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BY FEDERAL EXPRESS

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Rm. 1061 (HFA-305)
Rockville, Maryland 20852

RE: Require Certain Bioequivalence Criteria and other Actions Before Approving an ANDA for Mesalamine Rectal Suppositories, 500 mg and 1000 mg

Dear Sir or Madam:

CITIZEN PETITION

Aptalis Pharma US, Inc. ("Aptalis") submits this Citizen Petition under Sections 505 and 505(q) of the Federal Food, Drug, and Cosmetic Act ("FDC Act") and in accordance with the Food and Drug Administration's ("FDA's" or the "Agency's") regulations set forth at 21 C.F.R. §§ 10.25 and 10.30 to request that the Commissioner of Food and Drugs take certain actions with respect to generic versions of Canasa® (mesalamine) Rectal Suppositories, 500 mg and 1000 mg, submitted under FDC Act § 505(j) in an Abbreviated New Drug Application ("ANDA").[1] Specifically, Aptalis requests that FDA refuse to receive or approve any ANDA for a generic version of Canasa® until such applicant has demonstrated bioequivalence to Canasa® in a clinical endpoint study, as originally proposed by FDA, and pursuant to

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[1] Aptalis, formerly Axcan Scandipharm, Inc., submitted a Citizen Petition to FDA in July 2007 requesting that FDA require ANDA sponsors to demonstrate bioequivalence to Canasa® in a clinical endpoint bioequivalence study. See Citizen Petition of Axcan Scandipharm, Docket No. FDA-2007-P-0010 (Legacy Docket No. 2007P-0302) (July 27, 2007); Axcan Pharma US, Inc., Citizen Petition Supplement, Docket No. FDA-2007-P-0010 (June 16, 2009). FDA has not substantively responded to that Citizen Petition. Recently, FDA announced that the Agency received an ANDA containing a so-called "Paragraph IV certification" seeking approval to market Mesalamine Rectal Suppositories, 1000 mg, and citing Canasa® as the Reference Listed Drug ("RLD"). See FDA, Paragraph IV Patent Certifications at 23 (updated July 22, 2013)

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an assessment of certain critical quality attributes. In addition, FDA should hold in abeyance any approval decisions until ongoing FDA research studies have been completed and the results of those studies thoroughly reviewed and discussed by the Pharmaceutical Science and Clinical Pharmacology Advisory Committee. As discussed below, Aptalis believes that it is premature for FDA to receive or approve an ANDA for generic Canasa®.

I. ACTION REQUESTED

Aptalis requests that FDA:

(1) Refuse to receive or approve any ANDA for a generic version of Canasa® unless and until such sponsor demonstrates bioequivalence in a clinical endpoint study;

(2) Withdraw current bioequivalence guidance and publish new bioequivalence guidance on Mesalamine Rectal Suppositories identifying the bioequivalence study under item number (1);

(3) Refuse to approve any ANDA for a generic version of Canasa® unless and until such sponsor performs an 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 (including spreadability and *in vivo* irritation potential); and

(4) Hold in abeyance any final approval of an ANDA for Mesalamine Rectal Suppositories based on less than the bioequivalence study under item number (1) until ongoing FDA research studies have been completed and the results of those studies have been reviewed and discussed by the Pharmaceutical Science and Clinical Pharmacology Advisory Committee.

II. STATEMENT OF GROUNDS

A. Factual Background

FDA initially approved Canasa® on January 5, 2001 in a 500 mg strength under New Drug Application ("NDA") No. 021252 for the treatment of mild to moderately active Ulcerative Proctitis ("UP"), which is a disease that is characterized by inflammation of the rectum.[2] A new 1000 mg strength was approved on November 5, 2004, also for the treatment of mild to moderately active UP, under a supplement to NDA No. 021252 (Supplement No. S-005).

The rectal application of mesalamine suppositories, a 5-aminosalicylic acid compound, to the rectum allows for delivery of the active ingredient locally to the site of intended action within the GI tract. The mode of action of mesalamine, though not fully understood, is believed to be topical, and not systemic in nature. Therefore, the clinical goal is to deliver a therapeutic amount of active drug to the affected portions of the rectal mucosa while minimizing systemic absorption in efforts to reduce adverse effects.

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[2] A related disease, Ulcerative Colitis ("UC"), is a chronic disease of the gastro-intestinal ("GI") tract that is characterized by mucosal inflammation in the colon, and for which other versions of mesalamine are approved as treatment.

There are multiple formulations of mesalamine available for the treatment of UP, primarily differentiated by their means of delivering active mesalamine to the colon. Mesalamine is available in a number of locally-acting oral and rectal formulations including tablets, suppositories, and enemas. Several oral formulations have been developed including pro-drugs and delayed release characteristics, most of which have been designed with various mechanisms to postpone the release of the active mesalamine compound until reaching the terminal ileum/colon in order to prevent proximal absorption in the small intestine.[3]

Although there are systemic levels of mesalamine due to absorption through the GI tract, such systemic level of mesalamine remains very low after administration with rectal suppositories . We believe that plasma levels of mesalamine are relevant only from a safety perspective. Due to the unique properties of the rectal suppository dosage form and of UP, Aptalis believes that it is not possible to use conventional systemic pharmacokinetic ("PK") profiles in healthy volunteers and *in vitro* dissolution methodologies to adequately compare two mesalamine suppository drug products, and thereby to make a determination that two pharmaceutically equivalent drug products are bioequivalent, and thus therapeutically equivalent.

