DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

SEP 1 2 2013

Linda G. Young
Vice President, Regulatory Affairs
Salix Pharmaceuticals, Inc.
8510 Colonnade Center Drive
Raleigh, North Carolina 27615

Re: Docket No. FDA-2013-P-0470

Dear Ms. Young:

This letter responds to your citizen petition dated March 7, 2013 (the Petition), regarding mesalamine extended-release capsules. In your petition, you request that the Commissioner of the Food and Drug Administration (FDA or the Agency) amend the Agency's existing criteria for how to demonstrate bioequivalence (BE) for mesalamine extended-release capsules and apply such criteria to any abbreviated new drug application (ANDA) that relies upon the new drug application (NDA) 022301 for Apriso (mesalamine) extended-release capsules as the referenced listed drug (RLD) (Petition at 1).

In August 2010 FDA responded to two citizen petitions concerning bioequivalence requirements for generic[1] versions of Asacol, Asacol HD, and Pentasa, all orally ingested modified-release mesalamine drugs.[2] As explained in the joint letter response to those petitions, FDA determined that ANDAs for these products should contain data from comparative pharmacokinetic (PK) studies (rather than comparative clinical endpoint studies, as the Agency had previously recommended) and in vitro dissolution studies (Mesalamine Joint Response at 8, 11-12).[3] In September 2012, FDA's Office of Generic Drugs (OGD) issued draft bioequivalence guidance for all orally ingested modified-release mesalamine drug products then approved, including Apriso, recommending study designs and evaluation methods for comparative PK and in vitro dissolution studies.[4] You contend that the bioequivalence criteria established by FDA in this

[1] For the purposes of this response, a generic drug is a new drug product for which approval is sought in an ANDA submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 355(j)).

[2] See Dockets FDA-2008-P-0507 and FDA-2010-P-0111.

[3] See August 2010 Letter from Dr. Janet Woodcock, Director, Center for Drug Evaluation and Research, FDA, to Mr. Hara of Warner Chilcott and Dr. Jonas of Shire re: Docket Nos. FDA-2008-P-0507 and FDA-2010-P-0111 (Mesalamine Joint Response). In November 2012, FDA responded to a petition for reconsideration regarding these petitions. See November 2012 Letter from Ms. Leslie Kux, Director, Acting Assistant Commissioner for Policy, Center for Drug Evaluation and Research, FDA, to Dr. Karlstadt of Shire, re: Docket Nos. FDA-2008-P-0507 and FDA-2010-P-0111 (Mesalamine Joint Petition for Reconsideration Response).

[4] See http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm081327.htm (draft guidances associated with RLD application nos. 20049, 22301, 19651, 21830, and 22000).

September 2012 draft bioequivalence guidance fail to consider all of the properties you claim make the Apriso formulation unique and are insufficient to establish bioequivalence of a generic mesalamine product to Apriso. You therefore request that in the absence of a requirement of clinical endpoints to establish clinical bioequivalence, FDA require the following for any ANDA that relies on Apriso as the RLD:

- bioequivalence to be established under fasted and fed conditions in patients with ulcerative colitis in remission;
- pharmacokinetic (PK) parameters to be computed using the plasma analytes mesalamine (5-ASA) and its metabolite N-acetyl 5-aminosalicylic acid (N-Ac-5-ASA);
- bioequivalence to be established on plasma PK parameters computed on plasma analytes 5-ASA and N-Ac-5-ASA for the parameters: maximum plasma drug concentration (C_{max}), area under the plasma concentration versus time curve (AUC) from the time of dosing to 3 hours after dosing (AUC_{0-3}), AUC from 3 hours after dosing to the last measurable concentration (AUC_{3-t}), AUC from 8 hours after dosing to the last measurable concentration (AUC_{8-t}), AUC at the last measurable concentration (AUC_t), time to the occurrence of C_{max} (T_{max}), and AUC from time zero to time infinity (AUC_{inf});[5] and
- determination of the rate of N-Ac-5-ASA formation detected in the soluble fraction of fecal samples derived from subjects participating in the above pharmacokinetic studies.

(Petition at 1-2, 26-27). You also ask that FDA not approve any ANDAs for mesalamine without resolving the issues raised in this citizen petition (Petition at 2).

As explained below, FDA denies your specific requests that we change our bioequivalence recommendations regarding Apriso and denies your petition.

I. BACKGROUND

A. Apriso

Salix Pharmaceuticals, Inc. (Salix) holds NDA 022301 for Apriso (mesalamine) extended-release capsules, 375 milligrams (mg). Apriso is indicated for the maintenance of remission of ulcerative colitis in patients 18 years of age and older.

[5] Although the AUC_{inf} parameter is not included among the parameters you request in bullet 3 on page 1 of the Petition, we include it here because you include it among the requested parameters on pages 25 and 27 of the Petition.

Ulcerative colitis is an idiopathic chronic inflammatory disease of the colon and rectum. 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.[6] Thus, mesalamine must be delivered to the affected region of the gastrointestinal (GI) tract (primarily the colon) to treat ulcerative colitis effectively. Modified-release orally ingested mesalamine drug products, including Apriso, use various formulation technologies to deliver mesalamine to the colon. Apriso targets drug release to the colon through a pH-sensitive enteric coating; each Apriso capsule contains granules composed of mesalamine in a polymer matrix with an enteric coating that dissolves at pH 6 or above.

B. August 2010 Joint Petition Response to Mesalamine Petitions

We provide a brief summary of the relevant portions of the August 2010 Mesalamine Joint Response here; readers are referred to that response for additional information and details. The Mesalamine Joint Response also provides the relevant statutory and regulatory framework, which need not be repeated in this response.

