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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-01461

**SUPPLEMENT TO CITIZEN PETITION**

The undersigned, Salix Pharmaceuticals, Inc. ("Salix"), submits this supplement to its Citizen Petition filed on April 13, 2005, and supplement filed July 14, 2006. The petition, the previous supplement and the present supplement request that the Director of the Office of Generic Drugs ("OGD") of the Food and Drug Administration ("FDA") adopt guidance applicable to orally administered, locally-acting gastrointestinal ("GI") drug products prior to approval of any generic versions of such drugs. The Citizen Petition further requests that approvals of generic versions include efficacy data from comparative clinical trials as the only reasonable method by which to ensure proper performance of untested new formulations (generics) of pro-drug and modified release formulations. While pharmacokinetic bioequivalence used as a measure of safety may be required as a condition of approval for oral drug products containing balsalazide disodium, comparative measures of pharmacokinetic bioequivalence are inadequate as a substitute for clinical efficacy. This supplement maintains that OGD's contemplated recommendations for demonstrating bioequivalence for balsalazide disodium products are not supported by scientific fact and are inconsistent with the approved labeling for the Reference Listed Drug (RLD) Colazal® (balsalazide disodium) capsules, 750 mg.

**I. ACTION REQUESTED**

Salix continues to support the actions requested in its April 13, 2005, Citizen Petition and July 14, 2006, Supplement to the Citizen Petition. Salix believes that the newly approved Colazal® label (effective September 21, 2006) provides further support for the position that clinical studies are necessary to establish bioequivalence for balsalazide disodium because the clinical efficacy of balsalazide disodium "is presumed to be primarily due to the local effects of 5-ASA on the colonic mucosa."<sup>1</sup> Salix believes the only legitimate role of bioequivalence studies would be to establish the safe, not effective, interchangeability of the generic with the RLD Colazal®. Under this use of

<sup>1</sup> Colazal Package Insert: *Absorption*, p. 5.

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bioequivalence studies, the new label supports requiring a fed study, a study of sprinkles, and measurement of N-Ac-5-ASA in addition to balsalazide and 5-ASA. Finally, as detailed in the previously submitted July 14, 2006, Supplement to the Citizen Petition, the most appropriate, scientifically valid subject population for these studies are patients with ulcerative colitis, not normal, healthy volunteers.

## II. STATEMENT OF GROUNDS

### A. 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 a targeted location in the gastrointestinal tract, namely the colon, where it acts locally to reduce inflammation associated with ulcerative colitis. The marketed pro-drug formulation is an immediate release formulation which, in and of itself, is considered 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 and absorption of the pro-drug, delivery to the colon, metabolism of the pro-drug by colonic bacteria and ultimate biological activity of the active moiety result in very low and extremely variable systemic blood levels of the pro-drug and its therapeutically active moiety (5-ASA). Indeed, the balsalazide-delivered active metabolite is only detected in the systemic blood after the pro-drug reaches the intended site of action (and is metabolized by colonic azo-reductase enzymes), penetrates the target tissue and finally is absorbed into the portal blood circulation. Therefore, comparable systemic 5-ASA blood concentrations do not guarantee that a generic balsalazide disodium pro-drug was metabolized and 5-ASA released at the optimum colonic site to effect the efficacious treatment of ulcerative colitis. Thus, typical systemic bioequivalence measures do not adequately predict the efficacy performance and thus the safe interchangeability of a generic balsalazide disodium-containing compound with the RLD Colazal®.

