Thus, mesalamine must be delivered to the affected region of the gastrointestinal (GI) tract (primarily the colon) to effectively treat UC. Currently approved oral mesalamine drug products use various methods to deliver the active ingredient to the colon. Some are modified-release products that, like Uceris, are designed to release the drug substance in and along the colon.[3]

In a 2007 letter, the Division of Bioequivalence in FDA's Office of Generic Drugs recommended that comparative clinical endpoint studies, rather than PK studies, be used (along with in vitro dissolution studies) to show bioequivalence in orally administered extended- or delayed-release mesalamine drugs.[4] Relying on this letter, holders of the three NDAs approved at the time for modified-release mesalamine products (Asacol (NDA 19-651), Asacol HD (NDA 21-830), and Pentasa (20-049)) submitted citizen petitions asking, among other things, that FDA require data from comparative clinical endpoint studies and comparative in vitro dissolution tests in all abbreviated applications referencing those products.[5]

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[2] Draft guidance on *Budesonide* (October 2009), available on the Internet at http://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/default.htm under Bioequivalence Recommendations for Specific Products. This draft guidance, once finalized, will represent FDA's current thinking on this topic. Guidances do not create or confer any rights for or on any person and do not operate to bind FDA or the public. An alternative approach may be used if the approach satisfies the requirements of the applicable statutes and regulations.

[3] See Letter from Dr. Janet Woodcock to Mr. Izumi Hara and Dr. Jeffrey Jonas (August 20, 2010) (Mesalamine Joint Response), at 3 (FDA-2010-P-0111 and FDA-2008-P-0507).

[4] Id. at 7.

[5] Id. at 9-10.

In response, FDA continued to recommend in vitro dissolution testing, but concluded that applicants proposing generic versions of the modified-release mesalamine products should conduct studies with PK endpoints rather than comparative clinical endpoint studies to satisfy the bioequivalence requirement.[6] FDA explained that it had formerly believed that PK data might not be a good proxy for the amount of mesalamine available at the sites of drug action for orally ingested, modified-release mesalamine products because mesalamine from these products may be absorbed throughout the GI tract, not just at the sites of drug action, the colon and rectum.[7] But, as explained in the Mesalamine Joint Response, FDA ultimately changed its position, reasoning that "[i]f PK data are analyzed using other metrics in lieu of or in addition to AUC and C_{max}, . . . it is possible to detect significant differences, if any, between the mesalamine release profiles of test and reference products at the sites of action."[8] Specifically, "PK profiles can be analyzed over defined time intervals using partial AUC or other profile comparison tools. . . . Using these tools, FDA can analyze systemic mesalamine concentrations over specified time intervals to determine whether mesalamine from test and reference products is absorbed at the same rate and to the same extent at the colon and rectum."[9] FDA further concluded that "comparative clinical endpoint bioequivalence studies would be less sensitive, accurate, and reproducible than PK studies. That is, [FDA] expect[s] that PK studies will better detect significant differences, if any, in the drug release patterns of test and reference formulations of Pentasa, Asacol, or Asacol HD at the sites of drug action."[10]

In September 2012, FDA published draft bioequivalence guidances covering all orally ingested, modified-release mesalamine drugs.[11] Consistent with the approach described in the Mesalamine Joint Response, these guidances recommend study designs and evaluation methods for studies with PK endpoints and in vitro dissolution studies. FDA has also addressed certain aspects of these guidances in subsequent citizen petitions.[12]

C. Applicable Statutory and Regulatory Background

The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the Hatch-Waxman Amendments) created section 505(j) of the FD&C Act, which established the ANDA approval process for generic drugs. To obtain approval, an ANDA applicant is not

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[6] Id.

[7] Id. at 6-7.

[8] Id. at 10.

[9] Id.

[10] Id.

[11] See http://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/default.htm under Bioequivalence Recommendations for Specific Products (Mesalamine) (draft guidances associated with NDAs 20-049, 22-301, 19-651, 20-830, and 22-000).