FDA's position on the types of studies necessary to support ANDAs for generic versions of mesalamine drug products generally, and for mesalamine rectal suppositories specifically, has changed dramatically over time.

Mesalamine's efficacy is tied to local action rather than systemic action, even for orally administered drug products.[4] As such, there were initially questions regarding the applicability of the traditional PK-based bioequivalence approach to generate evidence that two different drug products deliver mesalamine to the colon and rectum (sites of drug action) at the same rate and to the same extent. For mesalamine pro-drugs, FDA initially determined that data from traditional PK studies would be sufficient to conclude comparability between two pro-drug products since the active ingredient, mesalamine, is generated from its pro-drug entity by colonic bacteria at or close to site of drug action, hence considered to exhibit immediate release characteristic. However, for modified release mesalamine drug products, FDA was apparently concerned that PK data might not be an appropriate surrogate for local concentrations, and by extension, efficacy and safety, because mesalamine is absorbed throughout the GI tract and not just at the sites of drug action. In addition, local concentrations are not readily accessible for monitoring and exhibit large inter-individual variability. Hence, in 2007, FDA published a bioequivalence guidance recommending comparative clinical endpoint studies in addition to PK studies to establish bioequivalence for orally administered modified-release mesalamine drug products.

In 2010, in a response to two Citizen Petitions from Shire Pharmaceuticals and Warner Chilcott concerning the approval of generic PENTASA and ASACOL/ASACOL HD, FDA reversed course.[5] FDA reconsidered the 2007 recommendations and now recommends that an appropriately designed PK bioequivalence study – i.e., examining PK profiles over defined time intervals such as partial AUC or other profile comparison tools like mean residence time and steady-state C_{max} – coupled with an analysis

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3 FDA-approved mesalamine drug products, in addition to Canasa®, include: APRISO Extended-release Capsules (NDA No. 022301); ASACOL Delayed-release Tablets (NDA No. 019651); ASACOL HD Delayed-release Tablets (NDA No. 021830); DELZICOL Delayed-release Capsules (NDA No. 204412); LIALDA Delayed-release Tablets (NDA No. 022000); PENTASA Extended-release Capsules (NDA No. 020049); ROWASA Rectal Enema (NDA No. 019618); SFROWASA Rectal Enema (NDA No. 019618); and ROWASA Rectal Suppositories (NDA No. 019919).

4 See generally, FDA, Citizen Petition Response, Docket No. FDA-2005-P-0314 (Dec. 28, 2007).

5 See generally, FDA, Citizen Petition Response, Docket Nos. FDA-2008-P-0507 & FDA-2010-P-0111 (Aug. 20, 2010).

of data from *in vitro* dissolution testing, would be sufficient to detect any significant differences in the rate or extent of mesalamine absorption at the sites of action between test and reference formulations. FDA explained that this decision was based on the Agency's prior experience in reviewing distinct PK profiles from several orally administered modified-release mesalamine products with materially different release profiles (ASACOL HD, LIALDA, and APRISO) submitted for approval around 2007-2008. A similar sequence of regulatory decision-making events appears to have happened with rectal suppository mesalamine formulations for UP, however without communication of new data and thinking in the Agency that preceded the changing in the guidance for oral mesalamine products for ulcerative colitis. In May 2007, FDA, in a "Draft Guidance on Mesalamine: for rectally administered suppositories," initially recommended that *in vivo* bioequivalence be demonstrated with: (1) a clinical endpoint bioequivalence study; and (2) a bioequivalence study with PK endpoints under fasted state. In March 2013, FDA unexpectedly withdrew the Draft Guidance of May 2007 and published a revised draft guidance for industry, the Draft Mesalamine Rectal Suppository BE Recommendations of 2013. In this revised draft guidance, FDA recommends *in vivo* and *in vitro* studies to demonstrate bioequivalence of generic mesalamine rectal suppositories. Specifically, FDA recommends that ANDA applicant now conduct: (1) a fasting bioequivalence study with PK endpoints; and (2) comparative *in vitro* studies (melting point, differential scanning calorimetry, density, and viscosity) provided the test product is qualitatively ("Q1") and quantitatively ("Q2") the same as the RLD. Importantly, FDA is no longer recommending a clinical endpoint bioequivalence study for demonstration of bioequivalence of generic mesalamine rectal suppositories, including generic versions of Canasa®.

Based on evidence from the scientific literature and Aptalis data, Aptalis believes, as further expanded in Section C, that for rectally administered mesalamine suppositories for the treatment of UP, PK data on plasma mesalamine levels are not indicative of drug concentrations at the local sites of action that determines efficacy. Therefore, systemic PK data is inadequate in demonstrating bioequivalence for rectal suppository products with similar in-vitro release characteristics.

Aptalis is of the opinion that mesalamine rectal suppositories should be considered similarly to other topically applied drugs as addressed in the FDA guidance on individual product bioequivalence for topical and vaginal drugs (including a suppository dosage form), which are designed to act locally. These dosage forms require clinical endpoint bioequivalence studies. Examples of FDA guidances are:

- 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 (head lice and their ova);
- Estradiol vaginal cream for treatment of symptoms of vulvar and vaginal atrophy; and
- Metronidazole vaginal gel for treatment of bacterial vaginosis.