Salix has previously shared its own scientific experience and that of the published literature with OGD concerning the need for 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 filed a supplement to the petition on July 14, 2006. This supplement was submitted by Salix in response to bioequivalence recommendations that OGD provided for balsalazide-containing drug products. Specifically, the supplement reviewed the scientific inadequacies of the *in vitro* dissolution and *in vivo* bioequivalence approach being considered by OGD. The present supplement provides additional review of the scientific inadequacies of the *in vitro* dissolution and *in vivo* bioequivalence recommendations currently proposed by OGD. The OGD recommendations: 1) fail to demonstrate a correlation with clinical efficacy, 2) ignore the effect of feeding on the bioavailability of the three key analytes, and 3)

disregard the new label information regarding sprinkling Colazal on applesauce. Without considering the effect of food and sprinkling on bioavailability, the OGD-recommended bioequivalence testing arbitrarily ignores, and is not consistent with, the approved labeling of the RLD Colazal®.

### **1. Food-Effect Study**

As a Phase IV commitment, FDA required Salix to assess the effect of food on the absorption of balsalazide.<sup>2</sup> Salix had established the safe and effective use of Colazal® in patients through rigorous clinical trials where patients were allowed to take Colazal® with and without food. Because of this, Salix agreed to conduct a food-effect study as directed by the GI Division of FDA to assess the effect of food on the absorption of balsalazide and this agreement is noted by the GI Division of FDA in the Approval Letter for Colazal®.<sup>3</sup>

The objective of the food-effect study was to assess the bioavailability of a single oral dose of balsalazide disodium administered under each of three conditions: 1) as an intact capsule following an overnight fast, 2) as an intact capsule following a high-fat breakfast and, 3) as unencapsulated powder sprinkled on applesauce after opening the capsule. Study periods were separated by a minimum of 4 days. Standard pharmacokinetic parameters were computed from the plasma ( $C_{max}$ ,  $T_{max}$  and  $AUC_{last}$ ) and urine (% excreted and Clr) concentrations for balsalazide and its metabolites (5-ASA, N-Ac-5-ASA, 4-ABA and N-Ac-4-ABA) for the 17 subjects who completed the three study periods as per protocol. The results of this study are shown in Table 1.

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<sup>2</sup> NDA 20,610 Approvable Letter. June 15, 1998 (asking Salix to commit to post-marketing assessment of the effect of food on the absorption of balsalazide).

<sup>3</sup> NDA 20,610 Approval Letter. July 18, 2000.

**Table 1: Plasma Pharmacokinetics for Balsalazide and Key Metabolites (5-ASA and N-Ac-5-ASA) with Administration of COLAZAL® Following a Fast, a High-Fat Meal, and Drug Contents Sprinkled on Applesauce (Mean ± SD)**

	Fasting n = 17	High-fat Meal n = 17	Sprinkled n = 17
$C_{max}$ (µg/mL)			
Balsalazide	0.512 ± 0.323	0.446 ± 0.390	0.214 ± 0.123*
5-ASA	0.218 ± 0.117	0.112 ± 0.136*	0.286 ± 0.169
N-Ac-5-ASA	0.871 ± 0.385	0.642 ± 0.534*	1.04 ± 0.566
$AUC_{last}$ (µg·hr/mL)			
Balsalazide	1.35 ± 0.727	1.52 ± 1.01	0.872 ± 0.484*
5-ASA	2.59 ± 1.46	2.10 ± 2.58*	2.99 ± 1.70
N-Ac-5-ASA	17.8 ± 8.14	17.7 ± 13.7	20.0 ± 11.4
$T_{max}$ (h)			
Balsalazide	0.8 ± 0.85	1.2 ± 1.11	1.6 ± 0.44*
5-ASA	8.2 ± 1.98	22.0 ± 8.23*	8.7 ± 1.99
N-Ac-5-ASA	9.9 ± 2.49	20.2 ± 8.94*	10.8 ± 5.39

\*  $P$  value was  $\leq 0.05$  when compared to fasting.  $P$  value derived from Dunnett's test for multiple comparisons for log-transformed  $C_{max}$  and  $AUC_{last}$ , and from Wilcoxon Rank-Sum test for observed values of  $T_{max}$ .