[12] Letter from Dr. Janet Woodcock to Mr. Alvin D. Howard (March 22, 2013) (FDA-2012-P-1087); Letter from Dr. Janet Woodcock to Ms. Linda G. Young (September 12, 2013) (FDA-2013-P-0470).

required to provide independent evidence of the safety and effectiveness of the proposed generic drug product. Instead, the applicant relies on FDA's previous finding that the RLD is safe and effective. The ANDA applicant must identify the listed drug on which it seeks to rely, and with limited exceptions, a drug product described in an ANDA must contain the same active ingredient, conditions of use, route of administration, dosage form, strength, and (with certain permissible differences) labeling as the listed drug it references (section 505(j)(2)(A) and (j)(4) of the FD&C Act).

The applicant must also demonstrate that its proposed generic drug is bioequivalent to the listed drug. Section 505(j)(8)(B)(i) of the FD&C Act states that a generic drug is bioequivalent to the listed drug if:

> the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses . . . .

Congress also recognized that some drugs do not reach their site of action through absorption into the bloodstream. Thus, section 505(j)(8)(C) of the FD&C Act states the following:

> For a drug that is not intended to be absorbed into the bloodstream, the Secretary may establish alternative, scientifically valid methods to show bioequivalence if the alternative methods are expected to detect a significant difference between the drug and the listed drug in safety and therapeutic effect.

In 21 CFR 320.1(e), FDA defines bioequivalence (in pertinent part) as:

> the absence of a significant difference in the rate and extent to which the active ingredient or active moiety . . . becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.

A showing that the active ingredient or therapeutic ingredient in the proposed generic drug reaches the site of drug action at a rate and to an extent not significantly different from that of the listed drug, along with other information required for approval, permits FDA to conclude that the proposed generic drug can be expected to perform the same way in the body as the listed drug. Bioequivalence testing determines whether differences in formulation (e.g., differences in inactive ingredients) between a proposed generic drug and the RLD have an effect on the rate and extent to which the active ingredient becomes available at the site of action.

The determination of bioequivalence of drug products whose primary mechanism of action depends on systemic absorption (i.e., two solid oral dosage forms) generally rests on a comparison of drug and/or metabolite concentrations in an accessible biologic fluid, such as blood or urine, after administration of a single dose or multiple doses of each drug product to healthy volunteers. When this methodology is not appropriate, FDA may, as described in provisions of the FD&C Act and 21 CFR part 320, rely on other in vivo and/or in vitro methods to assess bioequivalence. FDA regulations describe these methods in general descending order of accuracy, sensitivity, and reproducibility. They include (1) in vivo PK studies, (2) in vivo

pharmacodynamic (PD) effect studies, (3) clinical endpoint studies, and (4) in vitro studies. In addition, consistent with section 505(j)(8)(C) of the FD&C Act, § 320.24(b)(6) of the regulations states that FDA has the flexibility to use "[a]ny other approach deemed adequate by FDA to . . . establish bioequivalence."

If a drug is intended to act locally rather than systemically, traditional PK studies that measure systemic concentrations of a drug over time may be inadequate to demonstrate bioequivalence. Some locally acting products may not produce measurable concentrations of drug or metabolite in an accessible biologic fluid. For those that do, we often lack evidence of any correlation between these systemic concentrations and concentrations at the site of drug action. For some of these products, the Agency can review data from PD effect studies to assess bioequivalence. For others, however, no PD endpoints can be readily measured. In these cases, the Agency often relies on data from "appropriately designed comparative clinical trials" (21 CFR 320.24(b)(4)) or, in appropriate cases, from in vitro studies to assess bioequivalence. However, because comparative clinical studies are generally considered to be insensitive, FDA recommends that they be used to establish bioequivalence only when it is not possible to use another study design.

FDA has discretion to determine how the bioequivalence requirement should be met for a given product or class of products as long as its determination is not contrary to the governing statute and regulations and is based on a "reasonable and scientifically supported criterion."[13] Courts have consistently upheld FDA's implementation of the FD&C Act's bioequivalence requirements.[14]

II. DISCUSSION

Your Petition requests that FDA develop and publish an individual bioequivalence recommendation for budesonide extended-release tablets. As described below, FDA is today publishing a draft individual bioequivalence recommendation for budesonide extended-release tablets (draft Budesonide ER BE Guidance). FDA is publishing a notice in today's *Federal Register* announcing the availability of this draft guidance for public comment. Because we are publishing a draft guidance for comment, this request is granted in part.

