

1171 '06 JUL 14 P4:01

July 14, 2006

Dockets Management Branch (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: FDA Docket No. 2005P-0146

SUPPLEMENT TO CITIZEN PETITION

The undersigned, Salix Pharmaceuticals, Inc. ("Salix"), submits this supplement as an addendum to its Citizen Petition filed on April 13, 2005. The petition and this supplement request that the Director of the Office of Generic Drugs ("OGD") of the Food and Drug Administration ("FDA") adopt guidance applicable to oral locally-acting gastrointestinal ("GI") drug products prior to approval of any generic versions of such drugs. The Citizen Petition further requests that comparative clinical trials be required as a condition of approval for oral drug products containing balsalazide disodium. This supplement maintains that OGD's contemplated recommendations for demonstrating bioequivalence for balsalazide disodium products are not supported by scientific fact.

I. BACKGROUND

As described in Salix's April 13, 2005, petition, balsalazide disodium is a pro-drug that, when taken orally, delivers the active agent, 5-amino salicylic acid, to the colon where it acts locally to reduce inflammation associated with ulcerative colitis. The marketed formulation is an immediate release formulation but the drug substance contained therein is a Class 4 substance of low solubility and low permeability according to the August 2000 Guidance for Industry: *Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System*.

The complexity of the various stages of dissolution, delivery to the colon, activation of the pro-drug by colonic bacteria and ultimate biological activity of the active moiety result in very low and extremely variable blood levels of the active substance and its primary metabolite. Indeed, appearance of balsalazide-delivered, active metabolites in the plasma are only detected after the drug reaches the intended site of activity and penetrates the target organ. Thus, typical bioequivalence measures do not adequately predict the efficacy performance, nor ensure the safe interchangeability of a generic balsalazide disodium-containing compound.

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Salix has previously shared its own scientific experience and that of the published literature with OGD concerning the issuance of appropriate guidelines for the approval of safe and effective balsalazide-containing compounds in a White Paper submitted to OGD on November 12, 2004 and publicly in a Citizen Petition filed April 13, 2005. In addition, Salix is aware of recommendations that OGD has considered regarding bioequivalence measures for balsalazide-containing drug products. Specifically a letter dated March 24, 2006 provided to a third party, discusses a possible approach, combining *in vitro* dissolution and *in vivo* bioequivalence, but states that such an approach is subject to change as a result of the Salix Citizen Petition filed April 13, 2005 (hereinafter, the "recommendations"). Thus, we take this opportunity to provide a scientific review of the inadequacies of the *in vitro* dissolution and *in vivo* bioequivalence approach being considered by OGD.

II. ACTION REQUESTED

Salix continues to support the actions requested in its April 13, 2005, Citizen Petition. In addition to those requests, Salix respectfully requests that OGD withdraw the recommendations contemplated by the March 24, 2006, letter to a third party. OGD's proposed recommendations require a series of tests that are not proven equivalency measures, and that consequently will not ensure the safe interchangeability of balsalazide disodium products. Better measures would require a more appropriate *in vitro* dissolution test coupled with a study of bioequivalence in ulcerative colitis patients in remission that measures the bioequivalence of balsalazide, 5-ASA, and N-acetyl-5-ASA (NASA). Even if this more rigorous approach is adopted, there remain serious scientific questions about the import of plasma measurements for a drug with such low and variable absorption. The influence of disease activity, food and age also remain unresolved. In the absence of scientifically-supported bioequivalency measures, Salix maintains that the only scientifically proven measure of bioequivalency between two balsalazide-containing products are comparative measures of therapeutic outcomes in patients.

III. STATEMENT OF GROUNDS

Salix requests that OGD withdraw its proposed recommendations because they are not supported by scientific fact. The recommended combination of *in vitro* dissolution and *in vivo* pharmacokinetic studies are inadequate to predict formulation performance *in vivo*.