The results of this study show that feeding influences the bioavailability of balsalazide disodium. When balsalazide was administered with a standard high-fat meal there was a statistically significant difference when compared to administration in a fasting state in  $C_{max}$  of 5-ASA and N-Ac-5-ASA, and of  $AUC_{last}$  of 5-ASA as well. In addition, the  $T_{max}$  for both 5-ASA and N-Ac-5-ASA were significantly prolonged from 8-9 hours to 20-22 hours. When balsalazide was administered as sprinkles on applesauce, significantly lower bioavailability of balsalazide was observed when compared to administration in a fasting state as measured by lower  $C_{max}$ , lower  $AUC_{last}$ , and a significantly prolonged  $T_{max}$ . No statistically significant changes in the bioavailability of 5-ASA and N-Ac-5-ASA were observed when the capsule contents were administered as sprinkles on applesauce.

To determine if balsalazide administered with food or sprinkled on applesauce is bioequivalent to balsalazide administered in the fasting state, the ratios and 90% confidence intervals of the geometric mean for  $C_{max}$  and  $AUC_{last}$ , for balsalazide, 5-ASA, and N-Ac-5-ASA were computed according to the FDA, *Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies*, p. 3-4 (December 2002). The results are presented in Table 2.

**Table 2. Ratios and 90% Confidence Intervals of Different Treatments for Plasma Pharmacokinetics for Balsalazide, 5-ASA, and N-Ac-5-ASA**

	Treatment B/A <sup>a</sup>			Treatment C/A <sup>a</sup>		
	Ratio	Lower Limit	Upper Limit	Ratio	Lower Limit	Upper Limit
<b>C<sub>max</sub><sup>b</sup></b>						
Balsalazide	0.791	0.597	1.048	0.435	0.329	0.577
5-ASA	0.427	0.294	0.620	1.234	0.856	1.780
N-Ac-5-ASA	0.639	0.505	0.809	1.147	0.907	1.452
<b>AUC<sub>last</sub><sup>b</sup></b>						
Balsalazide	1.146	0.971	1.352	0.648	0.549	0.765
5-ASA	0.589	0.401	0.864	1.173	0.807	1.707
N-Ac-5-ASA	0.819	0.649	1.034	1.097	0.869	1.385

<sup>a</sup> Treatment A = Fasted; Treatment B = High Fat Breakfast; Treatment C = Sprinkled on Applesauce

<sup>b</sup> Ratio estimates and 90% CIs from ANOVA fitting mixed model using log-transformed values: log (parameter) = study group period treatment subject (study group), where subject (study group) was a random effect, comparing high-fat diet vs. fasting, sprinkled vs. fasting, and sprinkled vs. high-fat diet.

There is a clear lack of bioequivalence for balsalazide or either of its main metabolites under fasting versus fed (high fat) conditions or fasting versus sprinkling on applesauce when compared to balsalazide or either of its main metabolites when dosed while subjects are fasting.

## 2. Label Change

On September 21, 2006, FDA's GI Division approved a label change for the RLD Colazal® incorporating Salix's food-effect study. The new label information includes Table 1 (see Section II(A)(1) above) comparing the plasma pharmacokinetic parameters for balsalazide and the key metabolites (5-ASA and N-Ac-5-ASA) with administration following a fast, with a high-fat meal, or sprinkled on applesauce. The GI Division also included the following paragraph in the label describing the food-effect study:

A relatively low systemic exposure was observed under all three administered conditions (fasting, fed with high-fat meal, sprinkled on applesauce), which reflects the variable, but minimal absorption of balsalazide disodium and its metabolites. The data indicate that both C<sub>max</sub> and AUC<sub>last</sub> were lower, while T<sub>max</sub> was markedly prolonged, under fed (high-fat meal) compared to fasted conditions. Moreover,

the data suggest that dosing balsalazide disodium as a sprinkle or as a capsule provides highly variable, but relatively similar mean pharmacokinetic parameter values. No inference can be made as to how the systemic exposure differences of balsalazide and its metabolites in this study might predict the clinical efficacy under different dosing conditions (i.e., fasted, fed with high-fat meal, or sprinkled on applesauce) since clinical efficacy after balsalazide disodium administration is presumed to be primarily due to the local effects of 5-ASA on the colonic mucosa.