You also request that FDA refrain from approving any ANDA that identifies Uceris as the RLD unless the proposed generic product is shown to be bioequivalent to Uceris based on appropriate data from a clinical efficacy endpoint study, comparative PK testing, in vitro dissolution testing, and pharmacoscintigraphy studies. We agree that it would be appropriate for applicants for budesonide extended-release tablet ANDAs to demonstrate bioequivalence to Uceris using PK testing and in vitro dissolution testing. We have developed the draft Budesonide ER BE Guidance accordingly, although the specific study design and evaluation methods we recommend differ in some respects from those suggested in the Petition. We disagree, however, that budesonide extended-release tablet ANDA applicants should be required to demonstrate

[13] *Schering Corp. v. Sullivan*, 782 F.Supp. 645, 651 (D.D.C. 1992).

[14] See, e.g., *Schering Corp. v. FDA*, 51 F.3d 390 (3rd Cir. 1995); *Fisons Corp. v. Shalala*, 860 F. Supp. 859 (D.D.C. 1994).

bioequivalence through clinical efficacy endpoint studies or through pharmacoscintigraphy studies, and we decline to require[15] or recommend these studies. Each of your requests is discussed in more detail below.

A. Individual Bioequivalence Recommendation

In the Petition, you request that FDA develop and publish an individual product bioequivalence recommendation for budesonide extended-release tablets prior to approving an ANDA for any such drug product. In addition, you contend that the bioequivalence recommendation in our draft guidance for budesonide capsules is not appropriate for demonstrating bioequivalence in budesonide extended-release tablets (Petition at 4-6). Today FDA is issuing a draft individual product bioequivalence recommendation for budesonide extended-release tablets and this recommendation is different from our draft individual product bioequivalence recommendation for budesonide capsules. Because this is a draft guidance for comment, your request is granted in part. We note, however, that although FDA often publishes recommendations for bioequivalence studies for specific generic drug products (and has published a draft guidance in this case), we are not required to do so. In addition, even where an individual product bioequivalence recommendation has been published, the guidance is not binding on the Agency or the public; applicants can use an alternative approach to establish bioequivalence of a drug product if the approach satisfies the requirements of the applicable statutes and regulations as determined by FDA.[16]

B. Bioequivalence Requirements: Additional PK Parameters

In the Petition, you request that FDA not approve any ANDA that identifies Uceris as the RLD unless bioequivalence is demonstrated by, among other things, PK testing using additional metrics beyond total area under the plasma concentration versus time curve (AUC), time to maximum plasma concentration (T_{max}),[17] and maximum plasma concentration (C_{max}). Specifically, the Petition states that bioequivalence to Uceris should be demonstrated under fed and fasted conditions in patients with active, mild to moderate UC. You maintain that using PK metrics in lieu of or in addition to AUC, T_{max} and C_{max} measurements would ensure that the proposed generic drug product releases budesonide at the same rate and to the same extent as Uceris at the site of drug action in the colon (Petition at 9-10). The particular PK metrics the Petition states should be required are the following:

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[15] At several points in the Petition, you request that FDA "require" ANDA applicants to provide certain data in support of a demonstration of bioequivalence. As indicated in section II.A, as well as in our guidances and regulations, recommendations for demonstrating bioequivalence are not mandatory. If an ANDA applicant for budesonide extended-release tablets seeks approval using an alternative approach that satisfies the requirements of the applicable statutes and regulations, FDA has the discretion to accept that approach. Thus, any request that FDA require ANDAs to include specific types of data is denied throughout. To the extent that the Agency indicates in this response that it will grant your request to require certain data, those statements should be construed to be FDA's agreement to recommend that ANDA applicants submit such data to demonstrate bioequivalence.

[16] See the FDA guidance for industry *Bioequivalence Recommendations for Specific Products* (June 2010).