A. *In Vitro* Dissolution

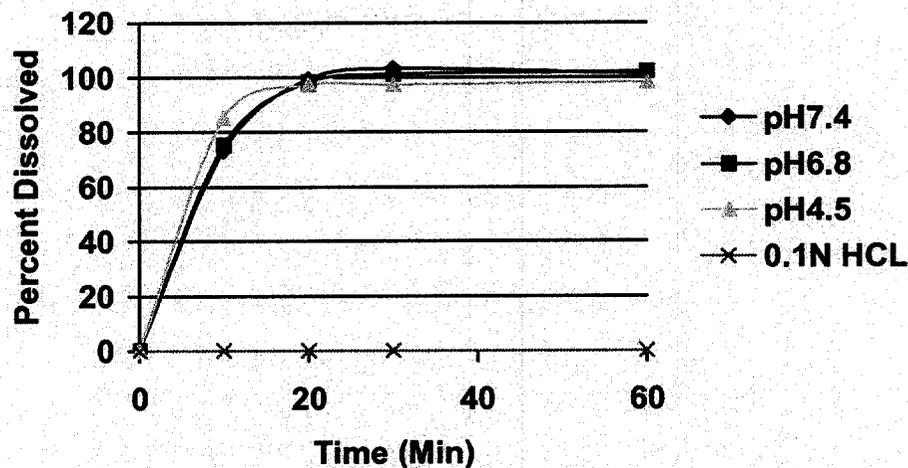
The recommendations recognize that because balsalazide acts locally in the GI tract, rather than systemically, some mechanism is necessary to determine "whether an equivalent amount of drug from each formulation, test and reference, is delivered to the sites of activity in the GI tract." OGD's recommendations propose a



comparative dissolution test to fulfill this function. The OGD recommendation is to perform dissolution testing at pH levels that reflect the pH of the stomach, small intestine and colon as an *in vitro* mimicry of *in vivo* conditions. Thus, the Agency suggests that dissolution should be carried out in 0.1N HCL, pH 4.5, pH 6.8 and pH 7.4.

Salix submits that the proposed dissolution profile is insufficiently discriminatory to detect differences in formulation performance. Balsalazide is insoluble in 0.1 N HCL, but rapidly and completely solubilizes *in vitro* in the range pH 4.5-7.4. This is demonstrated in **Figure 1** below using the RLD Colazal capsules:¹

Figure 1: Influence of pH on Dissolution of Colazal Capsules In Vitro



Because balsalazide rapidly dissolves above pH 4.5, the recommended dissolution profile is not sufficiently discriminatory to detect differences in formulation performance without a pH condition that yields some level of intermediate dissolution rate.

Furthermore, the recommended *in vitro* conditions do not approximate *in vivo* conditions. When balsalazide is formulated and processed as it is in Colazal capsules, it becomes an insoluble balsalazide crystalline structure in the stomach, where

¹ Apparatus: paddles with sinkers (USP Apparatus 2), Temperature: 37 +/- 0.5 degrees C, Paddle Speed: 50 rpm, Volume: 900 mL, Sample Volume: 10 mL, Method of Detection: UV, Sample Size: 6 capsules



the average 24 hour pH is well below pH 4.5.² This crystalline structure is exposed to a sequential pH gradient as it moves into the duodenum. The recommended dissolution profile does not capture this gradient. Instead, the pH conditions recommended for comparative dissolution testing expose formulated, processed, balsalazide powder directly to each pH condition. The sequential exposure experience *in vivo* is not reflected in the recommended *in vitro* study.

This is significant because it is not known where in the GI tract *in vivo* dissolution takes place. As outlined below, less than 1% of the balsalazide dose is absorbed systemically and this absorption generally occurs within an hour of dosing. The cause of this limited absorption is unknown; it may be due to either low solubility or low permeability in the small intestine, or some combination of both.

Given these characteristics of balsalazide, formulation performance as tested *in vitro* cannot be used as a surrogate for the complexities of *in vivo* dissolution. The dissolution testing proposal is even more questionable given the interaction of crystalline balsalazide with stomach contents and the effect of feeding on dissolution, absorption, and delivery of the intact pro-drug to the intended site of action in the colon. Consequently, *in vitro* dissolution is only appropriate for use as a release specification, not as a bioequivalence measure.

