DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

MAR 12 2014

Guy Rousseau, Ph.D.
Executive Director, Regulatory Affairs
Aptalis Pharma US, Inc.
100 Somerset Corporate Boulevard
Bridgewater, NJ 08807

Re: Docket No. FDA-2013-P-1287

Dear Dr. Rousseau:

This letter responds to Aptalis Pharma US, Inc.'s (Aptalis's) citizen petition dated October 15, 2013 (Petition), and supplemental petition dated November 25, 2013 (Supplement). In the Petition, you request that the Food and Drug Administration (FDA or Agency) refuse to receive or approve any abbreviated new drug application (ANDA) for a generic[1] version of Canasa (mesalamine) rectal suppositories, 500 milligrams (mg) and 1000 mg, unless:

- Bioequivalence to Canasa is demonstrated in a clinical endpoint study, and
- Assessment of critical quality attributes is performed (demonstration of qualitative (Q1), quantitative (Q2), and structural (Q3) sameness), including dissolution testing using United States Pharmacopeia (USP) apparatus that is more discriminating for in vivo performance and in vivo assessment of spreadability and irritation potential.

You also request that FDA withdraw its current bioequivalence guidance on mesalamine rectal suppositories and publish a new guidance for this product that includes a bioequivalence study with clinical endpoints. You also request that FDA hold in abeyance any final approval of an ANDA for a mesalamine rectal suppository not based on a bioequivalence study with clinical endpoints until ongoing FDA research studies of mesalamine bioequivalence methodologies have been completed and the results have been reviewed by the Pharmaceutical Science and Clinical Pharmacology Advisory Committee. In the Supplement, you provide a clinical study report for an investigation of MAX-002, a new formulation of Canasa that you reference in the Petition.[2]

[1] The term *generic* refers to a drug product for which approval is sought in an ANDA submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

[2] You request that FDA not make the contents of this report public because it contains proprietary information that you state is exempt from disclosure under Exemption 4 of the Freedom of Information Act.

As explained below, the requests in your Petition are denied.

I. BACKGROUND

A. Canasa

Canasa (mesalamine) rectal suppositories (new drug application (NDA) 21-252), 500-mg and 1000-mg strengths, were approved by FDA in January 2001 and November 2004, respectively. The 500-mg strength is no longer marketed. Canasa is indicated for the treatment of mild to moderately active ulcerative proctitis.

Ulcerative proctitis is an idiopathic mucosal inflammatory bowel disease of the rectum. Mesalamine is an anti-inflammatory agent. Although its mechanism of action is not fully understood, it appears to be topical rather than systemic.[3] Thus, mesalamine must be delivered to the affected region of the gastrointestinal tract to effectively treat ulcerative proctitis. Multiple strategies have been developed for mesalamine to target the lower gastrointestinal tract, including prodrugs,[4] extended-release capsules, delayed-release tablets, rectal enemas, and rectal suppositories. The use of rectal suppositories for ulcerative proctitis permits the mesalamine to be delivered directly to the site of intended action. Mesalamine administered as a rectal suppository distributes in rectal tissue to some extent and is variably absorbed.[5]

B. Statutory and Regulatory Standards

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 Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 355(j)), which established the ANDA approval process. To obtain approval, an ANDA applicant is not required to submit clinical studies to establish the safety and effectiveness of the proposed generic drug product. Instead, an ANDA applicant relies on the Agency's previous finding that the reference listed drug (RLD) is safe and effective.[6] To rely on FDA's previous finding of safety and effectiveness, an ANDA applicant must demonstrate, among other things, that

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[3] See the *Mechanism of Action* subsection of the CLINICAL PHARMACOLOGY section of CANASA's labeling (Revised February 2013).

[4] A *prodrug* is an inactive substance that is converted to a drug within the body by the action of an enzyme or other chemical.

[5] See the *Pharmacokinetics* subsection of the CLINICAL PHARMACOLOGY section of CANASA's labeling (Revised February 2013).

[6] A *reference listed drug* (RLD) is "the listed [i.e., approved] drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application" (21 CFR 314.3). RLDs are identified in FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations*, generally known as "the Orange Book."

the proposed generic drug product is bioequivalent to the RLD (section 505(j)(2)(A)(iv) of the FD&C Act).[7] In addition, with limited exceptions, an ANDA must contain sufficient information to show that the proposed generic drug product has the same active ingredient(s), previously approved conditions of use, route of administration, dosage form, strength, and (with certain permissible differences) labeling as the RLD (section 505(j)(2)(A) and (j)(4) of the FD&C Act). The Agency must approve the ANDA unless, among other things, the ANDA applicant has provided insufficient evidence of the foregoing, or if the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are inadequate to assure and preserve its identity, strength, quality, and purity (section 505(j)(4) of the FD&C Act).

FDA regulations at 21 CFR 314.94(a)(7) set forth the bioequivalence requirements for an ANDA, and 21 CFR part 320 sets forth procedures for determining bioequivalence. The regulations discuss the various methods of determining bioequivalence in descending order of accuracy, sensitivity, and reproducibility. These include pharmacokinetic studies, pharmacodynamic studies, comparative clinical trials, and in vitro studies (§ 320.24(b)). In addition, section 320.24(b)(6) of the regulations states that an applicant may use "[a]ny other approach deemed adequate by FDA to . . . establish bioequivalence."