[17] As explained in section II.B.4, FDA has not developed statistical criteria to test equivalence for this PK parameter.

(1) partial AUC (pAUC) values for 6 to 19 hours after dosing ($AUC_{6\text{ to }19}$) and for 19 to 36 hours after dosing ($AUC_{19\text{ to }36}$), in addition to total AUC, or at such other time point(s) as FDA may deem appropriate to meet the bioequivalence standard of 90 percent confidence interval within the range 80 to 125 percent;

(2) extensive sampling points around T_{max} to ensure there is an accurate estimation of C_{max} and T_{max} and at least four non-zero measurements of concentration before T_{max} and between T_{max} and 36 hours post-dose; and

(3) a determination of absorption lag time (T_{lag}) to ensure appropriate delayed release of the proposed generic (Petition at 10).

The Petition relies on the Mesalamine Joint Response, in which FDA recognized that while the standard PK metrics of AUC and C_{max} would not distinguish between products with materially different release profiles at the sites of drug action if peak concentrations and total amount of drug substance released throughout the GI tract are not significantly different, these differences could be detected by analyzing PK metrics in lieu of or in addition to AUC and C_{max}.[18] The Petition states the same standard should be used in a comparison between Uceris and any drugs that list Uceris as the RLD (Petition at 10).

FDA agrees that using pAUC as an additional PK metric to demonstrate bioequivalence for budesonide extended-release tablets is appropriate. Thus, your request that FDA require the use of PK metrics is granted in part as we recommend that they be used to establish bioequivalence in the draft Budesonide ER BE Guidance. However, the Petition is denied in part because our recommendations for PK testing differ in some respects from those requested in the Petition, as discussed in more detail below.

1. Study Population for PK Testing

You request that bioequivalence PK testing be conducted in patients with active, mild to moderate UC. The purpose of a bioequivalence study in this situation is to demonstrate equivalent formulation performance, i.e., to show that there is no significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents becomes available at the site of action when administered at the same molar dose under similar conditions in an appropriately designed study.[19] You have provided no data or analysis suggesting that testing in patients with active, mild to moderate UC would be more discriminating for the purpose of assessing bioequivalence than testing in healthy subjects, i.e., would be expected to reveal significant formulation performance differences between Uceris and proposed generic versions of Uceris. In addition, we have not identified any reason why PK testing in a patient population would be more sensitive in evaluating bioequivalence.

Instead, we have identified several reasons why conducting PK studies in healthy volunteers is preferable to PK studies in patients for the purpose of demonstrating bioequivalence of a generic

[18] Mesalamine Joint Response, at 10.

[19] 21 CFR 320.1(e).

extended-release budesonide tablet to Uceris. The variability of PK parameters is known to be much greater in patients with UC than in healthy subjects related to both inter- and intrapatient variability in the disease state.[20] Because of the high variability, more patients (subjects) would likely be needed to meet the bioequivalence criteria if testing in a patient population. On the other hand, the use of healthy subjects reduces uncontrollable variability caused by disease and provides greater sensitivity for the detection of small differences in the bioavailability of pharmaceutically equivalent formulations. Another concern with using patients is that conducting a bioequivalence study in a patient population generally requires a parallel design (i.e., the same patient would not receive both the test and reference products) due to the changes in disease state that administration of the drug product induces. The ability to use a crossover study design with a healthy subject population further reduces the impact of variability because the subject serves as his or her own control. In addition, the reference scaled approach[21] could not be used with a parallel design and that approach would minimize the number of patients that would need to be included in the study. However, with a healthy subject population, reference scaling can be used to minimize the number of subjects exposed to the study drug. Thus, use of healthy volunteers will provide more accurate results using fewer subjects and would also be consistent with our desire to avoid unnecessary human research.[22]

The Petition also requests that PK testing be conducted in both fed and fasted patients (Petition at 9). Although we disagree that testing should be conducted in patients, our draft Budesonide ER BE Guidance recommends bioequivalence studies under both fed and fasting conditions. This is consistent with our general recommendation for orally administered, modified-release drug products.[23]

For the foregoing reasons, we do not agree that a bioequivalence study should be conducted in patients with active, mild to moderate UC rather than healthy subjects. Instead, as reflected in the draft Budesonide ER BE Guidance, FDA recommends that bioequivalence studies with PK endpoints be conducted in healthy volunteers, in both fed and fasting conditions, with a crossover design and use of reference-scaling, if needed.