In announcing the change in bioequivalence recommendations for mesalamine rectal suppositories, FDA did not provide any scientific explanation or rationale for the change. Instead, FDA merely states in the Federal Register notice announcing the following information:

> In May 2007, FDA posted on its Web site a draft guidance for industry on the Agency's recommendations for BE studies to support ANDAs for mesalamine rectal suppositories (Draft Mesalamine Rectal Suppository BE Recommendations of May 2007). In that draft guidance, FDA recommended *in vivo* studies to demonstrate BE of generic mesalamine rectal suppositories: A BE study with clinical endpoints and a fasting BE study with pharmacokinetic endpoints. FDA has reconsidered the recommendations in the Draft Mesalamine Rectal Suppository BE Recommendations of May 2007 and has decided to revise it. In March 2013, FDA withdrew the Draft Mesalamine Rectal Suppository BE Recommendations of May 2007 and posted on its Web site a revised draft guidance for industry, the Draft Mesalamine Rectal Suppository BE Recommendations of 2013.[6]

FDA's lack of transparency and lack of communication of data to scientifically support the change in bioequivalence recommendations hampers the ability of the public and industry to offer meaningful comments on the new draft bioequivalence recommendation.

Indeed, FDA's publication of the draft bioequivalence guidance for mesalamine rectal suppositories may have been premature. During a June 21, 2013 Part 15 hearing on various regulatory initiatives identified as part of the process for negotiation of the Generic Drug User Fee Amendments of 2012, Dr. Robert Lionberger, acting Deputy Director for Science in the Office of Generic Drugs, commented that there are ongoing studies of mesalamine bioequivalence methodologies:

> "For GI-acting products, . . . traditionally it's been difficult to develop bioequivalence. But in this area since 2011, we've posted guidance for several different drug products in this area, especially the mesalamine products.
>
> We have ongoing research studies to look at direct measurements of GI concentration and their correlation with PK and dissolution. There are the studies at the University of Michigan, and subject dosing is ongoing. So we're in the middle of that study."[7]

The outcome of these studies may inform FDA's current thinking on the issue and cause the Agency to reconsider its draft bioequivalence recommendations.

B. Bioequivalence Standards

Under the FDC Act and FDA's implementing regulations, in order for FDA to receive and approve an ANDA for a proposed generic version of a brand-name drug product, the application must contain, among other things, information showing that the proposed generic drug product is "bioequivalent" to the RLD identified in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* ("the Orange Book").[8]

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6 FDA, Draft Guidance for Industry on Bioequivalence Recommendations for Mesalamine Rectal Suppositories; Availability, 78 Fed. Reg. 46,965 (Aug. 2, 2013).

7 FDA, Generic Drug User Fee Amendments of 2012; Regulatory Science Initiatives: Request for Public Input for FY 2014 Generic Drug Research, Part 15 Public Hearing, June 21, 2013, Transcript at 12.

8 See FDC Act §§ 505(j)(2)(A)(iv), 505(j)(4)(F); 21 C.F.R. §§ 314.94(a)(7), 314.127(a)(6)(l) (stating that FDA shall refuse to approve an ANDA if information submitted in the application is insufficient to show that the proposed drug product is bioequivalent to the RLD identified in the ANDA).

The FDC Act states that a generic drug is bioequivalent to the RLD 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. . . .[9]

FDA, in the Agency's regulations, defines bioequivalence (in part) as:

> . . . the absence of a significant difference in the rate and extent to which the active ingredient or active moiety . . . becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.[10]

The purpose of demonstrating bioequivalence is to determine whether changes in a proposed drug product's formulation or manufacturing affect the rate or extent to which the active ingredient reaches the primary site of action. A showing that the active ingredient or therapeutic ingredient in the proposed generic drug reaches the site of action at a rate and extent that is not significantly different from that of the RLD, along with other information required for approval, permits FDA to conclude that the proposed generic drug can be expected to perform the same way in the body as the RLD.

The determination of bioequivalence of drug products whose primary mechanism of action depends on systemic absorption generally rests on a comparison of drug (and/or metabolite) concentrations in an accessible biologic fluid, such as blood or urine, after administration of a single or multiple doses of each drug product to healthy volunteers. When this methodology is not appropriate – for example, when a drug product, like Mesalamine Rectal Suppositories, is locally acting – FDA may rely on other *in vivo* and *in vitro* methods to assess bioequivalence. FDA regulations describe these methods in descending order of accuracy, sensitivity, and reproducibility. They include: (1) *in vivo* PK studies; (2) *in vivo* pharmacodynamic effect studies; (3) clinical endpoint studies; and (4) *in vitro* studies.[11] In addition, FDA has the discretion to use "any other approach deemed adequate by FDA to . . . establish bioequivalence,"[12] however, such discretion must be exercised in a manner that is not contrary to the FDC Act and the Agency's implementing regulations, and that is based on a "reasonable and scientifically supported criterion."[13]

C. Argument

1. Mesalamine acts locally

The mode of action of mesalamine, though not fully understood, is believed to be topical, and not systemic in nature. Mucosal tissue concentration of mesalamine has been shown to be an important determinant of therapeutic response, as anti-inflammatory effect of mesalamine is thought to be related to

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9 FDC Act § 505(j)(8)(B)(i).