If a drug is intended to act locally rather than systemically, pharmacokinetic studies 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 may lack evidence of a correlation between these systemic concentrations and concentrations at the site of drug action. For some of these products, the Agency can review data from pharmacodynamic effect studies to assess bioequivalence. For others, however, no pharmacodynamic endpoints can be readily measured. In these cases, the Agency relies, if it can, on other kinds of data from appropriately designed comparative clinical trials or, in appropriate cases, from in vitro studies, to assess bioequivalence. Applying the methodological hierarchy described above, FDA has issued guidance to industry stating that comparative clinical studies are generally disfavored, but may be appropriate when other reliable studies are infeasible:

> Where there are no other means, well-controlled clinical trials in humans can be useful to provide supportive evidence of [bioavailability] or [bioequivalence]. However, we recommend that the use of comparative clinical trials as an

[7] Under the FD&C Act, "[a] drug shall be considered to be bioequivalent to a 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." See section 505(j)(8)(B)(i); see also implementing regulations at 21 CFR part 320.

Section 505(j)(8)(C) of the FD&C Act further provides: "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."

approach to demonstrate [bioequivalence] generally be considered insensitive and be avoided where possible.[8]

It is well accepted that FDA has considerable discretion in determining how the bioequivalence requirement is met. FDA's discretion need only be based on a "reasonable and scientifically supported criterion, whether [the Agency] chooses to do so on a case-by-case basis or through more general inferences about a category of drugs. . . ." (*Bristol-Myers Squibb Co. v. Shalala*, 923 F. Supp. 212, 218 (D.D.C. 1996) (quoting *Schering Corp. v. Sullivan*, 782 F. Supp. 645, 651 (D.D.C. 1992), vacated as moot sub nom, *Schering Corp. v. Shalala*, 995 F.2d 1103 (D.C. Cir. 1993))). The courts have expressly upheld FDA's regulatory implementation of the FD&C Act's bioequivalence requirements (see, e.g., *Schering Corp. v. FDA*, 51 F.3d 390, 399-400 (3d Cir. 1995); *Fisons Corp. v. Shalala*, 860 F. Supp. 859, 863-67 (D.D.C. 1994)).

C. Mesalamine Rectal Suppository Bioequivalence Guidance

In May 2007, FDA posted on its Web site a draft bioequivalence guidance on mesalamine rectal suppositories (2007 Mesalamine Suppository Draft Bioequivalence Guidance) to support ANDAs for this product. FDA recommended two in vivo studies to demonstrate bioequivalence of generic mesalamine rectal suppositories: (1) a bioequivalence study with clinical endpoints and (2) a fasting bioequivalence study with pharmacokinetic endpoints (the PK study).[9]

In 2010, FDA revised its bioequivalence recommendations for *oral formulations* of mesalamine to no longer recommend an in vivo bioequivalence study with clinical endpoints.[10] Instead, the Agency recommended that bioequivalence be shown using data from a PK study together with data from in vitro dissolution studies.[11] The change in

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[8] See FDA guidance for industry on *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations* (March 2003) (the BA and BE Guidance) at 9, available on the Internet at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[9] We recommended the PK study because it was considered the most accurate, sensitive, and reproducible approach for demonstration of bioequivalence for mesalamine rectal suppositories. However, the therapeutic effect of mesalamine rectal suppositories was thought to be mostly due to local rather than systemic mesalamine concentrations. Thus, we also recommended conduct of a bioequivalence study with clinical endpoints to detect any differences between the generic and RLD products at the site of action.

[10] See August 2010 Letter from Dr. Janet Woodcock, Director, Center for Drug Evaluation and Research, FDA, to Mr. Hara, Warner Chilcott Company, LLC and Dr. Jonas, Shire Pharmaceuticals, Inc., re: Docket Nos. FDA-2010-P-0111 and FDA-2008-P-0507 (Mesalamine Joint Response).

[11] As discussed in the Mesalamine Joint Response, FDA revised the bioequivalence recommendations for oral formulations of mesalamine because we determined that PK profiles can be analyzed over defined time intervals using partial AUC or other profile comparison tools (including but not limited to mean residence time and steady-state Cmax) to determine whether mesalamine from generic and RLD products is absorbed at the same rate and to the same extent at the colon and rectum. We concluded that if the PK profiles for these products are equivalent and if they have equivalent in vitro dissolution characteristics, drug availability at the site of action will be the same. We also analyzed available clinical efficacy data for oral mesalamine products and concluded that comparative clinical endpoint studies are less accurate, sensitive, and reproducible than PK studies.

bioequivalence recommendations for the oral mesalamine products prompted FDA to reconsider its bioequivalence recommendations for other mesalamine products.

Accordingly, in March 2013 FDA withdrew the 2007 Mesalamine Suppository Draft Bioequivalence Guidance and posted a revised draft bioequivalence guidance (the 2013 Mesalamine Suppository Draft Bioequivalence Guidance).[12] In this revised draft guidance, FDA recommends the following in vivo and in vitro studies to demonstrate bioequivalence of generic mesalamine rectal suppositories provided that the generic product is qualitatively (Q1) and quantitatively (Q2) the same as the RLD: (1) the PK study and (2) comparative in vitro studies (melting point, differential scanning calorimetry, density, and viscosity). For the PK study, FDA will permit use of a reference-scaled average bioequivalence approach for mesalamine if the applicant provides evidence of high variability in the bioequivalence parameters (i.e., within-subject variability $\geq$ 30 percent) for the RLD.[13] Finally, FDA no longer recommends a clinical endpoint bioequivalence study.[14]

II. DISCUSSION

You request that FDA refrain from approving ANDAs for a generic version of Canasa unless the following studies are conducted: (1) an in vivo bioequivalence study with clinical endpoints and (2) assessment of critical quality attributes (demonstration of Q1, Q2, and Q3 sameness), including dissolution testing using USP apparatus that is more discriminating for in vivo performance and in vivo assessment of spreadability and irritation potential. You also request that FDA withdraw the 2013 Mesalamine