In its 2008 citizen petition (FDA-2008-P-0507) Shire Pharmaceuticals, Inc., asked, among other things, that FDA require that all applications for generic or "follow-on" formulations of Pentasa (mesalamine) extended-release oral capsules submitted under section 505(b)(2) or 505(j) of the FD&C Act include data from comparative clinical endpoint studies and comparative dissolution tests (Mesalamine Joint Response at 1). In its 2010 citizen petition (FDA-2010-P-0111) Warner Chilcott asked, among other things, that FDA require that all applications for generic formulations of Asacol or Asacol HD (mesalamine) delayed-release tablets submitted under section 505(j) of the FD&C Act include data from comparative clinical efficacy endpoint studies, comparative in vitro dissolution tests, and comparative pharmacokinetic (PK) safety studies under fed and fasted conditions (Mesalamine Joint Response at 1). Both petitions relied on a 2007 letter from the Division of Bioequivalence in FDA's Office of Generic Drugs to counsel for Shire that recommended that ANDAs for generic versions of Pentasa and Asacol include data from comparative clinical endpoint studies and in vitro dissolution studies to satisfy the bioequivalence requirement (Mesalamine Joint Response at 2).[7]

In response, FDA continued to recommend in vitro dissolution testing, but concluded that applicants proposing generic versions of Asacol, Asacol HD, or Pentasa should conduct comparative PK studies rather than comparative clinical endpoint studies to satisfy the bioequivalence requirement (Mesalamine Joint Response at 2). Specifically, FDA explained that it had formerly believed that PK data might not be a good proxy for the amount of mesalamine

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[6] See Letter from Dr. Janet Woodcock, Director, Center for Drug Evaluation and Research, FDA, to Mr. Celestini and Mr. Forbes, Salix Pharmaceuticals, Inc., re: Docket No. FDA-2005-P-0314 and supplements thereto (December 28, 2007), at 3, 8, 13-14 (Colazal Petition Response). (This Citizen Petition from Salix was originally assigned FDA Docket No. 2005P-0146, but the number was changed to FDA-2005-P-0314 following FDA's transition to a new docketing system (Regulations.gov).)

[7] Letter from Dale P. Conner to Lawrence & Haug LLP (September 11, 2007).

available at the sites of drug action for Asacol, Pentasa, and other 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 (Mesalamine Joint Response at 6-7). But, as explained in the petition 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" (Mesalamine Joint Response at 10). 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" (Mesalamine Joint Response at 10). 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" (Mesalamine Joint Response at 11).

C. Mesalamine Draft Guidances

In September 2012, FDA published draft bioequivalence guidances covering all orally ingested modified-release mesalamine drugs approved at that time, including Apriso.[8] Consistent with the approach described in the Mesalamine Joint Response, these draft guidances recommend study designs and evaluation methods for comparative PK and in vitro dissolution studies. Certain particulars of the draft guidance covering Apriso are discussed below.

II. DISCUSSION

We address each of your requests below. We note that this discussion is limited to the issues raised in your petition, and does not constitute a full review or finalization of the draft bioequivalence guidances for Apriso or other mesalamine drug products. The draft guidances, when finalized, will represent FDA's current thinking on these topics.

[8] See http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm081327.htm (draft guidances associated with RLD application nos. 20049, 22301, 19651, 20830, and 22000).

A. Patient Population of Pharmacokinetic Studies

The Apriso Draft Guidance recommends that both fasting and fed in vivo PK bioequivalence studies with PK endpoints be conducted in normal healthy males and females.[9] You contend that PK profiles in healthy subjects are not predictive of profiles in ulcerative colitis patients treated with Apriso because "it is well appreciated that in most cases the colonic mucosa does not return to a histologically 'normal' appearance" and "[u]nless the Test formulation is identical in physico-chemical composition to the RLD, it is possible that the interaction of the two formulations with the diseased mucosal surface will differ [and] a difference in mucosal-granule interaction may not be detected in normal volunteers" (Petition at 24). For these reasons, you request that FDA require that bioequivalence be established under fed and fasted conditions with Apriso in patients with ulcerative colitis in remission rather than in healthy subjects (Petition at 1, 24, and 26-27).

We do not agree that bioequivalence studies with PK endpoints should be conducted in ulcerative colitis patients. The purpose of a bioequivalence study 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 or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study (21 CFR 320.1(e)). In this case, it is the mesalamine of Apriso that interacts with the diseased mucosal surface and generates pharmacological effects. Therefore, ensuring the test formulation delivers mesalamine to the site of action at a rate and extent that are not significantly different from that of the RLD, Apriso, will ensure the test formulation is bioequivalent to Apriso. The subject population for bioequivalence studies should be selected with this purpose in mind.

Your argument that "the interaction of the two formulations with the diseased mucosal surface will differ" is not supported by any evidence that there is any pharmacological activity of mesalamine products other than from the delivery of mesalamine to site of action. Therefore, ensuring the test formulation delivers mesalamine to the site of action at a rate and extent that are not significantly different from that of the RLD will ensure the test formulation is bioequivalent to Apriso.

You argue that "the altered morphology of the colonic mucosa results in N-Ac-5-ASA and 5-ASA permeability profiles that are different from healthy subjects and the interaction of the formulation's physicochemical characteristics with the diseased mucosa will be formulation specific" (Petition at 26-27). Although studies reported in the literature comparing the PK

[9] See Draft Guidance on Mesalamine (RLD number 22301), available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM320000.pdf (Apriso Draft Guidance).

profile data of healthy and diseased individuals treated with mesalamine products differ[10] in their conclusion about similarity between healthy subjects and patients, this fact is irrelevant with respect to establishing bioequivalence between two formulations that are compared to each other in the same population. Furthermore, you provide no data or analysis supporting your assertion that testing in patients with ulcerative colitis in remission would be more discriminating for the purpose of assessing bioequivalence than testing in healthy patients, such that testing in this patient population would be expected to reveal significant formulation performance differences between Apriso and proposed generic versions of Apriso that would be missed by testing in healthy patients, and we have no reason to think it would be. We conducted a simulation to assess whether the ulcerative colitis patient population would be more sensitive than healthy subjects in their ability to detect PK differences in formulation changes of Apriso,[11] and the results showed that healthy subjects and patients have similar sensitivity and ability to discriminate the PK differences.[12]

In fact, bioequivalence testing in diseased patients is generally disfavored, and in this case we believe it could introduce unnecessary complexity without increasing assay sensitivity. Conducting in vivo bioequivalence studies in healthy volunteers reduces the chance of inadvertently detecting potentially confounding variability not related to differences between products. As such, in vivo bioequivalence is almost always established in healthy volunteers unless the drug carries safety concerns that make this unethical. You do not contend in your petition, however, that there are any such safety concerns in the current case that would make an in vivo bioequivalence study in healthy volunteers unethical, nor are we aware of any.