B. *In Vivo* Bioequivalence Recommendations

OGD's recommendations require "[a] single-dose, two-way crossover, fasting *in vivo* bioequivalence study comparing Balsalazide Disodium Capsules, 750mg, to the reference listed drug (RLD) Colazal® (Balsalazide Disodium) capsules, 750mg." A fed bioequivalence study is not required. Furthermore, no specific subject population is recommended. Finally, the recommendations provide that parent pro-drug balsalazide and the active moiety mesalamine be measured in plasma. The two formulations would be declared "bioequivalent" if the 90% confidence intervals of the test/reference geometric mean ratios of AUC and Cmax for both balsalazide and mesalamine fall within the range 0.8 to 1.25

As Salix demonstrated in its April 13, 2005, Citizen Petition, measurements in plasma have no demonstrated relevance to the efficacy of balsalazide. The plasma drug levels of balsalazide and mesalamine are extremely low and variable. For example, urinary recovery (the primary route of elimination) of balsalazide and 5-ASA represents less than 1% of a single or multiple oral dose.³ Given this extremely low absorption, even if bioequivalence in plasma were a correlate of efficacy, the

² Merki HS, Fimmel, CP, Walt, RP *et al.* Pattern of 24 hour intra-gastric acidity in active duodenal ulcer disease and in healthy controls *Gut* 29; 1583, 1988

³ *Colazal Package Insert: Elimination.* July 18, 2000.



recommended study is not of sufficient rigor to compare the performance of two different balsalazide-containing formulations.

Because of the low absorption of balsalazide in pharmacokinetic studies, many data points for each subject in pharmacokinetic studies are below the limit of quantitation (the concentration at which quantitative results can be reported with high confidence).⁴ Furthermore, the coefficient of variation (the standard deviation expressed as a percent of the mean) can be as high as 100%.⁵ Therefore, to even attempt to compare formulation performance by pharmacokinetic studies, it is necessary to enroll subjects and measure analytes that show the greatest levels of absorption. It is also necessary to make these measurements under those *in vivo* conditions, such as feeding, that may influence *in vivo* dissolution.

Salix submits that there are at least three scientific weaknesses in the recommendations that make the proposed pharmacokinetic study a poor measure of bioequivalence. The scientific problems with the recommended study relate to 1) subject population, 2) analytes being measured and 3) the effect of *in vivo* conditions. These discrepancies are discussed individually below.

1. Subject Population

The OGD recommendations do not specify a specific subject population. It is therefore assumed that OGD believes that normal healthy subjects are suitable for the comparison of formulation performance. However, normal healthy subject are not a suitable study population because the target patient population -- subjects with ulcerative colitis -- have profound and long-standing changes in their entire gastrointestinal systems. Changes in GI transit time,⁶ small bowel mucosal architecture,⁷ overall small bowel length,⁸ and mucosal microflora⁹ have all been shown to occur in UC patients regardless of disease activity. Differences in absorption of parent pro-drug balsalazide as well as its active metabolites have been documented in studies submitted and reviewed under NDA 20,610. Specifically, greater absorption of balsalazide, 5-ASA and N-acetyl-5-ASA were observed in ulcerative colitis patients in remission than in normal healthy subjects.

These differences in absorption between normal healthy subjects and ulcerative colitis patients in remission were recognized by the pharmacologist in FDA's

⁴ *Clinical Pharmacology and Biopharmaceutics Review*, NDA 20,610, p. 9, para 1. May 19, 2000.

⁵ *Id.* at Table 1.

⁶ Reddy SN, Bazzocchi G, Chan S, Akashi K, Villanueva-Meyer J, Yanni G, Mena I, Snape WJ Jr. Colonic motility and transit in health and ulcerative colitis. *Gastroenterol.* 1991, 101(5):1289-97.

⁷ Arvanitakis C, Abnormalities of jejunal mucosal enzymes in ulcerative colitis and Crohn's disease. *Digestion.* 1979; 19(4):259-66.