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[12] Available on the Internet at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm088666.pdf. On August 2, 2013 (78 FR 46,965), FDA announced the availability of the 2013 Mesalamine Suppository Draft Bioequivalence Guidance. In this *Federal Register* notice, FDA noted that Axcan Scandipharm, Inc. (now Aptalis) had filed a citizen petition in July 2007 requesting that the Agency refuse to approve an ANDA for a mesalamine rectal suppository unless certain studies are conducted (Docket No. FDA-2007-P-0010, formerly 2007P-0302/CP1). In the notice, we stated that FDA was reviewing the issues raised in this petition, as well as supplemental information submitted to the docket for this petition, and would consider any comments on the 2013 Mesalamine Suppository Draft Bioequivalence Guidance before responding to the petition. We did not receive any comments on the 2013 Mesalamine Suppository Draft Bioequivalence Guidance other than your request for an extension of the comment period. On December 19, 2013, Aptalis withdrew its citizen petition of 2007 and supplement because the 2007 petition was effectively replaced by the petition to which this letter responds.

[13] In the reference-scaled average bioequivalence approach, an applicant includes a replicate administration of the RLD in the bioequivalence study. When the within-subject variability of the RLD is higher than 30 percent, the acceptable limits of the PK parameters of a generic product are allowed to expand in proportion to the variability of the RLD. This does not pose a risk to patients because drugs with high within-subject variability cannot have narrow therapeutic windows (the dose-to-dose variation of the RLD is known to be safe and effective). This approach allows demonstration of bioequivalence between two highly variable products using a smaller number of subjects.

[14] See section II.A.1 of this document for our rationale for the changes in bioequivalence recommendations for mesalamine rectal suppositories.

Suppository Draft Bioequivalence Guidance and publish new guidance for this product that includes a bioequivalence study with clinical endpoints. Finally, you request that FDA hold in abeyance any final approval of an ANDA for a mesalamine rectal suppository not based on a bioequivalence study with clinical endpoints until ongoing FDA research studies on mesalamine bioequivalence methodologies have been completed and reviewed by the Pharmaceutical Science and Clinical Pharmacology Advisory Committee.

We deny your request that we require a clinical endpoint bioequivalence study as well as your request that we revise our current bioequivalence guidance to include such a study for this product because we have determined that the recommended PK study together with the recommended in vitro comparative studies is a more accurate, sensitive, and reproducible approach for determining bioequivalence of mesalamine rectal suppositories. We also deny your request for holding in abeyance an ANDA for a mesalamine rectal suppository until FDA research studies on mesalamine bioequivalence methodologies are completed and reviewed because the studies to which you refer are unlikely to be relevant to mesalamine rectal suppositories. We also deny your request that we require additional comparative testing to assess the critical quality attributes of a proposed generic version of Canasa because we believe the recommended comparative testing is sufficient to establish bioequivalence. We address each of these requests in greater detail 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 guidance for mesalamine rectal suppositories.

A. Bioequivalence Determinations

1. Clinical Endpoint Studies

You request that FDA refrain from approving an ANDA for a generic mesalamine rectal suppository unless bioequivalence to Canasa is demonstrated in a clinical endpoint study because you claim that it is not possible to use the recommended PK study in healthy volunteers together with the recommended in vitro dissolution methodologies to adequately compare two mesalamine suppository drug products and thereby determine whether they are bioequivalent. You make the following points in support of your claim:

- Although there are systemic levels of mesalamine after administration of mesalamine rectal suppositories due to absorption through the gastrointestinal tract, these levels remain very low and are only relevant from a safety perspective (Petition at 3).
- Mesalamine's efficacy is tied to local action rather than systemic action and plasma mesalamine levels are not indicative of drug concentrations at the local sites of action (Petition at 3, 4, 8–10, and 15).
- Systemic levels of mesalamine are highly variable after rectal administration of mesalamine in both healthy subjects and ulcerative proctitis patients for reasons that are not well understood, but data indicate that retention time in the rectum,

location of suppository, and disease activity contribute to the variability (Petition at 7–10).

- Use of the novel reference-scaled average bioequivalence approach for analysis of pharmacokinetic parameters of highly variable drugs such as rectally applied mesalamine cannot be used to establish bioequivalence of generic mesalamine suppositories to the RLD (Petition at 8 and 10).
- Differences between healthy subjects and ulcerative proctitis patients in the amount and kinetics of mesalamine at the local site of action make evaluation of bioequivalence in healthy subjects problematic (Petition at 9).
- FDA guidance on individual product bioequivalence recommendations for other topical and vaginal drugs (including a suppository dosage form) designed to act locally recommend clinical endpoint studies (e.g., miconazole nitrate vaginal suppository for treatment of vulvovaginal candidiasis, calcipotriene topical ointment for treatment of plaque psoriasis, econazole nitrate topical cream for treatment of tinea pedis, malathion topical lotion for treatment of active infestation with Pediculus humanus capitis, estradiol vaginal cream for treatment of symptoms of vulvar and vaginal atrophy, and metronidazole vaginal gel for treatment of bacterial vaginosis) (Petition at 4).
- Data from a clinical study that you conducted to investigate the safety and efficacy of a new formulation of Canasa, MAX-002, indicate that with proper selection of endpoints, an appropriately powered clinical endpoint study is suitable to sensitively discriminate between mesalamine rectal suppositories with different physico-chemical properties, provides unequivocal evidence for efficacy over placebo, and should be preferred over a PK study in healthy volunteers (Petition at 10–11 and 15–16; Supplement).