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[10] One article described two studies comparing PK after administration of 500-mg mesalamine rectal suppositories in patients and healthy subjects. Both studies showed higher systemic exposure in the ulcerative colitis patients than in healthy subjects after single-dose administration. Aumais G, Lefebvre M, Tremblay C, Bitton A, Martin F, Giard A, Madi M, Spénard J. Rectal tissue, plasma and urine concentrations of mesalazine after single and multiple administrations of 500 mg suppositories to healthy volunteers and ulcerative proctitis patients. Aliment Pharmacol Ther. 2003 Jan;17(1):93-7.

However, another study that compared PK parameters after single-dose oral administration of a mesalamine product in patients and healthy subjects did not show significant difference between the two populations. Gionchetti P, Campieri M, Belluzzi A, Boschi S, Brignola C, Miglioli M, Barbara L. Bioavailability of single and multiple doses of a new oral formulation of 5-ASA in patients with inflammatory bowel disease and healthy volunteers. Aliment Pharmacol Ther. 1994 Oct;8(5):535-40.

[11] The simulation assumed that the GI tract in ulcerative colitis patients is more permeable than in healthy subjects.

[12] You do not address pH in your arguments requesting that bioequivalence testing be conducted in patients with ulcerative colitis in remission instead of healthy subjects. However, to the extent your concern is that the pH profiles of the GI tracts of healthy subjects and patients with ulcerative colitis in remission may systematically differ as a result of differences in colonic mucosa caused by ulcerative colitis, and that a test product that behaves similarly to Apriso in GI tracts with pH profiles associated with healthy subjects may not behave similarly in GI tracts with pH profiles associated with diseased subjects, we note that any such concern should be adequately addressed by the dissolution testing component of the recommended studies. That is, the test product must have comparable dissolution profiles to Apriso at various relevant pH levels for the products to be considered bioequivalent.

Further, the pharmacokinetics of mesalamine are highly variable as a general matter, and we believe using patients with ulcerative colitis in remission as the study population will add another layer of variability due to diseased mucosal surfaces associated with ulcerative colitis, which will make the evaluation of the PK data more difficult and sometimes not conclusive with respect to determining whether bioequivalence has been demonstrated.[13] Because of the high variability, it is likely that a large number of patients would be needed to meet the bioequivalence criteria in patients and the reference scaled approach could not be used because of the parallel design. As noted previously, we do not expect that testing in diseased patients would reveal significant formulation performance differences that would be missed by testing in healthy patients.

For the foregoing reasons, we do not agree that a BE study should be conducted in ulcerative colitis patients in remission rather than healthy subjects.

B. Metabolite N-Ac-5-ASA

The Apriso Draft Guidance does not currently recommend that any measurements be taken of the mesalamine metabolite N-acetyl 5-aminosalicylic acid (N-Ac-5-ASA). You contend, however, that measurements of N-Ac-5-ASA should be analyzed and that bioequivalence testing would provide an incomplete picture without this information. Specifically, you request that FDA require that PK parameters be computed using plasma measurements of N-Ac-5-ASA (Petition at 1 and 27) and that FDA require measurement of the rate of N-Ac-5-ASA formation detected in the soluble fraction of fecal samples from the PK study subjects to establish bioequivalence for any ANDA that lists Apriso as the RLD (Petition at 2, 27).

We disagree that assessment of mesalamine's metabolite, N-Ac-5-ASA, should be a requirement for PK bioequivalence studies of ANDAs that list Apriso as the reference listed drug. We first address your requests regarding requiring measurements of N-Ac-5-ASA for bioequivalence determinations generally. We then address more specifically the particular types of measurements you have requested of this metabolite.

As a general matter, the Apriso Draft Guidance recommends measurements of mesalamine and not N-Ac-5-ASA for the in vivo fasting and fed bioequivalence studies because N-Ac-5-ASA is a secondary metabolite formed from the parent drug mesalamine, and measurement of mesalamine is expected to be more sensitive to changes in formulation performance than N-Ac-5-ASA. This is consistent with our recommendations in FDA's guidance for industry on *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General*

[13] PK parameters both in patients with ulcerative colitis and in healthy subjects are highly variable, and the variability is known to be much greater in patients with ulcerative colitis than in healthy subjects. In patients, much of the increased variability is related to both inter- and intrapatient variability in the disease state. Therefore, FDA is concerned that conducting a crossover bioequivalence study in patients could introduce a disease progression factor into the study and complicate the interpretation of the results. Further, conducting a PK study in patients requires a parallel design, thus adding an additional confounding factor to interpretation of equivalence results.

Considerations (March 2003) (BA/BE Guidance),[14] which generally recommends that bioequivalence studies measure only the parent drug. The basis for this recommendation is that the "concentration-time profile of the parent drug is more sensitive to changes in formulation performance than a metabolite, which is more reflective of metabolite formation, distribution, and elimination."[15] The BA/BE Guidance (p. 18) describes the following two situations when this general recommendation (i.e., measuring the parent drug only) does not apply:

- Measuring a metabolite may be preferred when the parent drug levels are too low to allow reliable analytical measurement in blood, plasma, or serum for an adequate length of time. In such cases, the metabolite data should be subject to a confidence interval approach for the bioequivalence demonstration.

