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September 27, 2007

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 its Supplements filed on July 14, 2006, November 14, 2006 and June 14, 2007. This Supplement addresses safety issues with the bioequivalence recommendations of the Food & Drug Administration's (FDA's) Office of Generic Drugs (OGD), listed in a letter dated March 24, 2006. Specifically, this letter addresses the safety implications of a potential exposure of pediatric patients to generic versions of the RLD Colazal®. Salix asserts that both the intact Colazal® Capsule as well as the contents of the Colazal® sprinkled on apple sauce constitute appropriate pediatric formulations of Colazal®. Because both the Capsule and the contents of the Capsule are interchangeable, the proposed studies outlined by OGD to establish the therapeutic equivalence of the generic and the RLD fail to capture critical data predictive of the equivalence of a generic balsalazide disodium in the specific patient populations (adult and pediatric) included in the approved labeling for the listed drug (RLD) Colazal®. Thus, adequate safety and efficacy assurance can not be predicted from such recommendations lacking adequate scientific rigor for the patient population in which a generic substitute will be used.

ACTION REQUESTED

Salix continues to support the actions requested in its April 13, 2005, Citizen Petition and its July 14, 2006, November 14, 2006, and June 14, 2007 Supplements to the Citizen Petition. Salix maintains that OGD should issue guidance applicable to all orally administered, locally-acting gastrointestinal ("GI") drug products prior to approving generic versions of such drugs. FDA's "Draft Guidance for Industry: Bioequivalence Recommendations for Specific Products," which issued in May 2007, lists selected Draft Guidances for certain products but does not include balsalazide. Salix continues to assert (as it has in the Citizen Petition and prior Supplements thereto) that approvals of generic versions of Salix's Colazal® (balsalazide disodium) capsules should include efficacy and safety data from comparative clinical trials.

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Like the preceding Supplements, 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. Prior supplements demonstrated that if an in vivo pharmacokinetic study is used as a measure of safety it must measure plasma concentrations under fasted and fed conditions and when balsalazide is sprinkled on applesauce, the measurements should include all three key analytes (balsalazide, 5-ASA and N-Ac-5-ASA), and the study should be conducted using ulcerative colitis patients in remission. Salix also demonstrated that OGD's proposed dissolution testing does not mimic in vivo dissolution and presented evidence that data obtained through OGD's recommended dissolution testing differs from data obtained through dissolution testing that more closely mimics in vivo conditions.

In this Supplement, Salix demonstrates that OGD's proposed bioequivalence testing does not address the pharmacokinetics of balsalazide disodium in pediatric patients and therefore does not address potential safety issues in this population. As is demonstrated in the approved labeling for RLD Colazal, pediatric patients absorb balsalazide disodium very differently than adult patients. This inconsistency raises additional serious safety and equivalency concerns regarding the use of generic balsalazide products in the pediatric population. Salix continues to believe that OGD's obligation is to ensure the safe and effective interchangeability of commercially available balsalazide, and that the only plausible manner to ensure the safe and effectiveness of a new formulation of balsalazide is to conduct clinical trials in the target population. As is demonstrated below, if OGD nevertheless determines to require only bioequivalence studies, these studies should assess absorption of the drug and metabolites in the pediatric population because the safe use of the generic formulation can not be addressed by "carving out" this indication in the labeling.

I. STATEMENT OF GROUNDS

A. Background

1. Low Solubility and Permeability of Balsalazide Disodium

Balsalazide disodium, the active ingredient in Colazal 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. When taken orally, balsalazide disodium remains virtually unabsorbed (<1%) in the upper GI tract. Upon reaching the colon, balsalazide is metabolized by colonic bacteria to yield the therapeutically active substance, 5-amino salicylic acid (5-ASA), which reduces inflammation of the colonic mucosa associated with ulcerative colitis. Low and variable levels of 5-ASA are absorbed through the colon into the portal and subsequent circulation, while the majority of 5-ASA that penetrates the mucosa is converted to N-acetyl-5-amino salicylic acid (NASA). It is assumed that this conversion of balsalazide to 5-ASA only occurs when balsalazide is in solution, as it requires the cleavage of an azo-bond by the enzyme, azo-reductase, which is produced by colonic bacteria. This profile of absorption reduces the systemic exposure and results in a favorable safety profile of the drug for both the adult and pediatric patient populations for which Colazal is indicated.