We disagree with your request that we require sponsors of generic versions of Canasa to demonstrate bioequivalence in a clinical endpoint study because, as explained below, we have determined that the recommended PK study together with the recommended in vitro comparative studies is a more accurate, sensitive, and reproducible approach for determining bioequivalence. We first explain why we changed our position on clinical endpoint studies for this product, then respond to your specific contentions.

As discussed above, in 2007 we recommended that both a clinical endpoint study and a PK study be conducted to demonstrate bioequivalence of mesalamine rectal suppositories.[15] We recommended a PK study because PK studies are generally considered the most accurate, sensitive, and reproducible approach for determination of bioequivalence (§ 320.24(b)(1)(i)). We also recommended a clinical endpoint study because the therapeutic effect of mesalamine is thought to be mostly due to local rather than systemic mesalamine concentrations.

In 2010, we revised our bioequivalence recommendations for oral mesalamine products.[16] We no longer requested a clinical endpoint study for demonstration of bioequivalence

[15] See section I.C of this document.

[16] See the Mesalamine Joint Response.

and, instead, recommended use of a PK study and in vitro dissolution testing to demonstrate bioequivalence. We determined that PK profiles can be analyzed over defined time intervals using partial AUC or other profile comparison tools (including but not limited to mean residence time and steady-state Cmax) to determine whether mesalamine from generic and RLD products is absorbed at the same rate and to the same extent at the colon and rectum. We concluded that if the PK profiles for these products are equivalent and if they have equivalent in vitro dissolution characteristics, drug availability at the site of action will be the same. We also analyzed available clinical efficacy data for oral mesalamine products and concluded that comparative clinical endpoint studies are less accurate, sensitive, and reproducible than PK studies.[17] We had also gained greater experience in dealing with highly variable drug products, which permitted sponsors to use less subjects in the PK study (see Mesalamine Joint Response at 12–13).

The change in bioequivalence recommendations for oral mesalamine products prompted us to reconsider our bioequivalence recommendations for other mesalamine products. Accordingly, in 2013 we revised our bioequivalence recommendations for mesalamine rectal suppositories.[18] We continue to recommend the PK study but no longer recommend a clinical endpoint study.[19] While mesalamine is thought to be locally acting, this is not in itself a reason to recommend a clinical endpoint bioequivalence study. Rather, clinical endpoint studies are considered "the least accurate, sensitive, and reproducible of the general approaches for measuring bioavailability or demonstrating bioequivalence" (§ 320.24(b)(4)), should be avoided where possible, and should only be considered when the other general approaches for assessing bioequivalence, including PK studies, are unavailable (BA and BE Guidance at 9–10). In the case of mesalamine rectal suppositories, we believe PK data together with in vitro characterization are a reliable proxy for mesalamine availability at the site of action.

As explained in the Mesalamine Joint Response, FDA has examined the PK data associated with multiple mesalamine products and has determined that the data can be used to assess bioequivalence:

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[17] This conclusion follows the governing regulations, which provide that clinical studies are "the least accurate, sensitive, and reproducible of the general approaches for determining ... bioequivalence," and that "they may be considered acceptable only when" none of the higher-ranked methods is available (§ 320.24(b)(4)). In contrast, PK studies are generally considered the most accurate, sensitive, and reproducible of the general approaches for determining bioequivalence (§ 320.24(b)(1)). Consistent with these regulations, FDA has stated that comparative clinical bioequivalence studies in orally administered drugs should "generally be considered insensitive," should "be avoided where possible," and should only be used when both PK studies and pharmacodynamic effect studies are "infeasible" (BA and BE Guidance at 9-10).

[18] See 2013 Mesalamine Suppository Draft Bioequivalence Guidance.

[19] In addition, we now recommend in vitro comparative studies (melting point, differential scanning calorimetry, density, and viscosity). We have further limited our bioequivalence recommendations to products that are qualitatively (Q1) and quantitatively (Q2) the same as the RLD.

> Having examined the PK profiles of various mesalamine products, we believe that any significant differences in drug release profiles between test and reference formulations of Pentasa, Asacol, or Asacol HD can be readily detected from properly analyzed PK data (together with in vitro dissolution data). Specifically, the mesalamine PK profile of Colazal (prodrug, mesalamine released exclusively in the colon) is materially different from the PK profiles of Asacol, Pentasa, Lialda, and Apriso (modified-release formulations, mesalamine released throughout the GI tract), and these differences would be detected using the analytical methods described above.
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> More important, the PK profiles of the various modified-release orally administered mesalamine products are all materially different from each other. Three of these products (Asacol HD, Lialda, and Apriso) were approved in 2007 and 2008, providing additional evidence not available when FDA considered this issue in 2004 and 2005 that PK profiles of mesalamine products with different formulations are distinct. This supports FDA's conclusion that an appropriately designed PK analysis (together with an analysis of data from in vitro dissolution testing) can detect any significant difference in the rate or extent of mesalamine absorption at the sites of action between test and reference formulations of Pentasa, Asacol, or Asacol HD.

(Mesalamine Joint Response at 10–11). As we further explained in that petition response, systemic mesalamine levels can be expected to correlate with mesalamine availability at the site of action:

> For mesalamine to exert its therapeutic effect in the intestinal mucosa, it must be released from the drug product and locally dissolved in the GI tract. Any mesalamine that is locally dissolved in the GI tract is also potentially available for systemic absorption, and the rate of absorption is directly proportional to local concentration. This is confirmed by PK studies of different doses of mesalamine which show that the rate and extent of absorption increases almost proportionately with the dose.

(Mesalamine Joint Response at 10 n.26). While the site of action for rectal suppositories differs slightly from the sites of action associated with the orally administered mesalamine products discussed in the Mesalamine Joint Response, we believe the same reasoning applies.[20] Accordingly, given our conclusion that comparative PK data (together with data from the recommended in vitro studies) can be used to reliably assess bioequivalence for these products, there is no basis for continuing to recommend or require clinical endpoint studies as well.