10 21 C.F.R. § 320.1(e).

11 See 21 C.F.R. § 320.24.

12 Id. § 320.24(b)(6); see also FDC Act § 505(j)(8)(C).

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

local drug concentration (Greenfield et al. 1993).[14]- The FDA response to the citizen petition regarding oral mesalamine acknowledged the local mode of action of mesalamine.[15]

In treatment of UP, the clinical goal is to deliver a therapeutic amount of active drug to the affected portions of the rectal mucosa while minimizing systemic absorption to reduce adverse effects. Mesalamine administered by suppositories or in enemas to the rectum achieve higher local drug concentrations compared to oral tablets alone (Frieri G et al 1999)[16] and hence found to be more effective at inducing remission in patients with UP (Karagozian and Burakoff 2007[17]; Gionchetti et al 1998[18]).

2. Systemic levels of mesalamine are highly variable

As shown below in Tables 1 and 2, mesalamine is poorly absorbed after rectal administration of mesalamine suppositories, and systemic blood levels of mesalamine are highly variable in both healthy subjects and UP patients. According to the FDA review: "this could be related to variability in bioavailability secondary to differences between individuals in suppository location and/or retention time in the rectum."[19]

Table 1. Variability of Mesalamine in healthy subjects treated with Mesalamine 500 mg Rectal Suppositories as a single dose and on the last day of multiple-dose administration every 8 hours for 6 days.

	Single Dose		Multiple dose	
	Mean	**CV (%)**	**Mean**	**CV (%)**
C_{max} (ng/mL)	192.8	53.3	359.4	166.3
AUC_{0-T}	1111.6	78.4	NC	NC
AUC_{inf}	1697.7	96.3	NC	NC
AUC_{0-8}	NC	NC	1614.8	64.7
AUC_{0-12}	NC	NC	1789.5	67.9

14 Greenfield SM, Punchard NA, Teare JP, Thompson RP. Review article: the mode of action of the aminosalicylates in inflammatory bowel disease. Aliment Pharmacol Ther 1993;7:369-383.

15 See FDA, Citizen Petition Response, Docket No. FDA-2013-P-0470 (Sept. 12, 2013).

16 Frieri G, Pimpo MT, Palumbo GC, Onori L, Viscido A et al. Rectal and colonic mesalazine concentration in ulcerative colitis: oral vs. oral plus topical treatment. Aliment Pharmacol Ther 1999;13:1413-1417.

17 Karagozian R, Burakoff R. The role of mesalamine in the treatment of ulcerative colitis. Ther Clin Risk Manag 2007;3:893-903.

18 Gionchetti P, Rizzello F et al. Comparison of Oral with Rectal Mesalazine in the Treatment of Ulcerative Proctitis. Dis Colon Rectum 1998;41: 93-97.

19 FDA, Summary Basis of Approval, NDA No. 021252, Clinical Pharmacology and Biopharmaceutics Review, at 7.

Table 2. Summary of PK Variability of Mesalamine in Patients with Ulcerative Proctitis treated with Mesalamine 500 mg Rectal Suppositories as a single dose and on the last day of multiple-dose administration every 8 hours for 6 days.

	Single Dose		Multiple dose	
	Mean	**CV (%)**	**Mean**	**CV (%)**
C_{max} (ng/mL)	352.9	56.5	361.1	66.7
AUC_{0-T}	3969.7	65.4	NC	NC
AUC_{inf}	4185.2	61.0	NC	NC
AUC_{0-8}	NC	NC	1813.2	65.2
AUC_{0-12}	NC	NC	2455.7	63.0

Highly variable drugs are generally defined as those for which within-subject variability in AUC and/or C_{max} is greater than 30%. FDA has recently provided a path forward to conduct reasonably sized PK bioequivalence studies (even for highly variable drug products). The Agency recommends a reference-scaled average bioequivalence approach where the bioequivalence criteria is scaled to reference variability. This allows determination of bioequivalence with a smaller sample size as compared to traditional bioequivalence approach. FDA mentioned in their revised bioequivalence guidance for mesalamine rectal suppository that applicants may consider using a reference-scaled average BE approach for mesalamine. However, the applicant needs to provide evidence of high variability in the bioequivalence parameters (i.e., within-subject variability > 30%) for the reference product in order to take this approach.

When this issue of high-variability for some drug products was taken to FDA's Pharmaceutical Science and Clinical Pharmacology Advisory Committee in 2004, one of Committee's recommendations was that there is a need to understand where the variability originated.[20] Prior knowledge of all biostudies may help set more appropriate specifications to make decisions. The variability of systemic PK parameters of rectally administered mesalamine is not well understood. Data indicate that retention time, location, and disease activity contribute to the variability, as discussed below.

3. Systemic levels of rectal administered mesalamine are not a surrogate for clinical efficacy

The question is whether systemic levels of mesalamine using the novel reference-scaled average bioequivalence approach can be a surrogate for drug concentrations at the local site of drug action following administration of rectal suppositories. Similar to oral mesalamine therapy, there are wide ranges of systemic exposure for rectal therapy. However oral mesalamine therapy covers a large surface area of interest and results in a long duration of exposure. Rectal therapy for a focal area of disease such as UP relies on local residence time and local drug release that cannot be extrapolated from the oral therapy/pancolonic model used to understand metrics to establish bioequivalence for oral mesalamine products.