Also included in the amended labeling are dosing and administration instructions regarding administration by sprinkling on applesauce

**B. The New Label Approved by the GI Division Further Corroborates that Plasma Concentration Data is Not Correlated with Efficacy**

The label change illustrates the misconception that there is a relationship between blood levels and efficacy. The OGD bioequivalence recommendations for balsalazide disodium state that:

Plasma mesalamine should be measured because its absorption from the colon reflects availability of the active moiety at the site of activity.

As Salix demonstrated in its Citizen Petition, this is not accurate - plasma concentrations do not provide any information about the concentration at the site of action. The Colazal® label as amended, now states that:

No inference can be made as to how the systemic exposure differences of balsalazide and its metabolites in this study might predict the clinical efficacy under different dosing conditions (i.e., fasted, fed with high-fat meal, or sprinkled on applesauce) since clinical efficacy after balsalazide disodium administration is presumed to be primarily due to the local effects of 5-ASA on the colonic mucosa.

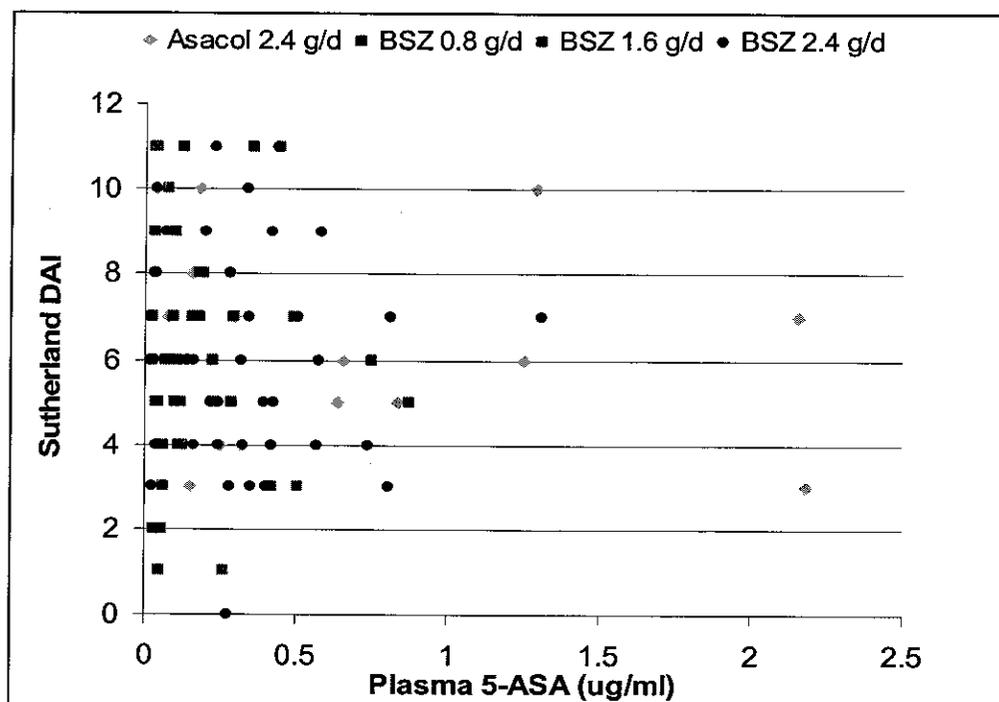
The label explicitly says that no inference can be made as to the clinical efficacy under different dosing conditions. The same logic should apply to different formulations. Thus, comparative clinical trials should be required as a condition of approval for oral drug products containing balsalazide disodium.