In addition, our review of relevant clinical endpoint study data indicates that these studies are likely to be less discriminating than PK studies.[21] We reviewed published clinical trials conducted with mesalamine rectal formulations (suppository or enema) and

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[20] This issue is further discussed below in section II.A.1.b of this document.

[21] We reached the same conclusion with respect to the orally administered controlled-release mesalamine products. See Mesalamine Joint Response at 11.

mesalamine prodrugs for induction of remission.[22] These studies indicated that when mesalamine's dose was greater than 1 gram (g), different treatments resulted in comparable efficacy.[23] Thus, it is likely that the pharmacological effects of mesalamine reach their maximum when the dose is greater than 1 g. The dosage for Canasa is 1 g.[24] Therefore, a bioequivalence study with clinical endpoints is not a sensitive measurement for formulation discrimination of mesalamine rectal suppositories. On the other hand, evaluation of PK data associated with Lialda, a mesalamine delayed-release tablet, indicates that systemic exposure due to absorption from the colon is unlikely to be saturated in healthy subjects after administration of 1 g mesalamine rectal suppository.[25]

For these reasons, we concluded that the recommended PK study (together with the recommended in vitro studies) was both sufficiently discriminating and superior to the previously recommended clinical endpoint study for this product and revised our bioequivalence recommendations accordingly.

We now respond to your specific contentions.

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[22] The mesalamine pro-drugs, balsalazide disodium, olsalazine sodium and sulfasalazine, are all cleaved by bacteria azo-reductases in the colon to release mesalamine in the colon. Thus, clinical trials comparing these pro-drugs are applicable for assessment of the accuracy, sensitivity and reproducibility of clinical trials in discriminating formulation differences of mesalamine rectal suppositories.

[23] See the CLINICAL STUDIES sections of CANASA's labeling (Revised December 2013) and COLAZAL's (Balsalazide Disodium, NDA 020610) labeling (Revised February 2007); Campieri, M et al., Optimum dosage of 5-aminosalicylic acid as rectal enemas in patients with active ulcerative colitis. *Gut*, 32: 929 – 931, 1991; Hanauer, S.B. Dose-ranging study of mesalamine (PENTASA) enemas in the treatment of acute ulcerative proctosigmoiditis: results of a multicentered placebo-controlled trial. *Inflammatory Bowel Diseases*, 4: 79 – 83, 1998; Marteau, P and Florent, C, Comparative, open, randomized trial of the efficacy and tolerance of slow-release 5-ASA suppositories once daily versus conventional 5-ASA suppositories twice daily in the treatment of active cryptogenic proctitis: French Pentasa Study Group, *Am J Gastroenterol*, 95:166 – 170, 2000; Mansfield, J.C. et al., A double-blind comparison of balsalazide, 6.75 g, and sulfasalazine, 3 g, as sole therapy in the management of ulcerative colitis, *Aliment Pharmacol Ther*, 16: 69 – 77, 2002; Willoughby, C.P. et al., Double-blind comparison of olsalazine and sulphasalazine in active ulcerative colitis. *Scand J Gastroenterol Supp*, 148: 40 – 44, 1988; and Rao, S.S. et al., Olsalazine or sulphasalazine in first attacks of ulcerative colitis? A double blind study, *Gut*, 30: 675 – 679, 1989.

[24] See the DOSAGE AND ADMINISTRATION section of CANASA's labeling (Revised December 2013).

[25] See the *Pharmacokinetics* subsection of the CLINICAL PHARMACOLOGY section of Lialda's labeling (Revised September 2013). We considered data for Lialda, a delayed-release mesalamine tablet which is designed to release mesalamine in the lower gastrointestinal tract, because a dose proportionality study (i.e., PK data are obtained after different doses of a drug are administered to the same subjects) has been conducted with Lialda but not Canasa. Lialda's dose vs. pharmacokinetic proportionality study showed that after a single-dose administration of the drug to fasted healthy subjects, the arithmetic mean of AUC_t and AUC_∞ was linearly correlated with the doses ranging from 1.2 g to 4.8 g. We estimated based on data available to FDA that the 4.8 g dose of Lialda is likely to result in 1.4 g of rectal mesalamine. Thus, 1 g of mesalamine rectal suppository is very likely in the linear range of the mesalamine dose vs. PK curve, which supports use of the PK study for discriminating formulation differences of mesalamine rectal suppositories.

a. Plasma mesalamine concentrations

We disagree with your claim that after administration of a mesalamine rectal suppository, the levels of plasma mesalamine are very low and only relevant from a safety perspective (Petition at 3). You provide data in the Petition from Canasa's NDA that showed that following a single dose of 500-mg mesalamine rectal suppository, plasma concentrations of mesalamine were sufficiently measureable to obtain pharmacokinetic parameters in healthy subjects and patients with ulcerative proctitis.[26] In addition, in another study detectable plasma concentrations of mesalamine were reported after administration of 500 mg mesalamine rectal suppository.[27] Further, plasma levels of mesalamine after administration of a mesalamine rectal suppository are comparable to plasma levels after oral administration of mesalamine.[28] Thus, plasma mesalamine levels are sufficiently measureable for the recommended PK study.