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[20] See Letter from Dr. Janet Woodcock to Ms. Linda G. Young (September 12, 2013), at 7.

[21] FDA has recommended a reference-scaled average bioequivalence analysis approach for highly variable drugs. The referenced-scaled average bioequivalence approach adjusts the bioequivalence limits of highly variable drugs by scaling to the within-subject variability of the RLD in the study and imposes a limit of 0.8 to 1.25 on the geometric mean ratio rather than the conventional average bioequivalence criteria. See the draft guidance for industry *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA* (December 2013).

[22] 21 CFR 320.25(a).

[23] See the draft guidance for industry *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA* (December 2013).

2. *AUC Measurements for PK Testing*

The Petition asks FDA to require both AUC and pAUC to demonstrate bioequivalence to Uceris. With regard to AUC, FDA agrees that total AUC should be measured in PK testing for budesonide extended-release tablets. Specifically, we recommend total AUC from 0 hours to the last measurable time point (AUC_{0-t}) in place of AUC extrapolated to infinity ($AUC_{0-\infty}$). Generally, $AUC_{0-\infty}$ is extrapolated based on the elimination rate constant after absorption. However, this approach would not lead to an accurate estimate of total exposure for budesonide extended-release tablets because the terminal phase of the PK profile reflects continuous absorption and elimination. We recommend that the last sampling time point should be at least at 72 hours to ensure that the full PK profile is captured.

We also agree that pAUC is an appropriate PK parameter in the demonstration of bioequivalence for budesonide extended-release tablets, but we recommend the use of AUC from 8 to 48 hours after dosing (AUC_{8-48}), and not the AUC_{6-19} and AUC_{19-36} intervals suggested in the Petition. In the Petition, you state that the AUC_{6-19} time point was selected based on the average T_{max} of Uceris of 13.3 $\pm$ 5.9 hours and that the AUC_{19-36} time point was selected because there are still appreciable levels of budesonide in the plasma of patients from 19 to 36 hours after they have been administered Uceris, which levels contribute to demonstrated efficacy in inducing remission in patients with active, mild to moderate UC (Petition at 10). Given available data on GI tract transit times,[24] we believe the exposure from 8 to 48 hours after dosing would reflect budesonide absorption from the ascending colon down to the sigmoid colon and sufficiently distinguish between products with materially different budesonide release profiles at the site of action. Our examination of PK data for budesonide extended-release tablets indicates that AUC_{19-36} also shows higher intrasubject variability than does AUC_{8-48}. The use of a pAUC with lower intrasubject variability would reduce the number of subjects that would need to be enrolled in the PK study and thereby limit the number of subjects that would be exposed to the drug product. Accordingly, we decline to recommend or require pAUC intervals of AUC_{6-19} and AUC_{19-36}, and instead recommend AUC_{8-48}, as reflected in the draft Budesonide ER BE Guidance.

3. *T_{max} sampling for PK Testing*

The Petition further states that PK testing should include "extensive sampling points around T_{max} to ensure there is an accurate estimation of C_{max} and T_{max} and at least four non-zero measurements of concentration before T_{max} and between T_{max} and 36 hours post-dose with respect to the test composition" (Petition at 10). FDA generally recommends adequate sampling to characterize PK features of a drug product, including absorption, distribution and elimination phases. However, we do not routinely recommend specific sampling time points; instead, it is an applicant's responsibility to select appropriate sampling time points based on the PK characteristics of the product. For budesonide extended-release tablets, FDA recommends at least four non-zero measurements of plasma concentration between 8 and 48 hours post-dose to

[24] Brunner, M, Ziegler, S, Di Stefano, AFD, Dehghanyar, P, et al., "Gastrointestinal transit, release and plasma pharmacokinetics of a new oral budesonide formulation", Br J Clin Pharmacol, 2005, 61:1: 31-38.

get an accurate estimate of AUC_{8-48}. The applicant should select appropriate sampling time points adequate to characterize PK features. Therefore, we decline to recommend at least four non-zero measurements of concentration before T_{max} and between T_{max} and 36 hours post-dose.