As has been outlined in previous papers, there is no meaningful correlation between the clinical effectiveness of the pro-drug balsalazide and the active moiety 5-ASA. The data plot provided below (Figure 1) demonstrates the lack of concurrence between plasma concentrations of the active moiety 5-ASA and symptom relief as measured by the 12-point Sutherland Disease Activity Index (SDAI), where a lower score is reflective of less active ulcerative colitis symptoms. The data are from the original Colazal® NDA

submission and includes information from 113 patients that had both plasma concentration and the SDAI evaluated at their week two visit (Study CP069101 and Study CP099301<sup>4</sup>). The graph essentially depicts no correlation between 5-ASA plasma concentrations and total SDAI Score with a result of  $r = -0.02242$ , ( $p=0.8137$ ).

**Figure 1. Week 2, Plasma 5-ASA Concentrations vs. Sutherland Disease Activity Indices for Patients With Active Ulcerative Colitis Dosed With Different Oral Mesalamine Preparations**

(BSZ = balsalazide; oral doses in legend expressed as mesalamine content)



The Office of Generic Drug defines a generic drug as “identical, or bioequivalent to a brand name drug in dosage form, safety, strength, route of administration, quality, performance characteristics and intended use.” Disease Activity Indexes like the SDAI have long been held as the gold standard for assessing efficacy and the clear lack of correlation between plasma concentrations and clinical efficacy underscores the topical, not systemic, importance of 5-ASA agents in this disease. The only reasonable manner to assure equivalence in performance characteristics for the intended use of a generic balsalazide is to conduct clinical trials. Salix believes the only rational use of pharmacokinetic bioequivalence, as outlined in OGD’s recommendation, is to establish a

<sup>4</sup> Levine DS, Riff DS, Pruitt R et al. A randomized, double-blind, dose-response comparison of balsalazide 6.75g, balsalazide 2.25g and mesalamine 2.4g daily in the treatment of active, mild to moderate ulcerative colitis. *Am. J. Gastroenterol.* 2002;9:1398-1407

high degree of certainty as it relates to the safe, not effective, interchangeability of the new generic when compared to the RLD Colazal®

C. **If Bioequivalence Studies are Used To Establish Safe Interchangeability, Fed and Fasted Measurements Should be Taken**

According to FDA, a food-effect study is required for a drug product with the characteristics of balsalazide disodium.<sup>5</sup> The food-effect study guidance outlines the following:

In addition to a BE study under fasting conditions, we recommend a BE study under fed conditions for all orally administered immediate-release drug products, with the following exceptions:

- When both test product and RLD are rapidly dissolving, have similar dissolution profiles, and contain a drug substance with high solubility and high permeability (BCS Class 1) . . . , or
- When the DOSAGE AND ADMINISTRATION section of the RLD label states that the product should be taken only on an empty stomach, or
- When the RLD label does not make any statements about the effect of food on dosage or administration.

Based on the above, a study under fed conditions for generic balsalazide products is required since none of the scenarios listed apply to balsalazide disodium.(i.e., balsalazide disodium is not a Class 1 drug;<sup>6</sup> balsalazide disodium is also **not** limited to dosing on an empty stomach; and the new RLD label makes statements about the effect of food on dose and dose administration).

In addition, other FDA guidance further supports requiring a food-effect study. Co-administration of food with oral drug products may influence drug BA and/or BE.<sup>7</sup>

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<sup>5</sup> FDA, *Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies*, p. 3-4 (December 2002) (“Food-Effect Study Guidance”).

<sup>6</sup> FDA, *Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System* (Aug. 2000).

<sup>7</sup> FDA, *Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products -- General Considerations*, § VI(A), p. 18, July 2002.

To ensure comparable safety, additional studies with and without food may help to understand the degree of systemic exposure that occurs following administration of a drug product intended for local action in the gastrointestinal tract.<sup>8</sup>

### 1. FDA's Food-Effect Guidelines are Scientifically Justified

Salix's food-effect study showed a lack of equivalence between dosing in fed and fasted conditions. Thus Salix's food-effect study demonstrates that it cannot be assumed that a product that is bioequivalent under fasted conditions will necessarily be bioequivalent under fed conditions. Food can influence GI conditions such as pH<sup>9</sup> and transit,<sup>10</sup> and food interactions can alter *in vivo* dissolution.<sup>11</sup> Therefore food effects are relevant to **formulation performance**.