b. Assessment of local mesalamine concentrations

We disagree with your claim that plasma mesalamine levels are not indicative of drug concentrations at the local sites of action that determine mesalamine's efficacy (Petition at 3, 4, 8–10, and 15). For mesalamine to exert its therapeutic effect, it must be released from the drug product. Any mesalamine released from the drug product is also potentially available for systemic absorption and thus the rate of absorption is directly proportional to local concentration. As discussed above, we have found that the data for the oral mesalamine products are consistent with this expectation (see Mesalamine Joint Response at 10 n.26). Although we believe data from PK studies for all of the oral mesalamine products are supportive, the data associated with Lialda, a delayed-release mesalamine tablet which is designed to release mesalamine in the lower gastrointestinal tract, are particularly persuasive because the available Lialda data show that the rate and absorption increases almost proportionately with the dose.[29] FDA also uses PK studies to demonstrate the bioequivalence of mesalamine rectal enemas.[30] Data available to FDA

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[26] See Tables 1 and 2 in the Petition. See also the Clinical Pharmacology and Biopharmaceutics Review of Canasa (NDA 21-252) pp. 7 and 10, available on FDA's Drugs@FDA Web site at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/21-252_CANASA_biopharmr.pdf and Aumais, G, 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*, 17: 93 – 97, 2003. (Mesalazine is an alternative name for mesalamine.)

[27] Vree, T.B. et al., Mono- and biphasic plasma concentration-time curves of mesalazine from a 500 mg suppository in healthy male volunteers controlled by the time of defecation before dosing. *J Pharm Pharmacol*, 52: 645 – 652, 2000.

[28] See the Clinical Pharmacology and Biopharmaceutics Review of Delzicol (NDA 204-412) p. 56, available on FDA's Drugs@FDA Web Site at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204412Orig1s000ClinPharmR.pdf.

[29] See note 25 above for information regarding Lialda's dose proportionality study.

[30] Available on the Internet at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm088662.pdf.

show differences between the PK profiles of mesalamine rectal enemas and suppositories, which confirm that differences in product formulations for rectal delivery of mesalamine are reflected in different PK profiles. Based on this consistent picture of mesalamine absorption, we are convinced that plasma mesalamine levels after rectal administration are a reliable surrogate for drug levels at its site of action.

c. Highly variable drug product and use of reference-scaled average bioequivalence approach

We disagree that highly variable systemic levels of mesalamine after rectal administration of mesalamine suppositories in healthy subjects and ulcerative proctitis patients preclude reliance on PK studies to establish bioequivalence (Petition at 7–10).[31] For highly variable drug products like Canasa (i.e., within-subject variability > 30 percent), we recommend use of a reference-scaled average bioequivalence approach.[32] We have considerable experience successfully using this approach with various highly variable drug products,[33] including the controlled-release oral mesalamine products. Further, you did not provide any evidence to support your claim that this approach cannot be used besides citing the 2004 FDA Pharmaceutical Science and Clinical Pharmacology Advisory Committee's recommendation that there is a need to understand where the variability originates for the highly variable drug product.[34] Regarding that issue, we disagree with the Committee's recommendation. Understanding where the variability originates is not necessary with the reference-scaled bioequivalence approach. Rather, the variability from various sources is considered in aggregate in this approach. Thus, we disagree with your claim that the reference-scaled average bioequivalence approach cannot be used for establishing bioequivalence of generic mesalamine rectal suppositories (Petition at 8 and 10).

d. Evaluation of bioequivalence in healthy subjects

We disagree with your claim that use of healthy subjects for bioequivalence studies is problematic because of differences between healthy and ulcerative proctitis patients in the amount and kinetics of mesalamine at its site of action (Petition at 9). As we explained in a recent citizen petition response about Apriso (one of the orally

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[31] The variability referred to in the Petition is between-subject variability (i.e., variation in response between different subjects when they receive the same treatment). This is in contrast to within-subject variability (i.e., variation in response within the same subject when the subject is administered two doses of the same drug on two different occasions). In a crossover bioequivalence study, the within-subject variability and not the between-subject variability determines the sample size and study power.

[32] See note 13 above for a description of the reference-scaled average bioequivalence approach.

[33] Davit, B.M. et al., Implementation of a reference-scaled average bioequivalence approach for highly variable generic drug products by the US Food and Drug Administration. *AAPS* 14: 915 – 924, 2012.

[34] See generally, FDA, Advisory Committee for Pharmaceutical Science, Apr. 13-14, 2004, at http://www.fda.gov/oc/advisory/accalendar/2004/cder12539dd04131404.html.

administered mesalamine products),[35] the relevant issue is not whether such differences exist but whether such differences lead us to think that a PK study in diseased patients would reveal significant formulation performance differences that would be missed by testing in healthy subjects:

> Although studies reported in the literature comparing PK profile data of healthy and diseased individuals treated with mesalamine products differ 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....
>
> 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....
>
> 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. 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....We do not expect that testing in diseased patients would reveal significant formulation performance differences that would be missed by testing in healthy patients.

We believe the same reasoning applies here. Therefore, we continue to think the PK study should be conducted in healthy subjects.

e. Bioequivalence recommendations for other locally acting drug products

We agree that the effect of mesalamine rectal suppositories is primarily local, but disagree that all locally acting drugs should be treated in the same way. The characteristics of individual products and disease states should be considered in determining the most appropriate approach for demonstrating bioequivalence of a locally acting drug product. As discussed above, a PK study is the first choice for demonstrating bioequivalence of a drug product because of its accuracy, sensitivity, and reproducibility.[36] However, when this option is not feasible because, for example, very

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[35] See September 12, 2013, Letter from Dr. Janet Woodcock, Director, Center for Drug Evaluation and Research, FDA, to Ms. Young, Salix Pharmaceuticals, Inc., re: Docket No. FDA-2013-P-0470 at pp. 5–6 (footnotes omitted).