- Measuring a metabolite may be preferred when a metabolite may be formed as a result of gut wall or other presystemic metabolism and the metabolite contributes meaningfully to safety and/or efficacy. In this instance, the metabolite should be measured in addition to the parent drug, but data regarding the metabolite are only used to provide supportive evidence of comparable therapeutic outcome; the metabolite data *should not* be subject to a confidence interval approach to demonstrate bioequivalence.

We do not believe, based on the evidence before us, that either of these two exceptions applies here. You do not argue that the first situation applies here (i.e., that N-Ac-5-ASA should be measured because mesalamine levels are too low to allow reliable analytical measurement in blood, plasma, or serum for an adequate length of time). Your claim that the concentrations of mesalamine and its metabolite exist in an equilibrium in the gut and it is the concentrations of both of these in equilibrium in the ileo-cecal junction and colon that are responsible for the therapeutic effect of Apriso could be considered an argument that the second exception described above applies here. However, we are not persuaded by this claim and address it more particularly in section II.B.1 below. We also note that you concede that N-Ac-5-ASA is not considered to have significant pharmacologic activity (Petition at 7).

The evidence before FDA indicates the major metabolite, N-Ac-5-ASA, is pharmacologically inactive and therefore does not contribute meaningfully to safety and/or efficacy, while it is the mesalamine that interacts with the diseased mucosal surface and generates pharmacological effects. Consequently, consistent with the BA/BE Guidance, we would not recommend measurement of N-Ac-5-ASA.

1. Plasma Concentrations of Metabolite N-Ac-5-ASA

[14] Available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070124.pdf.

[15] BA/BE Guidance at 18.

The Apriso Draft Guidance recommends PK measurements of mesalamine and not N-Ac-5-ASA for the in vivo fasting and fed bioequivalence studies. As mentioned above, you request that FDA require that PK parameters be computed using the plasma analytes mesalamine (5-ASA) and its metabolite N-acetyl 5-aminosalicylic acid (N-Ac-5-ASA) (Petition at 1 and 27). You contend that "the systemic [mesalamine] concentrations alone are not representative of the therapeutic concentrations at the primary site of pharmacological action in the colon" and that instead "5-ASA and N-Ac-5-ASA exist in equilibrium in the gut and this equilibrium is distinct from the systemic 5-ASA and N-Ac-5-ASA equilibrium" (petition at 7). You state that "[i]t is the concentrations of [mesalamine and its metabolite] N-Ac-5-ASA in equilibrium in the ileo-cecal junction and colon that [are] responsible for the therapeutic effect of Apriso in ulcerative colitis" (Petition at 7). You also contend that "some of the N-Ac-5-ASA may convert back into 5-ASA by deacetylation" (Petition at 7). You further argue that the active pharmaceutical ingredient (API)/metabolite equilibrium varies as a function of the area of distribution of the formulation granules and that measuring only the API does not reflect the true rate of drug delivery to the colon (See Petition at 27). Finally, you argue that "the criteria set forth in the [Apriso] Draft Guidance appear to characterize the *initial* rate of mesalamine release" (Petition at 17, emphasis added) but that "formation of N-Ac-5-ASA – and by extension, its plasma pharmacokinetics, are representative of the interaction between the Apriso formulation granules and the colonic epithelial cells, and therefore provide an essential indicator of the extended phase of mesalamine release *after* initial activation at pH 6.0" (Petition at 7, emphasis added).

We disagree that plasma concentrations of mesalamine's metabolite, N-Ac-5-ASA, should be required in PK bioequivalence studies. Your contention — that it is the concentrations of mesalamine and N-Ac-5-ASA in equilibrium in the ileo-cecal junction and colon that are responsible for the therapeutic effect of Apriso in ulcerative colitis — is contingent on your claim that some of the N-Ac-5-ASA may convert back into mesalamine by deacetylation (Petition at 7). However, you do not provide evidence to support your claim that some of the metabolite may convert back into mesalamine by deacetylation, and we are not aware of any support for this claim in the published scientific literature. In fact, the scientific literature indicates that the acetylation of 5-ASA is irreversible and, therefore, none of the metabolite is converted back into mesalamine.[16] Accordingly, to our knowledge there is no reason to believe that equilibrium exists between the API mesalamine and its metabolite N-Ac-5-ASA in the ileo-cecal junction and colon and that such equilibrium is responsible for the therapeutic effect of Apriso in ulcerative colitis.

We also disagree with your suggestion that measuring mesalamine concentrations in the in vivo PK studies as is currently recommended in the Apriso Draft Guidance would characterize only the initial rate of mesalamine release and would not adequately capture the extended phase of mesalamine release the way you contend measuring the metabolite concentrations would. As you point out, FDA previously considered whether it is necessary to measure plasma N-Ac-5-

[16] E.g., Meese CO, Fischer C, Klotz U. Is N-acetylation of 5-aminosalicylic acid reversible in man? Br J Clin Pharmacol. 1984 Oct;18(4):612-5.

ASA concentrations in our Mesalamine Joint Response, and we determined it was not necessary. We disagree with your argument that the rationale FDA applied in that response is not applicable to Apriso (Petition at 9). We explained in our Mesalamine Joint Response that N-Ac-5-ASA concentrations are expected to be highly correlated with mesalamine concentrations; therefore, FDA determined there is no need to separately measure and report N-Ac-5-ASA plasma concentrations.[17] You contend that the data included in Tables II and III and Figure 3 of your petition clearly demonstrate this correlation is not applicable to the case of Apriso (Petition at 9). You also claim these data suggest that plasma PK is sensitive to and reflects the initial dissolution kinetics of the RLD but reveal very little about the relative kinetics of the extended-release phase of the Apriso formulation (Petition at 9). We disagree. Indeed, we find that the data you supply in your petition as well as other data available to FDA regarding mesalamine drug products indicate that (1) there is a correlation between the concentration of mesalamine and its metabolite, and (2) bioequivalence metrics comparing the PK parameters of the metabolite, N-Ac-5-ASA, are less discriminating of formulation differences than comparing those of mesalamine. In particular, Figure 3 appears to support our assessment that bioequivalence metrics comparing the PK parameters of the parent compound, 5-ASA, are more discriminating of formulation differences than bioequivalence metrics comparing the PK parameters of the metabolite, N-Ac-5-ASA. Figure 3 plots the ratios of the mean values of the data presented in Tables II and III, and the data demonstrate that the measurements of the parent drug always show larger differences than the measurements of the metabolite. Therefore, we believe that for both the initial and extended-release phases, comparing the PK profiles of the parent drug as recommended by the Apriso Draft Guidance is more discriminating of formulation differences between a test product and Apriso than is comparing the PK profiles of the metabolite.