### 2. FDA Required a Fed Study for another Mesalamine Product - Asacol®

FDA followed its own guidelines in requiring a food-effect study for the drug product Asacol. FDA stated that "[i]t is the Agency's policy to request food effect studies in ANDA applications for delayed-release drug products."<sup>12</sup>

The same logic should apply to Colazal, which also acts like a delayed release product because of the negligible gastric solubility, low permeability and resultant bioavailability of the pro-drug (balsalazide) and the delayed mechanism by which the pro-drug releases the active therapeutic moiety in the colon.

### 3. Food-Effect Cannot Be Carved Out

The dosage and administration instructions of the RLD Colazal® do not require administration on an empty stomach. In addition, administration of a drug intended for TID dosing would be impractical if not impossible under fasting conditions. Finally, the instructions are not limited to specific patient populations, e.g., elderly patients. Thus, they are necessary instructions for all patients.

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<sup>8</sup> *Id.* at § VI(E), p. 20.

<sup>9</sup> Dressman JB, Berardi RR, Dermentzoglou LC, Russell TL, Schmaltz SP, Barnett JL, and Jarvenpaa KM. Upper gastrointestinal (GI) pH in young, healthy men and women. *Pharm Res.* 1990 Jul;7(7):756-61.

<sup>10</sup> Weisbrodt NW. Patterns of gastrointestinal motility. *Annu. Rev. Physiol.* 1981, 43:21-31. See also: Weisbrodt NW. *Motility of the small intestine*. In Johnson LR. (ed), *Physiology of the Gastrointestinal Tract*. 1981, New York, Raven.

<sup>11</sup> Charman WN, Porter CJ, Mithani S, and Dressman JB. Physiochemical and physiological mechanisms for the effects of food on drug absorption: the role of lipids and pH. *J Pharm Sci.* 1997 Mar;86(3):269-82

<sup>12</sup> *FDA response to Docket 96P-0414/CP1 & PSAl*, p. 3, para 2. Aug 25, 1997.

By not requiring a fed study, OGD's recommendations for bioequivalence do not fully account for the scientific data available on the dissolution and absorption of balsalazide-containing products.

**D. If Bioequivalence Studies are Used To Establish Safe Interchangeability, Dosing with Sprinkles Should be Studied**

FDA Guidance on demonstrating BE in products labeled for dosing in sprinkles also requires a single dose crossover study.<sup>13</sup> In the guidance, the Agency makes recommendations on the studies necessary to incorporate "sprinkling" of capsule contents on food prior to dosing:

In ANDAs, Bioequivalence of the test product to the RLD is demonstrated in a single dose crossover study. Both treatments should be sprinkled on one of the soft foods mentioned in the labeling, usually applesauce. The Bioequivalence data should be analyzed using average BE and the 90 percent CI criteria should be used to declare BE.

The guidance document contains no exceptions to the requirement that bioequivalence comparisons of a test product to a RLD product with a label that describes sprinkling also test sprinkles. There is no justification for carving the sprinkling instructions out of the label. The sprinkling instructions are not specific to any particular patient population, e.g., elderly patients or patients with difficulties in swallowing. Thus, a sprinkle study is needed for the directions of use for all patients. To support these sprinkle instructions, a sprinkle bioequivalence study as well as a sprinkle (applesauce) stability study should be required.