[36] Section 320.24(b).

little drug is absorbed and/or there are undetectable systemic drug levels, clinical endpoint studies may be appropriate.[37]

With regard to the locally acting drug products that you identified, clinical endpoint studies are currently used to demonstrate bioequivalence for calcipotriene topical ointment, econazole nitrate topical cream, malathion topical lotion, and miconazole nitrate vaginal suppository because little to no drug is absorbed into the systemic circulation. For estradiol vaginal cream and metronidazole vaginal gel, both pharmacokinetic and clinical endpoint studies are currently used to demonstrate bioequivalence because the physical and biopharmaceutics attributes that may affect the area of application of these products are not well understood (i.e., they are semi-solid dosage forms that are applied to an uncontrolled area).[38]

In addition, different dosage forms of a drug product such as mesalamine may be evaluated differently. We recommend that PK data associated with delayed- and extended-release oral formulations of mesalamine be analyzed using partial AUC metrics, while we make no such recommendation regarding mesalamine rectal suppositories.[39] Partial AUC metrics are useful for the delayed- and extended-release oral formulations because the mesalamine in these products can be absorbed throughout the gastrointestinal tract, but it is not necessary for the rectal suppository formulations because the mesalamine in these formulations is absorbed only at its site of action.

f. MAX-002/Canasa comparative clinical endpoint study

We disagree with your claim that your unfinished clinical endpoint study comparing MAX-002 to Canasa supports use of a clinical endpoint study over a PK study to establish bioequivalence of mesalamine rectal suppositories. First, you state that MAX-002 had a higher drug load (42 percent mesalamine per suppository mass compared to 33 percent mesalamine per suppository mass for Canasa),[40] but this would mean that the test product will fail the Q1/Q2 sameness criteria recommended in the 2013 Mesalamine Suppository Draft Bioequivalence Guidance. Our bioequivalence recommendations only apply to Q1/Q2 products, the clinical performance of which is likely to be closer than that of Canasa and MAX-002. Thus, your contention that your clinical endpoint study successfully discriminated between Canasa and MAX-002 is not particularly persuasive. Second, this study did not include comparative PK data, so we cannot use it to evaluate the relative ability of PK and clinical endpoint studies to discriminate amongst rectal mesalamine formulations. Third, the two-side Fisher's exact test comparing the responder rate of MAX-002 and Canasa as compared to placebo showed a p-value of

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[37] Ibid.

[38] This is in contrast to a suppository such as Canasa, which is a solid dosage form that is administered rectally to a controlled area.

[39] See note 10 above.

[40] Petition at 11.

0.2271 (>0.05, considering a 36.59 percent responder rate calculated based on the values provided in Table 3 of the Petition) or a p-value of 0.0032 (< 0.05, considering a 56.1 percent responder rate provided in the Supplement) for MAX-002, and a p-value of 0.0559 (>0.05) for Canasa suggesting that this clinical endpoint study was not a sensitive study to demonstrate Canasa was superior to placebo. Thus, comparison of MAX-002 to Canasa is irrelevant. In general, it is much more difficult to use clinical studies to demonstrate bioequivalence than to demonstrate efficacy.

Thus, we deny your request that we require applicants for generic versions of Canasa to demonstrate bioequivalence in a clinical endpoint study.

2. *Critical Quality Attribute Testing*

You request that FDA refrain from approving ANDAs for generic mesalamine suppositories unless an assessment of critical quality attributes (demonstration of Q1, Q2, and Q3 sameness) is performed, including dissolution testing using USP apparatus that is more discriminating for in vivo performance and in vivo assessment of spreadability and irritation potential (Petition at 2). You assert that it is important that the critical quality attributes of mesalamine rectal suppositories are well understood and controlled to ensure desired product performance in vivo (Petition at 12). You claim that for Canasa, demonstration of similarity between a generic mesalamine rectal suppository and the RLD based on Q1 and Q2 criteria alone is insufficient and, in addition, assessment of raw material quality attributes and manufacturing process parameters is needed (Petition at 12 and 14). You agree with the comparative in vitro physicochemical tests recommended by FDA in the 2013 Mesalamine Suppository Draft Bioequivalence Guidance (i.e., differential scanning calorimetry, viscosity, melting point and density), but claim that additional quality attributes are needed including:

- Dissolution testing using USP Apparatus IV
- Characterization of secondary structure of gel formation, including surface charge, particle/droplet size distribution, and rheology at rectal temperature
- In vivo spreadability assessment, animal model and/or clinical
- In vivo irritation potential assessment, animal model and/or clinical
- Particle characterization, including particle size and particle size distribution of the active pharmaceutical ingredient.

(Petition at 14 and 15).

First, you appear to contend that both the in vitro characterization studies we recommended in the 2013 Mesalamine Suppository Draft Bioequivalence Guidance together with the additional testing you believe we should require are necessary to show that proposed generic versions of rectal mesalamine suppositories and Canasa have "structural similarity (Q3)" (Petition at 14). You contend that this testing is necessary to assure "comparability of critical quality attributes" between Canasa and the test product (Petition at 12), and you characterize this testing as "detailed characterization studies …

carried out to ensure all critical quality attributes are compared and shown to be similar" (Petition at 15).

We disagree. "Structural similarity" and "comparability of critical quality attributes" are not independent approval requirements for generic versions of rectal suppositories. While the in vitro testing we recommend in the 2013 Mesalamine Suppository Draft Bioequivalence Guidance recommends that **some** of the proposed generic's critical quality attributes be compared to those of the RLD, the purpose of the testing recommended in that guidance is to assure bioequivalence, not to assure (or purport to require) that **all** critical quality attributes of the proposed generic are similar to those of the RLD.