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

The inter-individual variability of plasma levels of mesalamine after rectal administration is substantially greater than 30% and unpredictable, particularly in healthy subjects across different PK measures; the C_{max} varies as much as 166% across healthy subjects after multiple administrations of mesalamine rectal suppositories. This unpredictability of systemic exposure may arise from several in-use confounding factors as has been shown by Vree T.B. (2000)[21] in a BE study between two different suppository formulations with same dosage strength and similar dissolution profile. In this study, authors noted markedly different drug disposition kinetics based on the timing of defecation prior to dosing. Timing of defecation was found to be related to the drug release profile from one formulation while there was no correlation between time of pre-dose defecation and drug insertion for the other formulation. Therefore, it is clear that the timing of defecation has a differential impact on the drug release/absorption profiles between the two formulations with similar dissolution profile. Therefore, high variability in mesalamine systemic exposure and differential impact of covariates (both formulation- and subject-related) on the PK of rectally administered mesalamine released from different formulations limits the use of systemic PK as a surrogate for local bioavailability.

The severity of disease also impacts plasma drug concentration since plasma concentrations and mesalamine PK are different between healthy and UC and UP patients. FDA clearly recognizes the absolute differences in bioavailability between patients and healthy subjects but believes that relative bioavailability is still not affected by the presence of the disease whereas absolute bioavailability may, and hence testing in healthy volunteers is the most sensitive approach to demonstrating bioequivalence between two oral drug products.

For rectally administered mesalamine, there is lack of scientific rationale that relative systemic exposure in healthy subjects mimics the concentration at the local site in UP patients. The relative systemic bioavailability (estimated from urinary recovery data) after a single suppository dose of mesalamine was at least 35% in patients with active UP compared to 14% in healthy volunteers. This difference is most likely caused by increased systemic absorption of mesalamine through the ulcerated mucosa in patients with active disease (Aumais 2003)[22]. Moreover, the half-life at steady-state in UC patients is about 7 hours compared to 1 hour for healthy subjects indicating most likely flip-flop kinetics in UC patients. The time to peak plasma concentration (T_{max}) is prolonged in patients compared to healthy volunteers (6 hours vs. 2.3 hours). This indicates prolonged (slow) absorption in patients which in turn relates to prolonged residence time for the drug at the local site of absorption that will certainly be different between healthy subjects and patients. So, it is just not only the amount of drug at the local site but also the kinetics of residence at the local site which make evaluation in healthy subjects problematic.

Rectally applied mesalamine is superior to oral mesalamine to inducing remission in patients with UP (Karagozian and Burakoff 2007[23], Gionchetti P et al 1998).[24] While these studies did not analyze systemic exposure directly, it is well established that systemic levels of mesalamine after oral administration are

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21 Vree TB, Dammers E, Exler PS, Maes RA. 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 2000;52:645-652.

22 Aumais G, Lefebvre M, Tremblay C, Bitton A, Martin F et al. 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;17:93-97.

23 Karagozian R, Burakoff R. The role of mesalamine in the treatment of ulcerative colitis. Ther Clin Risk Manag 2007;3:893-903.

24 Gionchetti P, Rizzello F et al. Comparison of Oral with Rectal Mesalazine in the Treatment of Ulcerative Proctitis. Dis Colon Rectum 1998;41: 93-97.

higher than after rectal administration (Frieri G et al 1999).[25] Thus, this is additional, albeit indirect, evidence that efficacy cannot be correlated to systemic exposure, and especially in the case of UP with a smaller target area than UC, that systemic levels are not reflective of local concentrations over time.

Taken together, systemic PK parameters after rectal administration of mesalamine vary widely even in healthy subjects, and are fundamentally different in UP patients compared to healthy subjects. In contrast to oral mesalamine therapy which covers a large surface area of interest and results in a long duration of exposure, rectal therapy for a focal area of disease such as UP relies even more on local residence time and local drug release that cannot be extrapolated from the oral therapy/ pancolonic model used to understand metrics to establish bioequivalence for oral mesalamine products.

Therefore, on the basis of currently available data we cannot see how a different approach to analysis of PK parameters of highly variable drugs such as rectally applied mesalamine can be used to establish bioequivalence of generic mesalamine suppositories to the RLD. Lacking new PK/PD data that establish correlation between plasma PK and local anti-inflammatory activity, we are of the opinion that evaluation of efficacy in clinical endpoint studies remains necessary to establish bioequivalence of generic mesalamine suppositories for the treatment of UP.