**E. If Bioequivalence Studies Are Used To Establish Safe Interchangeability, N-Acetyl-5-ASA Must Also Be Measured**

The new label recognizes N-Ac-5-ASA as among the "key metabolites" of balsalazide disodium.<sup>14</sup> As Salix has previously demonstrated, measurement of N-Ac-5-ASA as well as 5-ASA is important (e.g., N-Ac-5-ASA is formed as 5-ASA passes through the site of action, appears in the plasma earlier than 5-ASA and reaches a greater  $C_{max}$  and AUC).<sup>15</sup> The food-effect study shows that N-Ac-5-ASA varies independently with different dosing conditions.<sup>16</sup> N-Ac-5-ASA may therefore also vary independently with different formulations.

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<sup>13</sup> Food-Effect Study Guidance, p. 8.

<sup>14</sup> Colazal Label, Table 1.

<sup>15</sup> Citizen Petition, *FDA Docket No. 2005P-0146, Supplement*, July 14, 2006

<sup>16</sup> Colazal Label, Table 1.

FDA previously recognized the importance of N-Ac-5-ASA in the Asacol<sup>®</sup> recommendations. Measuring balsalazide levels is necessary because it is the parent drug.<sup>17</sup> However, as FDA recognized in its Asacol<sup>®</sup> decision, bioequivalence with regard to the concentration of the therapeutic moiety (5-ASA) at the site of action -- if it can be determined at all through blood levels -- requires at a minimum bioequivalence of both 5-ASA and its primary metabolite N-Ac-5-ASA.<sup>18</sup> Balsalazide's very low and highly variable bioavailability and mechanism of action mean the blood levels of N-Ac-5-ASA do not correlate with 5-ASA, a point confirmed by the new label. If approval is based, in part on pharmacokinetic studies, measurement of both of the "key metabolites" must be required as a condition of approval.

**F. If Bioequivalence Studies Are Used To Establish Safe Interchangeability, Ulcerative Colitis Patients Should Be The 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 subjects 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,<sup>19</sup> small bowel mucosal architecture,<sup>20</sup> overall small bowel length,<sup>21</sup> and mucosal microflora<sup>22</sup> 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. Given the new information of the effect of food on bioavailability of balsalazide and its metabolites, it is not known how these profound changes in the mucosa architecture and intestinal environment will influence the *in vivo* dissolution and absorption of an alternative formulation of balsalazide. Consequently, it is necessary from both a scientific, as well as from a safety, perspective to confirm that a generic balsalazide offers

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<sup>17</sup> FDA Balsalazide Recommendations, OGD Reference No. 06-0182, para. 1(c) (March 24, 2006).

<sup>18</sup> FDA response to Docket 96P-0414/CP1 & PSA1, p. 3, para 2. Aug 25, 1997.

<sup>19</sup> 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.

<sup>20</sup> Arvanitakis C, Abnormalities of jejunal mucosal enzymes in ulcerative colitis and Crohn's disease. *Digestion.* 1979; 19(4):259-66.

<sup>21</sup> 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.

<sup>22</sup> 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.

the same formulation performance as the RLD Colazal® in the intended patient population.

### III. CONCLUSION

The recommendations 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 ensure true bioequivalence in respect to both the safe and effective interchange between the RLD and the generic and are inconsistent with the approved label of the RLD Colazal®. At a minimum, if an *in vivo* pharmacokinetic study is used, it must measure plasma concentrations under: 1) fasted and fed conditions and 2) when balsalazide is sprinkled on applesauce. Furthermore, if an *in vivo* pharmacokinetic study is used, the measurements should include; 3) all three analytes balsalazide, 5-ASA and N-Ac-5-ASA, and 4) it should be conducted using ulcerative colitis patients in remission.

Salix believes OGD's obligation is to ensure the safe and effective interchangeability of commercially available balsalazide. The only plausible manner to ensure the effectiveness of a new formulation of balsalazide is to conduct a clinical efficacy trial. Bioequivalence under various dosing options currently allowed by the existing Colazal® Label (fasting, fed and sprinkled), is only valuable in assessing equivalence in relation to the safe use of balsalazide.

In the absence of suitable *in vivo* dissolution and pharmacokinetic 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.

#### IV. 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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