4. Determination of T_{lag} for Comparative PK Testing

Finally, the Petition states that a determination of T_{lag}, the time from administration to first quantifiable concentration, should be performed to ensure appropriately delayed release of the generic formulation. We disagree. Although FDA routinely evaluates the difference in T_{lag} or T_{max} between a proposed generic product and RLD during its review process, FDA has not developed statistical criteria to test equivalence for these time-related PK parameters. Demonstration of bioequivalence in C_{max}, AUC_{0-t}, AUC_{8-48}, and dissolution profiles in various media with different pH values (as described below) will ensure that a test product has a lag time similar to that of the RLD. Therefore, we decline to recommend or require T_{lag} as a metric for the bioequivalence assessment of budesonide extended-release tablets.

In sum, we agree that PK testing is an appropriate method of establishing bioequivalence for budesonide extended-release tablets, when used in conjunction with dissolution testing, and recommend the use of PK studies in the draft Budesonide ER BE Guidance. The study design and evaluation methods differ in some respects from those requested in the Petition. Specifically, the draft Budesonide ER BE Guidance recommends the following PK parameters: log-transformed AUC_{8-48}, AUC_{0-t}, and C_{max}, where AUC_{8-48} is the area under the plasma concentration versus time curve from 8 to 48 hours, AUC_{0-t} is the area under the curve from 0 hours to the last measurable time point, and C_{max} is the maximum plasma concentration. There should be at least four non-zero measurements of concentrations between 8 and 48 hours post-dose. In addition, as AUC_{0-t} is recommended in place of $AUC_{0-\infty}$, the last sampling time point should be at least at 72 hours. This portion of the Petition is therefore granted in part and denied in part.

C. Bioequivalence Requirements: In Vitro Dissolution Testing

In addition to PK studies, the Petition states that ANDA applicants should be required to demonstrate bioequivalence to Uceris by conducting appropriate in vitro dissolution studies at various pHs (Petition at 10-11). The tablet core of Uceris is enteric coated to protect dissolution in gastric juice which delays budesonide release until exposure to a pH ≥ 7 in the small intestine. Upon disintegration of the coating, the core matrix provides extended release of budesonide in a time dependent manner.[25] According to the Petition, FDA should require that any in vitro dissolution testing with budesonide extended-release tablets be conducted such that the tablets are exposed to dissolution mediums having a pH less than 7 for extended periods of time to ensure their release profiles are not inconsistent, using the f2 metric,[26] with the release profile of

[25] See Uceris Prescribing Information (rev. Jan 2013), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/203634s000lbl.pdf.

Uceris under similar conditions. This testing, you claim, would confirm that budesonide is not released from the proposed generic product below pH 7, which would otherwise result in the early release of budesonide in the upper GI tract (Petition at 11).

The request in the Petition that FDA require in vitro dissolution testing to establish bioequivalence to Uceris is granted in part and denied in part. FDA recommends that in vitro dissolution studies at various pH levels should be part of bioequivalence testing for proposed generics of Uceris. This testing will mimic product performance in the gastrointestinal tract in vivo and help ensure that the proposed generic maintains the delayed and extended-release characteristics of Uceris. However, the specific dissolution testing conditions we recommend for budesonide extended-release tablets, which are described in detail in the draft Budesonide ER BE Guidance, differ in some respects from those suggested in the Petition. In particular, FDA recommends testing at additional pH levels. Dissolution testing is important because we are recommending PK studies in healthy subjects and the GI pH profiles in patients could be different from those in the healthy population. By recommending dissolution testing in multiple pH conditions that cover the pH range in the GI tract, we are able to ensure that a generic will release the active ingredient and dissolve at the same rate and extent as Uceris in the same GI segment in the same subject. We also note that the f2 metric requested in the Petition will be applied whenever possible but may not be feasible to use when, for example, the dissolution is very little and close to zero or when the variability of the dissolution data is high. In addition, we typically do not include specific sampling times in our bioequivalence recommendations, and decline to do so here. Instead, consistent with our usual practice, we will review dissolution testing submitted in support of an ANDA application on a case-by-case basis considering gastrointestinal physiology.