4. Clinical Endpoint Study Supporting Development of MAX-002, a New Formulation of Canasa®

In the course of developing a new formulation of Canasa® Aptalis conducted a Phase III clinical trial (Trial CD-ME-CAPSITUP508-01) to investigate the efficacy and safety of MAX-002 1 gram rectal suppository versus placebo administered daily in patients with mild to moderate UP. This was a randomized, multi-center, double-blind, parallel group, placebo- and active-controlled (Canasa®, placebo, MAX-002) study with treatment for 6 weeks, followed by an open-label treatment option for patients who completed the double-blind phase for an additional 8 weeks (Completers at Week 6 had the opportunity to receive MAX-002, standard therapy or no therapy). The placebo arm has been included to ensure assay sensitivity following FDA's recommendation with regard to the May 2007 bioequivalence guidance. Canasa®, the reference drug, was included to support the validity of the study but not for comparison purposes. In order to detect a difference of at least 20% with respect to the placebo response rate (25%) versus the MAX-002 treatment group (45%), a total sample size of 128 human subjects per treatment group was calculated based on a 2-sided Chi-square procedure, a significance level of 5% and a power of 90%.The primary efficacy endpoint was to compare the responder rate, defined as total score Mayo Disease Activity Index (DAI) of < 3 with no individual subscore ≥ 2) between the MAX-002 and placebo treatment groups after 6 weeks of treatment. For business reasons, the study was terminated early.

As shown in Table 3 below, despite the fact that the study was terminated early with about one third of the patients enrolled, the study demonstrated statistically significant higher responder rate for both MAX-002 and Canasa® over placebo ($p<0.05$) with response rates based on Mayo DAI scores of 56.1% with MAX-002, 46.2% with Canasa® and 23.1% with placebo. Although not shown below, additionally, statistically significant results between MAX-002 and placebo were also demonstrated with respect to 1) Mayo DAI response rate at week 3, 2) DAI Rectal Bleeding subscore, and 3) Time to Relief of Rectal bleeding.

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[25] Frieri G, Pimpo MT, Palumbo GC, Onori L, Viscido A et al. Rectal and colonic mesalazine concentration in ulcerative colitis: oral vs. oral plus topical treatment. Aliment Pharmacol Ther 1999;13:1413-1417.

Table 3: Responder Rate after 6 Weeks of Double-Blind Treatment (ITT Population using NR imputed data)

Treatment Groups	**MAX-002 (N = 41)**	**Placebo (N = 39)**	**Canasa® (N = 39)**
Responder Rate based on Mayo DAI score at Week 6* n (%)	15 (56.1%) p-value** 0.0047	9 (23.1%)	18 (46.2%) p-value*** 0.0346

* Responder classified as a patient with total Mayo DAI score of 0, 1 or 2 and with individual sub-score of 0 or 1. Patients with missing total Mayo DAI score or if total score is ≥3 are classified as non- responders

** P-value from a Cochran Mantel Haenszel test stratified by the DAI score at baseline (5-7 or 8-10) comparing MAX-002 and Placebo.

*** P-value from a Cochran Mantel Haenszel test stratified by the DAI score at baseline (5-7 or 8-10) comparing Canasa® and Placebo

These data establish the clinical efficacy of MAX-002 over placebo.[26]
Although the study was not powered to investigate therapeutic equivalence between the two active groups, MAX-002 and Canasa®, the study data did provide some comparative efficacy information between two rectally administered mesalamine suppositories with different physico-chemical properties. Indeed, the primary endpoint showed numerically a 10% difference in response rate. Other secondary endpoints such as Mayo DAI subscores, as well as symptom relief and Quality of Life parameters, did not reveal a difference between the two formulations. This data indicate that with proper selection of endpoints, a clinical endpoint study is suitable to sensitively discriminate between mesalamine rectal suppositories with different physico-chemical properties but with similar release characteristics. This result demonstrates that structural formulation characteristics (Q3) is a highly sensitive quality attribute with impact on clinical efficacy and bioequivalence.

The differences of MAX-002, compared to Canasa, consist of different specifications for the drug substance for particle size, the grade of suppository base used (lower melting point of the hard fat by 2°C) and the higher drug load (42% per suppository mass compared to 33% per suppository mass for Canasa®). Although the Q1/Q2 finished product specifications, including the dissolution rate, for both products are almost identical, differences in the above mentioned attributes can have an impact of the clinical efficacy of the final product because of lack of Q3 similarity, as demonstrated by the above mentioned primary clinical endpoint study. Higher drug load and different characteristics of the suppository base can influence the *in vivo* melting characteristics and drug release to the site of inflammation.

5. Critical Quality Attributes of Mesalamine Rectal Suppositories:

According to Drug Nomenclature Monographs in FDA's Data Standards Manual, a suppository is "A solid body of various weights and shapes, adapted for introduction into the rectal orifice of the human body; they usually melt, soften, or dissolve at body temperature." A suppository is a solid dosage form at

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26 Clinical Study Report CD-ME-CAPSITUP508-01, "A multicenter, double-blind, controlled, randomized, parallel group comparison Phase IIIa treatment investigation on the efficacy and safety of MAX-002 suppository versus placebo and active medicine in mild to moderate ulcerative proctitis." A copy of the study report will be submitted separately as a confidential exhibit to this petition once a docket number is assigned by FDA .

prescribed storage environment. After insertion into the rectum of patients, the suppository behaves like a semi-solid. Consequently, suppositories are grouped in the same chapter called "Medicated Topicals" in Remington's Pharmaceutical Sciences with dermal topicals, among others. Both dermal topicals and suppositories can fit into a broader class of locally acting products.