⁸ Nordgren S, McPheeters G, Svaninger G, Oresland T, Hulten L, Small bowel length in inflammatory bowel disease. *Int J Colorectal Dis.* 1997; 12(4):230-4.

⁹ Kleessen B, Kroesen AJ, Buhr HJ, Blaut M, Mucosal and invading bacteria in patients with inflammatory bowel disease compared with controls. *Scand J Gastroenterol.* 2002 Sep; 37(9):1034-41.



Division of Gastroenterology Products who reviewed the Colazal NDA. The absorption differences were extensively reviewed and discussed in the "Clinical Pharmacology and Biopharmaceutics Review" of NDA 20,610. The reviewer commented:

Clearly plasma levels of BSZ were much higher in patients (as per C_{min} , C_{max} and AUC). Indeed, some of the healthy subjects had no quantifiable plasma concentrations of BSZ and those that did had BSZ levels which were all near the assay LOQ. Overall there were very few plasma samples in Study #20061 (healthy subjects) with any BSZ detected. Conversely, all of the UC patients had readily measurable quantities of plasma BSZ.¹⁰

The differences in absorption between healthy subjects and patients led the reviewer to question the relevance of data in healthy subjects:

In conclusion, it appears that there were obvious differences in the systemic exposure to BSZ and its metabolites (with the exception of ABA) in Studies #20061 (healthy subjects) and #GLY01/93 (UC patients), with UC patients exhibiting greater and faster absorption when compared to healthy subjects. Therefore the relevance of BSZ PK data in healthy subjects is questionable.¹¹

The approved labeling for Colazal reflects the Division of Gastroenterology's review of these differences:

Systemic drug exposure, based on mean AUC values, was up to 60 times greater (8 ng*hr/mL to 480 ng*hr/mL) after equivalent multiple doses of 1.5 grams twice daily when compared to healthy subjects who received the same dose.¹²

Especially with regard to a controversial and previously undefined area of drug study, the NDA reviewer's concerns about the relevance of data in healthy subjects and the product's labeling emphasis of the distinction in absorption between the two subject populations should carry particular weight. Balsalazide is a drug for which less than 1% of the parent drug dose and between 0.5-2% of the active metabolite appear in the systemic circulation after delivery to the colon. From a scientific standpoint, the most sensitive measure of absorption would be the one most likely to detect differences in

¹⁰ *Clinical Pharmacology and Biopharmaceutics Review*, NDA 20,610, p.12, para 2. May 19, 2000.

¹¹ *Id.* at p.18, para 3.

¹² *Colazal Package Insert: Absorption*. July 18, 2000.



formulation performance. Since the level of plasma absorption of balsalazide from the RLD Colazal is already barely detectable and subject to extreme variability, it would appear scientifically prudent to select a subject population that has previously shown the greatest absorption. Any bioequivalence study designed to measure formulation performance compared to the RLD Colazal should therefore utilize ulcerative colitis patients as subjects.

2. Measurement of Analytes

OGD's current recommendations suggest that the analytes balsalazide and mesalamine (5-ASA) be measured in plasma. The proposed studies assume that the measurement of plasma balsalazide pro-drug and 5-ASA active metabolite are indicative of formulation performance and pro-drug cleavage profile in vivo. This proposal would permit approval of a generic balsalazide for which less than 2% of the oral dose is measured by bioequivalence. Salix believes such recommendations are not supported by experimental data and could lead to the approval of unsafe and/or ineffective generic balsalazide products.

The Division of Gastroenterology has consistently required measurement of all balsalazide metabolites. Specific requests for Phase IV studies in 1) active disease patients, 2) the effect of food, and 3) pediatric patients have all required that balsalazide, 5-ASA, NASA, 4-ABA and NABA be measured.¹³ Salix has consistently and completely complied with the requests of the Division to capture complete data on all analytes derived from balsalazide after delivery to the colon.