D. Bioequivalence Requirements: Use of Pharmacoscintigraphy Studies

In the Petition, you request that FDA require ANDA applicants to conduct pharmacoscintigraphy studies (single and multiple dose) to establish the bioequivalence of generic extended-release budesonide tablets (Petition at 11-13). Pharmacoscintigraphy studies can estimate the release of a drug in different parts of the GI tract over time by correlating drug plasma concentrations with the location of a labeled dosage form using techniques such as gamma scintigraphy (a nuclear imaging technique that allows in vivo imaging of a gamma-emitting radioisotope). You compare pharmacoscintigraphy study results for Entocort and Uceris, noting that such studies demonstrated that the products have different release profiles, each appropriately suited for the site of action of the respective drug products (Petition at 12). You claim that because the clinical effects of Uceris are due to its localized (rather than systemic) activity and because the product is known to be delivered almost exclusively to the colon, a pharmacoscintigraphy study is necessary to provide a reliable measurement of bioequivalence between a generic extended-release budesonide drug product and Uceris (Petition at 13).

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[26] The f2 metric is a measurement of the similarity in the percent (%) of dissolution between test and reference products based on a logarithmic reciprocal square root transformation of the sum of squared error. See the FDA guidance for industry *Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System* (August 2000).

FDA agrees that evaluating the release profile of budesonide extended-release tablets is important to establish that the product preferentially releases budesonide in and along the entire length of the colon. However, we disagree that pharmacoscintigraphy studies are necessary for this purpose. Pharmacoscintigraphy studies are generally not appropriate to demonstrate the bioequivalence of two different formulations because these studies require modification of the formulation being tested to integrate an isotope. This formula modification could affect the in vivo performance of the RLD. In any case, these tests are unnecessary because bioequivalence testing using PK endpoints and in vitro dissolution, as described above, adequately characterizes the modified-release properties of budesonide extended-release tablets. This is corroborated by information in the Petition regarding data from the comparative bioavailability study evaluating Uceris and Entocort, which was able to conclusively demonstrate that the drug products differ significantly in terms of their PK profiles (Petition at 5-6). We therefore deny your request to require pharmacoscintigraphy studies to demonstrate bioequivalence of budesonide extended-release tablets.

E. Bioequivalence Requirements: Clinical Endpoint Study

The Petition requests that FDA also require ANDA applicants to conduct comparative in vivo studies with clinical endpoints that demonstrate the noninferiority[27] of a proposed generic product to Uceris in the induction of remission in patients with active, mild to moderate UC (Petition at 6-9). You claim that this is necessary to ensure detection of significant differences in safety and therapeutic effect between proposed generic products and Uceris (Petition at 9). Specifically, you claim that unique release characteristics of Uceris, coupled with the high first-pass metabolism of budesonide, mean that measuring the concentration of budesonide in plasma is inherently inaccurate and does not provide sufficient information regarding the release of budesonide at the site of action (Petition at 7). You also claim that there are no reliable PD measurements that can be used to establish bioequivalence between Uceris and proposed generic products and that there are no reliable in vitro models available that can readily and accurately distinguish between the release profiles of Uceris and proposed generic products (Id.).

You cite the fact that Uceris is currently the only extended-release budesonide tablet approved for use in the treatment of UC as a basis for requiring clinical endpoint studies to establish bioequivalence (Petition at 9). You claim that FDA recommended in vivo clinical efficacy studies for the mesalamine modified-release products in 2007 because at that time the Agency had little clinical or scientific experience with these products and was concerned that PK data might not be a good proxy for local absorption, and you suggest a similar approach should be taken for budesonide extended-release tablets given the relative lack of experience with them (Petition at 9-10). Although FDA now recommends PK testing along with in vitro dissolution testing to establish bioequivalence of mesalamine modified-release products, you suggest that was a result of FDA's experience with "multiple" mesalamine modified-release products. Accordingly, you believe that FDA should continue to require comparative clinical endpoint

[27] We note that an ANDA applicant must demonstrate bioequivalence between the generic product and the RLD, and a clinical noninferiority study would not be adequate to demonstrate bioequivalence.

studies for proposed generics of Uceris for which there is a "relative lack of scientific knowledge and clinical experience" (Petition at 9).