A critical quality attribute is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.[41] Relevant critical quality attributes can be identified by an iterative process of quality risk management and experimentation that assesses the extent to which their variation can have an impact on the quality of the drug product. For example, critical quality attributes of solid oral dosage forms are typically those aspects affecting product purity, strength, drug release, and stability.

We agree that an applicant needs to assess the critical quality attributes of a proposed generic mesalamine rectal suppository but disagree that such assessment is necessarily incomplete or inadequate without data comparing the proposed generic's critical quality attributes to those of the RLD (again, apart from where such data are needed to assure bioequivalence). This assessment is generally considered as part of FDA's chemistry, manufacturing, and control (CMC) review. This review ascertains whether the approved generic product will have adequate in-process CMC controls and specifications to ensure, among other things, that the generic product will have adequate (not necessarily "comparable" or "similar") critical quality attributes.[42] Applicants develop their own controls (acceptable ranges) for critical quality attributes of a proposed generic product to ensure that every batch of the product performs consistently, and FDA reviews this information to ensure that it is adequate. As critical quality attribute testing serves a different purpose from bioequivalence testing, FDA recommendations regarding identification of critical quality attributes are generally not included in bioequivalence guidance documents.

With that in mind, we now address the additional testing that you believe should be required of proposed generic versions of Canasa.

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[41] FDA guidance for industry on International Conference on Harmonisation (ICH) topic *Q8(R2) Pharmaceutical Development* at 12, available on the Internet at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[42] FDA will not approve an ANDA if "the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are inadequate to assure and preserve the identity, strength, *quality*, and purity of the drug" (section 505(j)(4)(A) of the FD&C Act (emphasis added)).

We recommend comparative dissolution testing in the 2013 Draft Mesalamine Rectal Suppository Guidance, but we do not recommend use of the USP apparatus IV.[43] Dissolution testing using USP apparatus IV is not relevant for suppositories considering the very low fluid volume in the rectum and the physicochemical process whereby the active pharmaceutical ingredient is released from a suppository in vivo (i.e., melting).

We do not recommend comparative characterization of secondary structure of gel formation, including surface charge and particle/droplet size distribution. While we agree that these properties can affect drug delivery to the site of action, we do not believe they need to be separately assessed because any substantial differences in product performance arising from differences in gel formation should be reflected in differences in the test and reference products' PK profiles. Further, we note that as part of our bioequivalence recommendations we already request a comparative in vitro viscosity test, which should provide an assessment of the products' comparative rheology.[44]

We agree that in vivo spreadability should be assessed for the product, but additional testing beyond what is recommended in the 2013 Draft Mesalamine Rectal Suppository Guidance is not needed. Spreadability is determined by formulation factors such as melting point, viscosity, and density, and a comparative assessment of these factors is already recommended in the guidance.[45] Furthermore, in vivo spreadability is confirmed by the results of the in vivo PK study.

We do not recommend assessment of in vivo irritation potential. We do not expect that Q1 and Q2 formulations would have different irritation potentials. Thus, it is not necessary to recommend a comparative irritation potential assessment.

We do not recommend independent assessment of particle characterization, including particle size and particle size distribution of the active pharmaceutical ingredient. While we agree that particle size can affect drug delivery to the site of action, we do not believe it needs to be separately assessed because any substantial differences in product performance due to particle size will be reflected in differences in the test and reference products' PK profiles.

B. Individual Product Bioequivalence Recommendations for Mesalamine Rectal Suppositories

You request that FDA withdraw the 2013 Mesalamine Suppository Draft Bioequivalence Guidance and publish new guidance for this product that includes a bioequivalence study with clinical endpoints (Petition at 2).

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[43] See 2013 Mesalamine Suppository Draft Bioequivalence Guidance.

[44] Ibid.

[45] Ibid.

As discussed above, we do not agree with you that a bioequivalence study with clinical endpoints should be conducted for mesalamine rectal suppositories. Accordingly, we deny your request for withdrawing the 2013 Mesalamine Suppository Draft Bioequivalence Guidance and replacing it with a new guidance that includes a bioequivalence study with clinical endpoints.

C. Ongoing FDA Studies on Mesalamine Bioequivalence Methodologies

You request that FDA hold in abeyance any final approval of an ANDA for a mesalamine rectal suppository based on less than a bioequivalence study with clinical endpoints until ongoing FDA research studies on mesalamine bioequivalence methodologies have been completed and reviewed by the Pharmaceutical Science and Clinical Pharmacology Advisory Committee (Petition at 2). You assert that FDA's publication of the 2013 Mesalamine Suppository Draft Bioequivalence Guidance may have been premature based on comments made by Dr. Robert Lionberger, acting Deputy Director for Science in CDER's Office of Generic Drugs on June 15, 2013, at a Part 15 hearing on regulatory science initiatives pertaining to the Generic Drug User Fee Amendments of 2012 (Petition at 4). You state that Dr. Lionberger indicated that FDA was conducting research studies of mesalamine bioequivalence methodologies looking at direct measurements of gastrointestinal concentration and their correlation with pharmacokinetics and dissolution (Petition at 5). You allege that the outcome of these studies may inform FDA's current thinking on this issue and cause the Agency to reconsider its draft bioequivalence recommendations (Petition at 5).

We deny your request. The research studies to which you refer apply to investigation of mesalamine concentrations in the upper gastrointestinal tract (from stomach to ileum) after administration of oral formulations of mesalamine. The drug concentration in the lower gastrointestinal tract lumen, such as colon and rectum, will not be measured. Thus, these studies are unlikely to have a direct impact on our bioequivalence recommendations regarding the mesalamine rectal suppositories.

III. CONCLUSION

For the reasons discussed above, we deny the requests in your Petition.

Sincerely,

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