As you note, we recommended bioequivalence testing based on concentrations of both mesalamine and its metabolite, N-Ac-5-ASA, during our discussion with the sponsor in 2009 at a pre-IND meeting. You contend that FDA's advice to Salix in 2009 "recognized the necessity to compare the residence and distribution of two granule formulations in the GI tract as additional criteria for the determination of bioequivalence" (Petition at 25).[18] At that time, however, FDA was still reviewing the PK approach to establishing bioequivalence for mesalamine. FDA

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[17] See Mesalamine Joint Response at 13-14 and Colazal Petition Response at 24. As we explained in the Mesalamine Joint Response at note 36, we based this conclusion on currently available evidence. However, if evidence becomes available suggesting that N-Ac-5-ASA "contributes meaningfully to safety and/or efficacy" (BA/BE Guidance at 18), we may require applicants to measure and report plasma N-Ac-5-ASA concentrations as well as plasma mesalamine concentrations.

[18] According to the Petition, the minutes from that 2009 pre-IND meeting read in pertinent part:

> It is suggested that you use T_{max}, mean absorption time, and mean residence time in the intestine to estimate the percentage of dose released for absorption in the colon for the studied and approved products each, and compare such data between the two products. Such comparison would be helpful for understanding how the studied product behaves in the intestine as compared to the approved product. (Petition at p. 25)

subsequently determined that bioequivalence studies with clinical endpoints are less sensitive than bioequivalence studies with PK endpoints and recommended that applicants show bioequivalence to Apriso through a combination of PK studies and in vitro dissolution testing.[19]

2. Rate of N-Ac-5-ASA Formation in Fecal Samples

The Apriso Draft Guidance does not currently recommend that applicants measure the rate of N-Ac-5-ASA formation detected in the soluble fraction of fecal samples to establish bioequivalence for any ANDA that lists Apriso as the RLD. However, you request that FDA require such a determination be derived from the PK study subjects (Petition at 2, 27).[20] You contend that Figure 10 (Petition at 22) shows that although the sum of mesalamine plus N-Ac-5-ASA recovered from the soluble fraction of fecal samples throughout the 4 days of treatment of subjects in study MPPK1001 from Apriso's NDA with either 800 mg of Asacol (mesalamine delayed-release tablets, 2 x 400 mg) twice a day (BID) or 800 mg of Apriso granules BID is not markedly different, the percentage of the dose which has been converted to N-Ac-5-ASA is significantly greater when subjects are dosed with the granule rather than the tablet formulation (Petition at 23). You also contend that it is clearly evident from Figure 11 (Petition at 23-24) that there is a strong correlation between the total mesalamine and N-Ac-5-ASA concentrations collected from fecal samples in this study (Petition at 23). You state that this relationship is specific to each formula; that the calculated rates of generation of N-Ac-5-ASA for the two products imply that the surface area of the colon on which the mesalamine is distributed by the granule formulation (Apriso) is approximately double the surface area exposed to the dose provided by the tablet formulation (Asacol); and that these formulations of Asacol and Apriso cannot be considered bioequivalent because they do not distribute the active drug over the same surface area of the target organ as one another (Petition at 23). Finally, you claim that "[w]ithout considering a metric that directly compares formulation performance in the colon, [the PK

[19] See Mesalamine Joint Response at 11 (observing "[h]aving analyzed the available clinical efficacy data for orally administered modified release mesalamine products (including data published in the scientific literature and data included in the approved drug labeling), [FDA] conclude[d] that comparative clinical endpoint bioequivalence studies would be less sensitive, accurate, and reproducible than PK studies"); Mesalamine Joint Petition for Reconsideration Response at 3; and the Apriso Draft Guidance.

[20] One possible interpretation of your request that FDA "require a determination of the rate of N-Ac-5-ASA formation detected in the soluble fraction of fecal samples derived from subjects participating *in the above pharmacokinetic studies*" as it is written in the Petition on pages 2 and 27 (emphasis added) is that this fourth and last request is contingent on FDA granting the three preceding requests in your petition regarding the PK studies. However, as described in this response, we are denying your other requests pertaining to those PK studies: that FDA (1) require bioequivalence to be established under fasted and fed conditions in patients with ulcerative colitis in remission; (2) require PK parameters to be computed using plasma analytes mesalamine and N-Ac-5-ASA; and (3) require bioequivalence to be established on PK parameters for the additional parameters. Therefore, your request that FDA require a determination of the rate of N-Ac-5-ASA formation detected in the soluble fraction of fecal samples derived from subjects participating in the PK studies with the aspects you described in (1), (2), and (3) above is moot. However, we address here the alternative that FDA require a determination of the rate of N-Ac-5-ASA formation detected in fecal samples of those subject participating the PK studies currently recommended in the Apriso Draft Guidance.

studies recommend in] the [Apriso] Draft Guidance lack[] the robustness required to unequivocally confirm bioequivalence" (Petition at 23).

We do not agree that the rate of N-Ac-5-ASA formation detected in the soluble fraction of fecal samples should be measured for the purposes of a bioequivalence assessment for all ANDAs that list Apriso as the RLD.