Salix acknowledges that measurement of 4-ABA and NABA yield little useful information and should not be required. The extensive pharmacokinetic characterization carried out in fulfillment of the requirements under NDA 20,610 has shown that of the five analytes, the carrier molecule, 4-amino-benzoyl- β -alanine (4-ABA) and its N-acetyl derivative are largely not absorbed and do not contribute to any safety concerns surrounding the use of balsalazide. Therefore, of the five analytes, these two are the least likely to provide information relative to performance of a generic formulation.

Balsalazide should be measured, as OGD has recommended, because it is useful as a measure of safety. Plasma balsalazide levels achieve a C_{max} at approximately one hour after dosing and this C_{max} represents less than 1% of the oral dose. This time course reflects absorption from the small bowel only and is not indicative of the amount of pro-drug delivered to the site of action in the colon. It is a matter of public record, as stated in the review of NDA 20,610, that quantitation of absorbed balsalazide does not distinguish between doses, and is not dose proportional.¹⁴

¹³ NDA 20,610 Approval Letter: *Phase IV Commitments*. July 18, 2000.

¹⁴ *Clinical Pharmacology and Biopharmaceutics Review*, NDA 20,610, p. 12, para 4, May 19, 2000.



The comparison of balsalazide plasma levels is therefore only useful to determine the relative safety of two different balsalazide containing formulations.

As balsalazide is only useful as a measurement of safety, OGD's recommendations rely entirely on the measurement of 5-ASA to demonstrate equivalence in formulation performance as it relates to efficacy. Plasma 5-ASA levels from an oral dose of balsalazide achieve a Cmax at approximately 8.5 hours and result from the azo-reduction of pro-drug balsalazide in the colon. The plasma 5-ASA Cmax and AUC are both variable and low because of 1) low absorption in the colon and 2) rapid conversion of 5-ASA to N-acetyl-5-ASA in the colonic mucosa prior to absorption. These metabolites are ultimately recovered in the urine as 0.6-3.8% and 12-15%, respectively, of the oral dose.¹⁵ Thus, a bioequivalence measure of 5-ASA in plasma is a reflection of a complex process of pro-drug dissolution, azo-bond reduction of balsalazide and the interaction of 5-ASA with the colonic mucosa at the site of action.

A more meaningful indicator would include measurements of both 5-ASA and NASA. It is a scientifically unsound and unprecedented deviation from FDA's past requirements to ignore the fate of the mesalamine metabolite, N-acetyl-5-ASA (NASA). NASA appears in the plasma earlier than 5-ASA,¹⁶ and rises to a greater Cmax and AUC.¹⁷ Thus, measurement of both 5-ASA and NASA is the most sensitive marker of formulation performance as it relates to efficacy.

Furthermore, in addition to formulation performance as it relates to efficacy, there is a safety concern with NASA. Safety of mesalamine is not known to only be limited to 5-ASA. NASA may have safety issues for renal toxicity. NASA has a much longer half-life than 5-ASA.¹⁸ In renally impaired patients, dialysis reduces plasma 5-ASA with a much smaller effect on NASA.¹⁹ Thus renal elimination of the two is independent. NASA is of lower anti-inflammatory activity in the colon,²⁰ but does not lack activity as shown by improvement of UC symptoms when given to patients as a retention enema.²¹ Since 5-ASA to NASA conversion is dependent on the time of

¹⁵ *Id.* at p.14 and 16, Tables 4 and 6.

¹⁶ *Id.* at p. 9, para 4.

¹⁷ *Id.* at p. 9, Table 1.

¹⁸ Klotz U, Maier KE, Fischer C, Bauer KH. A new slow-release form of 5-aminosalicylic acid for the oral treatment of inflammatory bowel disease. Biopharmaceutic and clinical pharmacokinetic characteristics *Arzneimittel-Forschung*, 1985, 35:636; Meese CO, Fischer C, Klotz U. Is N-acetylation of 5-aminosalicylic acid reversible in man? *Br. J Pharmacol.* 1984, 18:612.

¹⁹ Verzijl, JM, Kamphuis, TJ, Rensma, PL, van Roon, EN. *Nephrol. Dial Transplant* 2000; 15:736-738; Klotz, U. In Goebel, H, Peskar, BM, Malchow, H, Eds. *Inflammatory Bowel Disease---Basic Research and Clinical Implications*. Lancaster: MTP Press, 1987: 339-347.