The composition of a suppository involves complex control strategy to assure consistency in product quality. As such, it is important that the critical quality attributes of mesalamine rectal suppositories are well-understood and controlled to ensure desired product performance *in vivo*. As mentioned above, different formulations can lead to different efficacy but comparable PK. While it is true in general that assurance of Q1 and Q2 similarity between a test and generic product helps establish generic comparability, this criteria does not assure comparability of critical quality attributes for Canasa®. Variability in the raw material quality attributes and manufacturing process parameters affect critical quality attributes of Canasa® rectal suppository product. These are discussed below.

Raw material quality attributes

Canasa® rectal suppository contains 1000 mg of mesalamine (USP) in a base of Hard Fat, NF. The USP/NF defines Hard Fat a mixture of glycerides of saturated fatty acids. The monograph quality requirements include residue on ignition, alkaline impurities, acid value, hydroxyl value, iodine value, saponification value, unsaponifiable matter, and melting range that is stated not to differ by more than 20°C from the nominal value given in labeling, which is 27°C – 44°C . These quality attributes do not fully ensure the right functional quality needed for Hard Fat to be used in the manufacture of Canasa®. In addition to conformance to USP/NF, additional functional testing is needed to ensure the quality of this critical excipient. According to "Handbook of Pharmaceutical Excipients, 6th edition 2009", the primary application of hard fat suppository bases is as a vehicle for the rectal or vaginal administration of a variety of drugs, either to exert local effects or to achieve systemic absorption. To the formulators, working for a brand or generic company, there are a number of commercial hard fats to choose from, a total of 73 to be exact. As stated in the handbook of excipient, "Selection of a suppository base cannot usually be made in the absence of knowledge of the physicochemical properties and intrinsic thermodynamic activity of the drug substance".

Some commercial Hard Fat, NF contains many additives as shown in the table below. Some of these additives have the potential to change drug diffusion and/or permeability in the rectum.

Table 4: Selected suppository additives

Property	Additive
Dispersants (release and/or absorption enhancers)	Surfactants
Hygroscopicity (reduced)	Colloidal silicon dioxide
Hardeners (or increasing melting point)	Beeswax Cetyl alcohol Stearic Acid Stearyl alcohol Aluminum monostearate (or di- and tristearate) Bentonite Magnesium stearate Colloidal silicon dioxide
Plasticizers (or decreasing melting point)	Glyceryl monostearate Myristyl alcohol Polysorbate 80 Propylene glycol

Manufacturing process variables

The manufacturing process includes several critical control steps and monitoring to ensure appropriate quality attributes are preserved consistently from batch to batch. As such, the manufacturing process needs to be adequately understood and controlled to ensure that consistent product quality is achieved batch-to-batch. In this regard the dispersion of mesalamine in the hard fat and the formation of right gel structure are critical to achieve the desired drug release characteristics. In this regard dissolution testing is a critical quality attribute, which may not be fully ensured by testing using USP Apparatus II.

Dissolution Testing

Lipophilic suppositories release the drug after melting in the rectal cavity and are significantly affected by the rectal temperature, reported as typically 36°C to 37.5°C. *In vitro* release testing also requires knowledge of the melting point/range of the product being tested. The test temperature should take into consideration physiological conditions but may also be at or slightly above the melting point, for example, at 37°C to 38.5°C (which can be justified, e.g., for suppositories used for patients with fever). After melting, the drug will have to partition between the lipophilic base and the receptor fluid. This may lead to distribution equilibrium between the 2 phases rather than complete dissolution. For this reason, sink conditions during the test are essential in order to simulate the *in vivo* situation, where absorption across the rectal membrane is continuously reducing the concentration of the drug in the rectal fluids. USP Apparatus IV is recommended for these dosage forms (Siewert et al, AAPS PharmSciTech 2003)[27]. This test method has also been described in a consensus paper following the AAPS/FDA/FIP workshop.

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[27] Siewert M, Dressman J, Brown CK, Shah VP; FIP; AAPS. FIP/AAPS Guidelines to dissolution/in Vitro Release Testing of Novel/Special Dosage Forms. AAPS PharmSciTech. 2003;4:E7.

Q3 Similarity

The 2013 draft Mesalamine Rectal Suppository BE recommendations require a second study which covers *in vitro* comparative physicochemical characterization of the test and RLD formulations. The generic sponsor is required to provide *in vitro* evidence that the test and RLD products have the same final physico-chemical characteristics, to include differential scanning calorimetry, viscosity, melting point, and density. We agree that such structural similarity (Q3) tests should be part of the prerequisites.

For a potential generic mesalamine rectal suppository drug product, the demonstration of similarity based on Q1/Q2 alone is insufficient. Structural similarity (Q3) will be primarily impacted by the appropriate selection of the suppository base which usually cannot be made in the absence of knowledge of the physicochemical properties and intrinsic thermodynamic activity of the drug substance. Other drug-related factors that can affect release and absorption and which must therefore be considered are the particle size distribution of insoluble solids, the oil: water partition coefficient, and the dissociation constant. The displacement value should also be known, as well as the ratio of drug to base. Properties of the suppository base that may or may not be modified by the drug, or that can influence drug release, are the melting characteristics, chemical reactivity, and rheology. The presence of additives in the base can also affect performance.