We agree that these two treatments of Asacol and Apriso cannot be considered bioequivalent, but do not believe that a measurement of the rate of N-Ac-5-ASA formation detected in the soluble fraction of fecal samples is necessary to reach this conclusion. Based on data available to us, the example from Study MPPK 1001 used to support your argument requesting measurement of fecal N-Ac-5-ASA (the treatment with 800 mg of Asacol (mesalamine delayed-release tablets, 2 x 400 mg tablets) BID for 4 days compared to 800 mg of Apriso granules BID for 4 days) would fail to demonstrate bioequivalence based on the criteria in the Apriso Draft Guidance. Specifically, the data before the Agency pertain to dissolution profiles of Asacol and Apriso in media with a variety of different pH values ranging from 6.0 to 7.5 after 2 hours of pretreatment in 0.1N HCl as well as data from various PK studies of Apriso and Asacol under fasting conditions. For example, comparisons of the plasma mesalamine AUC_{0-3} from various PK studies of Apriso and Asacol under fasting conditions clearly show that Asacol and Apriso will not demonstrate bioequivalence to one another under the criteria in the Apriso Draft Guidance. Therefore, the data demonstrate that the criteria in the Apriso Draft Guidance would be sufficiently robust to detect a significant formulation performance difference between Asacol and Apriso (the two formulations included in your selected example). Further, you do not provide evidence to show that the requested measurement of fecal N-Ac-5-ASA adds additional information to demonstrate bioequivalence and that a significant formulation performance difference would be missed if we did not seek this information. We also do not have any reason to believe this information is necessary.

Accordingly, we deny your request that FDA require a determination of the rate of N-Ac-5-ASA formation detected in the soluble fraction of fecal samples derived from subjects participating in PK studies for the purposes of a bioequivalence assessment for all ANDAs that rely upon Apriso as the RLD.

C. Partial AUC Time Intervals

The Apriso Draft Guidance recommends that the following PK parameters be evaluated to show that the test and reference products are bioequivalent: AUC_{0-3}, AUC_{3-t}, AUC_{0-t}, and C_{max}.[21] You state that FDA should require bioequivalence be established on plasma PK parameters computed on plasma analytes 5-ASA and N-Ac-5-ASA for the following parameters: AUC_{0-3}, AUC_{3-t}, AUC_{8-t}, AUC_t, C_{max}, T_{max} and AUC_{inf}; thus you propose that AUC_{8-t}, AUC_{inf}, and T_{max} should be

[21] See Apriso Draft Guidance. You specifically request these parameters be required for both mesalamine and N-Ac-5-ASA, however as discussed above, FDA does not agree that requiring any PK measurements of the metabolite N-Ac-5-ASA would be appropriate for ANDAs relying upon Apriso as the RLD.

added as required parameters in addition to the other PK parameters currently included in the Apriso Draft Guidance (Petition at 1-2, 27).[22]

We disagree for the reasons explained below.

You argue that a partial AUC_{8-t} is necessary to detect the differences in in vivo mesalamine release related to the extended-release mechanism of the RLD formulation. To support the argument for requiring the partial AUC_{8-t} parameter, you provide graphs of comparative dissolution tests among delayed-release tablets and mesalamine granules (Petition at 5, Figure 1). You also provide dissolution and PK parameters including a partial AUC_{8-24} for three granule formulations with different initial dissolution rates (Petition at 6, Figure 2 and Table II,[23] and at 7, Table III). FDA finds these graphs unpersuasive. For example, we note Table II indicates that AUC_{8-24} failed to detect the formulation difference. However, the same table also shows that other parameters currently listed in the Apriso Draft Guidance can adequately discriminate those formulations. Although you argue that a partial AUC_{8-t} is necessary to detect the differences in in vivo mesalamine release related to the extended-release mechanism of the RLD formulation, you do not provide a comparison between the RLD (formulated as delayed- and extended-release granules) and other delayed-release mesalamine granules to test the utility of a partial AUC_{8-t} for revealing the differences due to the extended-release mechanism (Petition at 6, Table II).

We evaluated PK parameters after oral administration of mesalamine products under fasting conditions. Among five mesalamine oral products (Apriso, Asacol, Asacol HD, Lialda, and Pentasa), Pentasa (mesalamine extended-release capsules) and Apriso (mesalamine extended-release capsules) have similar PK profiles. Analyses were performed to discriminate between these two products. Our analysis found that adding AUC_{8-t} as an additional metric to the combination of AUC_{0-3}, AUC_{3-t}, AUC_{0-t}, and C_{max} (the PK parameters currently recommended by the Apriso Draft Guidance) does not improve model performance in terms of discriminating Pentasa and Apriso. We also performed physiologically based modeling and simulation for Apriso under fasting conditions, which demonstrate that AUC_{3-t} better correlates with colon exposure than AUC_{8-t}.

Therefore, based on the evidence you provide and our independent analyses, we do not agree that adding AUC_{8-t} as an additional metric would potentially reveal significant formulation performance differences that could be missed by the currently recommended PK parameters.

We also do not agree that adding T_{max} as a metric would potentially reveal significant formulation performance differences that could be missed by the currently recommended PK parameters. When we review ANDA applicants' bioequivalence studies of mesalamine, we examine T_{max} values to see if there are differences that are potentially clinically significant. We

[22] Because you raise no objection to the use of AUC_{0-3}, AUC_{3-t}, AUC_t or C_{max}, this response does not address the appropriateness of these PK parameters.

[23] You state that the two formulations in Table II are dissimilar to the RLD but fail to provide details on the nature of the dissimilarity.

do not conduct a statistical comparison of T_{max} because appropriate statistical methods for T_{max} comparison have not been developed. The partial AUC measures recommended in the Apriso Draft Guidance provide a more sensitive measure of product comparison than T_{max}. As shown in Table II in the petition, even when mean T_{max} values were similar for different formulations, the metrics listed in the Apriso Draft Guidance (e.g., AUC_{0-3}, and AUC_{3-t}) reflected the difference in formulations.