²⁰ van Hogezaand RA, van Hees PA, van Gorp JP, van Lier HJ, Bakker JH, Double-blind comparison of 5-aminosalicylic acid and acetyl-5-aminosalicylic acid suppositories in patients with idiopathic proctitis. *Aliment Pharmacol Ther.* 1988 Feb; 2(1):33-40.

²¹ Willoughby CP, Piris J, Truelove SC. The effect of topical N-acetyl-5-aminosalicylic acid in ulcerative colitis. *Scand J Gastroenterol.* 1980; 15(6):715-9.



interaction with the colonic mucosa, differences in formulation performance can determine the relative amount of each metabolite in the systemic circulation.

Previous OGD recommendations for approval of generic pH-dependent mesalamine (i.e. Asacol®) included the measurement of both metabolites and, as previously noted, FDA required Salix to measure both metabolites in its Phase IV commitments.²² It is inconsistent for OGD to ignore this history and the advice previously given by the Division of Gastroenterology and only require a measurement of 5-ASA, while ignoring the fate of the majority of the active compound. If a generic formulation of balsalazide yields greater systemic NASA, a safety concern is raised. If, on the other hand, a generic formulation yields lower systemic NASA, it may be indicative of a different release pattern of 5-ASA in the colon and therefore represent an efficacy concern. Thus, any measure of formulation performance must show bioequivalent pharmacokinetic parameters of both mesalamine forms to ensure the adequacy of formulation performance.

3. **Influence of Disease Activity, Food and Patient Age on Balsalazide and Mesalamine Absorption**

The original approval of NDA 20,610 contained Phase IV requests from the Division of Gastrointestinal Drug Products for Salix to undertake additional pharmacokinetic studies in UC patients with active disease, a food effect study and a pediatric study.²³ Salix has complied with these requests and submitted this information to FDA. The present scientific review of OGD's recommendations regarding balsalazide bioequivalence measures **does not** reflect changes to the approved labeling that may occur as a result of submission of the Phase IV study results. It is therefore not possible at this time for OGD to provide a recommendation for bioequivalence that fully accounts for the scientific data available on the dissolution and absorption of balsalazide-containing products.

IV. **CONCLUSION**

The bioequivalency measures contemplated by OGD are an attempt to predict formulation performance *in vivo* by using a combination of *in vitro* dissolution and pharmacokinetic parameters *in vivo*. However, as currently proposed, these experiments lack sufficient scientific rigor to adequately address this question. Indeed, even if a more appropriate *in vitro* dissolution test is employed and is coupled with a study of bioequivalence that 1) is conducted in ulcerative colitis patients in remission and 2) measures bioequivalence of BSZ, 5-ASA and NASA, there still remains an unresolved influence of disease activity, food and age on the approved labeling of the RLD Colazal.

²² FDA response to Docket 96P-0414/CPI & PSA1, p. 3, para 2. Aug 25, 1997.

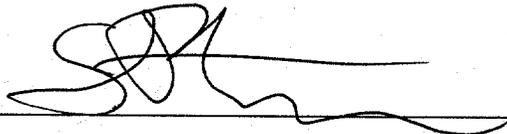
²³ NDA 20,610 Approval Letter. July 18, 2000.



In summary, OGD recommends a series of tests that after careful examination appear to be unproven, by scientific fact, as equivalency measures. Thus Salix believes that without undertaking a scientific evaluation of true *in vivo* dissolution measures and giving further consideration to other scientifically meaningful proposals offered by Salix, OGD's recommendations will not ensure the safe interchangeability of commercially available balsalazide. In the absence of such suitable bioequivalency measures, supported by scientific fact, we are left to conclude that the only proven measure of equivalency between two balsalazide-containing products are therapeutic outcomes in patients, as proposed in our previously submitted Citizen Petition.

V. CERTIFICATION

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 the petitioner which are unfavorable to the petition.



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