A bioequivalence study with a clinical endpoint is generally considered less sensitive and less reproducible for evaluating bioequivalence, and the use of these studies is generally considered to be appropriate to demonstrate bioequivalence only when a PK approach or PD approach is not reasonable or feasible.[28] Based on our review of the available clinical data, we believe that, in this case, bioequivalence studies with alternative PK endpoints together with comparative dissolution studies will be more sensitive than a bioequivalence study with clinical endpoints in detecting formulation differences of budesonide extended-release tablets.

It is true that some locally acting products do not produce any measurable concentration of drug or metabolite in an accessible biological fluid. However, that is not the case for budesonide. Although the plasma concentration of budesonide following oral administration of Uceris is relatively low (C_{max}: 1.35 ± 0.96 nanogram (ng)/milliliter (mL); AUC: 16.43 ± 10.52 ng•hour (h)/mL), the bioanalytical method for evaluating budesonide has a relatively high sensitivity (with a limit of quantification of 50.0 picograms (pg)/mL) making the PK approach to evaluating bioequivalence feasible. Also, the absorption of budesonide extended-release tablets into systemic circulation (as evidenced by the PK profile) can serve as a surrogate for its release at the colon. Thus, different extended-release budesonide products, such as Uceris and Entocort, have very different PK profiles because they are designed to release drug product at different sites in the GI tract, as noted in your Petition (Petition 5-6). Studies with clinical endpoints, however, may not distinguish between these formulation differences. Like PK bioequivalence studies, in vitro dissolution profile comparisons can detect formulation differences with high sensitivity. Therefore, with the availability of more sensitive and reliable methods, i.e., the combination of a PK study analyzing AUC_{0-t}, AUC_{8-48}, and C_{max}, and an in vitro dissolution profile comparison study, clinical endpoint testing is not needed to demonstrate bioequivalence between Uceris and proposed generic products.

Reliance on the history of the mesalamine bioequivalence recommendations is misplaced. As is clear from the Mesalamine Joint Response, when FDA recommended comparative clinical trials to establish bioequivalence for the modified-release mesalamine products, the Agency was focused on whether data from PK studies that analyzed only the standard PK metrics of AUC and C_{max} could meaningfully distinguish test and reference modified-release mesalamine products and found that they could not.[29] FDA later concluded that if PK data are analyzed using other metrics in lieu of or in addition to AUC and C_{max}, it is possible to detect significant differences in the release profiles of the test and reference products at the site of action.[30] Nothing in this history suggests, as the Petition seems to claim, that a number of different products must be available for evaluation before FDA can determine that additional PK metrics are sufficient to demonstrate bioequivalence.

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[28] 21 CFR 320.24.

[29] Mesalamine Joint Response, at 10.

[30] Id.

In any case, because the available evidence discussed in this letter is sufficient for us to conclude that expanded PK testing as described in the draft guidance and in vitro dissolution studies will detect meaningful differences in test and references products, FDA disagrees that more experience with budesonide extended-release tablets is needed before the Agency can rely on that testing to evaluate bioequivalence. In addition, experience with the mesalamine modified-release products provides useful information on the ability of PK studies along with in vitro dissolution tests to detect meaningful differences in the release profiles of modified-release drug products designed to act in the colon. Therefore, we deny your request to require that for an ANDA citing Uceris as the RLD, the generic product be shown to be noninferior to Uceris in inducing remission in patients with active, mild to moderate UC in a clinical endpoint study.

III. CONCLUSION

For the reasons explained above, your Petition is granted in part and denied in part.

Sincerely,

Janet Woodcock
Director
Centers for Drug Evaluation and Research