Finally, we do not agree that AUC_{inf} should be included as an additional metric in the Apriso Draft Guidance. The addition of AUC_{inf} is not recommended because for mesalamine oral products, the terminal phase represents continuing absorption rather than elimination,[24] and therefore measuring the apparent k_{elim} (elimination rate constant) and using it to calculate AUC_{inf} does not lead to an accurate estimate of the total exposure. A better estimate of exposure is obtained by sampling over a sufficient time period to encompass the drug absorption.

Consequently, we deny your request that we require AUC_{8-t}, AUC_{inf}, and T_{max} as additional metrics for the purposes of establishing bioequivalence for any ANDA that relies upon Apriso as the RLD.

D. Alleged Deficiencies of the Apriso Draft Guidance

You concede that the Apriso Draft Guidance appears to adequately profile the in vitro dissolution characteristics of the Apriso formulation but contend that with respect to the in vivo PK profiling, the Apriso Draft Guidance suffers from the following deficiencies:

1. At least 50 percent of the mesalamine dose remains in the formulation at time points when there is little meaningful additional signal detected in plasma.
2. There is no meaningful way to compare the transit of the remaining dose even though there is ample evidence that transit times (a) can diverge in the colon after appearing the same in the small intestine (i.e., where the plasma measurements are made), and (b) are specific to formulation chemical composition, particle size, and hydrodynamic properties.
3. There is no requirement to confirm that the dose remaining in the formulation after initiation of dissolution is distributed to the colon in a bioequivalent manner to that of

[24] Observations from various PK studies of mesalamine prove the appearance of mesalamine in the plasma is caused by its release from the formulation in the GI tract. The half-life of 5-ASA is short after intravenous (i.v.) administration. The mean elimination half-life of 5-ASA was 39 min. (range 28-63), 34 min. (range 22-47), and 42±5min. following i.v. administration of 100 mg, 250 mg, and 500 mg of 5-ASA, respectively. Bondesen S, Hegnhoj J, Larsen F, Hansen SH, Hansen CP, and Rasmussen SN. Pharmacokinetics of 5-aminosalicylic acid in man following administration of intravenous bolus and per os slow-release formulation. Dig Dis Sci. 1991 Dec; 36(12):1735-40; Myers B, Evans DN, Rhodes J, Evans BK, Hughes BR, Lee MG, Richens A, and Richards D. Metabolism and urinary excretion of 5-amino salicylic acid in healthy volunteers when given intravenously or released for absorption at different sites in the gastrointestinal tract. Gut. 1987 February; 28(2):196-200. The observation that the apparent half-life of plasma mesalamine was 9-10 hours after oral administration of 1500 mg of Apriso proves that mesalamine is continuously absorbed in the terminal phase.

> the RLD, even though there is evidence to show that such distribution is formulation dependent even when comparable amounts of active drug are delivered to the colon.

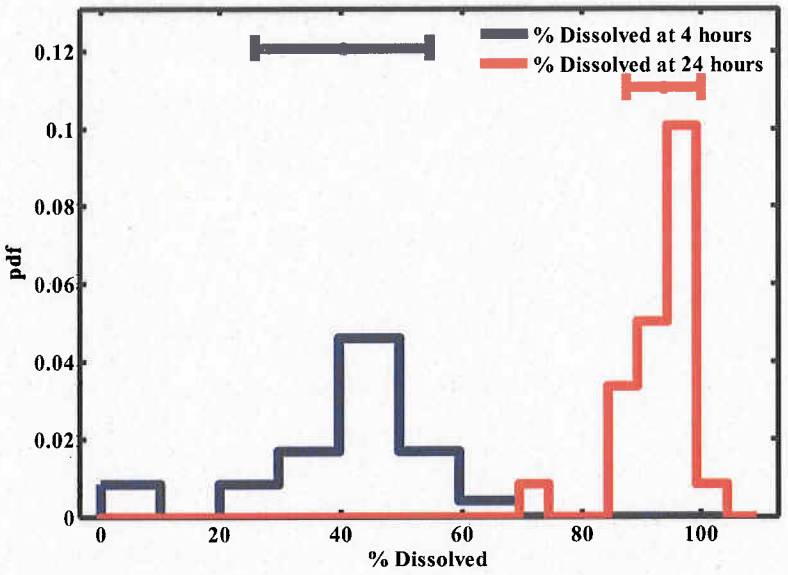
(Petition at 26).

We address each of these alleged deficiencies in turn below.

FDA does not agree with your claim that at least 50 percent of the mesalamine dose remains in the formulation at time points when there is little meaningful additional signal detected in plasma. First, the percentage remaining in the formulation is irrelevant to the determination of bioequivalence. Only mesalamine that is released from the formulation is pharmacologically active, and we know that when mesalamine is released from the formulation, it will become detectable in plasma.[25] Therefore, if two formulations differ in the percentage of mesalamine retained in the formulation, this will be readily apparent upon examination of the plasma concentration time curves. In addition, our physiologically based absorption model predicts that the average percentage dissolved in vivo is 40.4 percent after 4 hours of dosing and 93.7 percent after 24 hours of dosing. Figure 1 below shows the distribution of simulated percentage dissolved in vivo after 4 hours and 24 hours of dosing for each subject. The simulation is consistent with your observation that the plasma profile to T_{max} (about 4 hours) corresponds to a mean of about 52 percent of the dose of mesalamine (Petition 12). However, mesalamine concentrations remain detectable until at least 24 hours after dosing, by which time almost all of the mesalamine is released from the product and can be accounted for in the pharmacokinetic profile. Accordingly, your first claim that at least 50 percent of the mesalamine dose remains in the formulation at time points when there is little meaningful additional signal detected in plasma is not correct because plasma concentrations can be detected over a period of time that covers much more of the release and this ensures that any difference between brand and generic drug products in the amount of mesalamine retained in the formulation will be detected in the bioequivalence study.