Since the raw material quality attributes and process variables can potentially impact the product release characteristics the following additional quality attributes need to be considered:

- Secondary structure of gel formulation must be well-characterized and shown to be similar between the test a reference products (Q3). In addition to DSC, viscosity, melting point, and density, this should include surface charge, particle/droplet size distribution (Particle/Droplet/Excipient size distribution by microscopy and light scattering), and rheology at rectal temperature (Linear Viscoelasticity - Material response to oscillatory strain that combines solid and liquid behavior)

- Dissolution testing using USP Apparatus IV, which is directly relevant to the suppository dosage form

- Spreadability assessment *in vivo* (animal model and/or clinical assessment): This study should show that two products spread comparably within the colon. This critical attribute will help ensure comparable local delivery of mesalamine and its subsequent systemic absorption. Several factors have to be overcome for a drug to be absorbed after rectal administration. If the drug is administered as a suppository, melting or liquefaction of the base has to occur and the degree of this will partly determine the spreading of the dose through the rectum. The drug must then dissolve in the limited rectal fluid available, which has been estimated to be between 1 and 3 ml. The amount of drug available for absorption can be further reduced by degradation by luminal contents, adsorption to luminal contents and defecation. The drug must then diffuse across the unstirred water and mucous layers adjacent to the epithelium. The drug can spread beyond the site of disease or not reach the entire site of disease. The spreading of the suppositories of the generic test product could be very different from that of the RLD. Due to such complexity, the drug in plasma can come either from inside or outside the area of disease. The drug in plasma can also originate from portal vein or from general systemic absorption and therefore the concentration of drug in plasma cannot adequately reflect the concentration of drug at the site of action. Hence, drug spreadability becomes yet another critical quality attribute that needs to be assured between a reference and a test product.

- Irritation Potential Assessment (animal model and/or clinical assessment): Depending on the spreadability of suppositories and the rate and extent of local drug release, two products may have different irritation potential within the colon as local concentrations may vary due to low fluid level in colon. This assessment should be carried out to show comparable irritation potential for a potential generic product.

- Particle size and particle size distribution of the API have to be well controlled according to pre-defined and justified specifications since the *in-vitro* and *in-vivo* release characteristics are highly sensitive to these quality attributes

In addition to typical product quality attributes that are commonly included in product specifications (ID, assay, impurities, dissolution, water, content uniformity, residual solvents, physical analysis including visual examination, uniformity of weight, uniformity of texture, melting point, liquefaction time, melting and solidification time, and mechanical strength) detailed characterization studies should be carried out ensuring all critical quality attributes are compared and shown to be similar. As recommended in the draft Mesalamine Rectal Suppository BE recommendations,[28] *in vitro* evidence that the test and RLD products have the same final physico-chemical characteristics should be provided. The guidance recommends the following four quality attributes for characterization.

- differential scanning calorimetry:
- viscosity;
- melting point; and
- density

However, as discussed above, additional characterization data is needed to ensure similarity of product performance. Three such quality attributes are (i) Secondary structure elucidation; (ii) Dissolution testing using USP Apparatus IV; (iii) Spreadability assessment *in vivo* (nonclinical and clinical); (iv) Irritation potential assessment (nonclinical and clinical) and (v) Particle characterization.

D. Conclusion

- Mesalamine rectal suppositories have been deemed as a topical drug product with local concentrations driving efficacy and local safety.

- Drug release characteristics and kinetics of drug disposition at the local site such as local residence time, constitute critical parameters for local drug action.

- Systemic concentration of mesalamine, after administration with rectal suppositories, is likely not a surrogate for clinical efficacy due to lack of robust plasma concentration-response relationship for efficacy.

- A clinical endpoint study has been conducted supporting development of a new mesalamine rectal suppository formulation. This data 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 systemic PK

[28] See FDA, Draft Guidance for Industry on Bioequivalence Recommendations for Mesalamine Rectal Suppositories; Availability, 78 Fed. Reg. 46,965 (Aug. 2, 2013).

study in healthy volunteers to establish bioequivalence of rectally applied mesalamine suppositories.

- From the standpoint of product quality, confirmation of Q1/Q2 sameness and limited physical testing along with PK assessment is not adequate to establish bioequivalence. Assessment of additional critical quality attributes including dissolution testing using more appropriate USP apparatus IV, *in vivo* spreadability, and in vivo irritation potential should be compared as part of establishing performance equivalency. Structural similarity (Q3) tests should be part of the prerequisites with a specific focus on particle/droplet/excipient size distribution, spatial arrangements and homogeneity, particle interactions, description of the aqueous-lipid interface and characterization of the rheological properties

III. ENVIRONMENTAL IMPACT

Aptalis claims a categorical exclusion under 21 C.F.R. § 25.31.

IV. ECONOMIC IMPACT STATEMENT

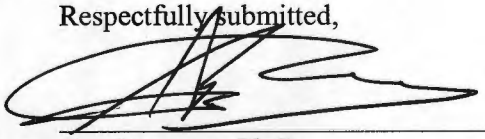
Aptalis will, upon request by the Commissioner, submit economic impact information, in accordance with 21 C.F.R. § 10.30(b).

V. CERTIFICATIONS

The undersigned certifies that, to the best knowledge and belief of the undersigned, this Petition includes all information and views on which the Petition relies, and that it includes representative data and information known to Aptalis which are unfavorable to the Petition.

Aptalis makes the following certification pursuant to FDC Act § 505(q)(1)(H): I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: March 31, 2013. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: Aptalis. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully submitted,



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