[25] See note 24.

Figure 1: Distribution of simulated percentage dissolved in vivo after 4 hours and 24 hours of dosing.



We also disagree with your second concern — that there is no meaningful way to compare the transit of the remaining dose even though there is ample evidence that transit times (a) can diverge in the colon after appearing the same in the small intestine (i.e., where the plasma measurements are made), and (b) are specific to formulation chemical composition, particle size and hydrodynamic properties (Petition at 26). Because the PK studies can measure mesalamine release over at least 24 hours (as described above), any difference in formulation transit due to differences in formulation design can be detected. The physiologically based absorption modeling and simulation for Apriso under fasting conditions that we describe earlier in this response demonstrate that $AUC_{3\text{-}t}$ is a reasonable metric to detect the difference in colon transit time caused by different dosage forms if such an effect exists.[26] Similarity in formulation performance is also ensured by the Apriso Draft Guidance recommendation that the test and reference product demonstrate similar in vitro release in various pH conditions.

[26] Specifically, in this simulation, caecum and colon transit time was varied over a range and compared to baseline transit time, and PK parameters for the baseline and varied transit times were compared. This demonstrated that plasma AUC_t and $AUC_{3\text{-}t}$ are the most sensitive PK parameters to the change of caecum transit time. When the colon transit time is low (less than 24 hours), colon AUC_t is the most sensitive parameter and plasma $AUC_{3\text{-}t}$ is the second-most sensitive parameter, but both colon AUC_t and plasma $AUC_{3\text{-}t}$ have the ability to detect whether different formulations are associated with a difference in transit time.

Finally, we do not agree with your third concern that there is no requirement to confirm that the dose remaining in the formulation after initiation of dissolution is distributed to the colon in a bioequivalent manner to that of the RLD, even though there is evidence to show that such distribution is formulation dependent even when comparable amounts of active drug are delivered to the colon (Petition at 26). Mesalamine is rapidly absorbed throughout the GI tract; therefore, the plasma profile of mesalamine serves as a surrogate of local availability of mesalamine in all regions of the GI tract.[27] AUC_{0-3} represents mesalamine absorption through the small intestine, and AUC_{3-t} corresponds to the absorption through the lower small intestine, caecum, and colon.[28] Together the recommended PK parameters will discriminate whether the dose remaining in the formulation of an ANDA after initiation of dissolution is distributed to the colon in a bioequivalent manner to that of the RLD. Further, although you claim there is evidence to show that distribution of mesalamine to the colon is formulation dependent even when comparable amounts of active drug are delivered to the colon, you do not address that the studies recommended in the Apriso Draft Guidance will discriminate between the formulation comparisons you cite in the petition.[29]

E. Approval of ANDAs and Resolution of Issues Raised in the Petition

In the Petition, you ask that FDA not approve any ANDAs for mesalamine without resolving the issues raised in this citizen petition (Petition at 2).

We deny your request because we are not required to resolve the issues and respond to your petition before approving any ANDAs. Section 505(q) of the FD&C Act, as amended by section 1135 of the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA), describes the limited conditions under which FDA may delay approval of a pending ANDA. Section 505(q)(1)(A) of the FD&C Act, as amended by section 1135 of FDASIA, states —

> The Secretary shall not delay approval of a pending application submitted under subsection (b)(2) [an NDA] or (j) [an ANDA] of this section ... because of any request to take any form of action relating to the application, either before or during consideration

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[27] As suggested by the same physiologically based absorption model, the mean difference was 9.2 percent between the simulated percentage of Apriso absorbed and simulated percentage of Apriso dissolved in vivo at any time for all 24 simulated subjects. Therefore, mesalamine is rapidly absorbed and the PK profile reflects mesalamine's local availability.

[28] Most studies reported the mean small intestinal transit time of various dosage forms to be about 3-4 hours. See Yuen KH. The transit of dosage forms through the small intestine. Int J Pharm. 2010 Aug 16;395(1-2):9-16.

[29] In particular, Test C and Test D in Table II of the Petition will not be bioequivalent to the reference drug in that table based on AUC_{0-3} (Petition at 7); Salofalk granules (500 mg, European brand of the RLD Apriso) and Salofalk tablets (500 mg, mesalamine delayed-release tablets) (Petition at 10) will not be bioequivalent based on dissolution testing and PK testing (See table IV, Petition at 11); and, as discussed above in section II.B of this response, 800 mg of Asacol (mesalamine delayed release tablets, 2 x 400 mg tablets) BID for 4 days compared to 800 mg of Apriso granules BID for 4 days (the example you referenced from Study MPPK 1001) will not demonstrate bioequivalence to Apriso based on dissolution testing and AUC_{0-3}.

> of the request, unless – (i) the request is in writing and is a petition submitted to the Secretary pursuant to [21 CFR] section 10.30 or 10.35; and (ii) the Secretary determines, upon reviewing the petition, that a delay is necessary to protect the public health.

Therefore, under section 505(q) of the FD&C Act, we may only delay an ANDA if we determine that a delay is necessary to protect the public health. As explained in FDA's guidance for industry entitled *Citizen Petitions and Petitions for Stay of Action Subject to Section 505(q) of the Federal Food, Drug, and Cosmetic Act*, we determine if a delay of approval is necessary to protect the public health based on our preliminary evaluation of the issues raised in the petition. For additional information regarding how FDA will determine if a petition would delay approval of an ANDA, see pages 7-9 of this guidance on petitions subject to section 505(q) of the FD&C Act.[30]

III. CONCLUSION

For the reasons explained above, your petition is denied.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

[30] A copy of the guidance is available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079353.pdf Please note that this guidance was issued before FDASIA was passed. Among other things, section 1135 of FDASIA reduced the timeframe from 180 to 150 days for the Secretary to take final Agency action on a petition subject to section 505(q) of the FD&C Act.