2. OGD Recommendations Regarding Patient Population for Bioequivalence Testing

As outlined in the March 2006 bioequivalence recommendations,¹ OGD has stated that bioequivalency testing is to be performed in normal healthy volunteers. Salix has previously submitted evidence showing that significant absorption differences exist between normal healthy volunteers and the patient populations addressed in the approved labeling for the RLD Colazal. The GI Division at FDA also noted this difference between healthy volunteers and patients by including guidance for physicians in the approved labeling stating that absorption in patients can be up to 60-fold that observed in volunteers.²

3. History of Filings on FDA Docket No. 2005P-01461

Salix has previously shared its own scientific experience with balsalazide disodium and that of the published literature with OGD in a White Paper submitted to OGD on November 12, 2004 and publicly in a Citizen Petition filed April 13, 2005. These filings demonstrated the need for the issuance of appropriate guidelines for the approval of safe and effective balsalazide-containing compounds.

In addition, Salix filed supplements to the petition on July 14, 2006, November 14, 2006 and June 14, 2007. These supplements were submitted by Salix in response to bioequivalence recommendations that OGD provided for balsalazide-containing drug products. Specifically, the July 2006 supplement reviewed the scientific inadequacies of the *in vitro* dissolution and *in vivo* bioequivalence approach being considered by OGD. The November 2006 supplement provided an additional review of the scientific inadequacies of the *in vitro* dissolution and *in vivo* bioequivalence recommendations proposed by OGD and argued that following the recommendations would disregard the new label information regarding the effect of food on dosing of Colazal and the adequacy of sprinkling Colazal on applesauce as an administration route. Finally, the June 2007 amendment provided experimental evidence showing the lack of correlation of the *in vitro* dissolution testing proposed in OGD's recommendation with dissolution observed under *in vivo* conditions.

In the present supplement, Salix provides experimental data showing that pediatric ulcerative colitis patients display altered blood levels of balsalazide and metabolites compared with adult patients. The supplement further argues that the generic balsalazide capsule will be used as a pediatric-specific formulation without verification of its

¹ On February 5, , Salix learned from outside counsel that OGD is no longer distributing these recommendations. There are no substitute recommendations and OGD has stated that the recommendations would be distributed in the form of FDA's response to the pending Citizen Petition.

² Colazal Label, p. 8 ("In a separate study of adult patients with ulcerative colitis, who received balsalazide, 1.5g twice daily, for over 1 year, systemic drug exposure, based on mean AUC values, was up to 60 times greater (0.008 µg·hr/mL to 0.480 µg·hr/mL) when compared to that obtained in healthy subjects who received the same dose.").

bioequivalence in this patient population, and therefore represent a significant safety risk to pediatric patients.

B. Pediatric Studies Required as Phase IV Agreements

As a condition for approval of Colazal, the GI Division requested that safety and efficacy studies be performed in pediatric ulcerative colitis patients.³ Specifically, the Phase IV requested studies were to include a pharmacokinetic component to gain information on the systemic adsorption of balsalazide and metabolites in this population. This allowed comparison of plasma drug levels and adverse event rates in the pediatric population with that of the adult population. The GI Division also requested that these studies be performed on a population-specific formulation. Salix agreed to and complied with all of these requests and studying the safety and efficacy of two different dosages of Colazal in pediatric UC patients. The study included 45 patients, 5-18 years of age with active ulcerative colitis confirmed by sigmoidoscopic and histological diagnosis. In addition 12 of these patients participated in a pharmacokinetic component of the study after two weeks of treatment. The pharmacokinetic study was similar to a previously submitted Phase IV required study in adults that examined the absorption of balsalazide and metabolites in adult ulcerative colitis patients with active disease.⁴ Both the adult and pediatric PK studies examined drug absorption after 2 weeks of treatment when plasma levels are at steady state and can therefore be compared. The results of the pediatric studies were submitted as an sNDA to the GI Division on June 19, 2006 and the pediatric indication was added to the approved Colazal labeling on December 20, 2006.⁵ Thus Salix adequately responded to and met the requirements of the Phase IV requests from the GI Division. Colazal is the only approved mesalamine-containing product approved for pediatric use. In addition, balsalazide has received Orphan Drug status for this patient population.

C. Capsule Formulation is the Pediatric Specific Formulation

Salix proposed and the GI Division concurred in a letter dated December 21, 2004⁶ that the current capsule formulation of Colazal was an age-appropriate formulation if supported by pharmacokinetic profiling of balsalazide and its metabolites after sprinkling on applesauce ("sprinkles"). In addition, the letter asked for stability data of balsalazide when mixed in applesauce. The use of sprinkles as a mode of delivery was confirmed in the pediatric safety and efficacy study and in a fed versus fasted PK study in adults. In addition, the stability of balsalazide once sprinkled on applesauce was also confirmed. The results of

³ Approval letter, July 18, 2000.

⁴ NDA 20-610/S-014 submitted March 26, 2006

⁵ Pediatric approval letter, *available at*: <http://www.fda.gov/cder/foi/applletter/2006/020610s016ltr.pdf>.

⁶ Communication letter to Salix Pharmaceuticals, Inc. from the GI Division, December 21, 2004

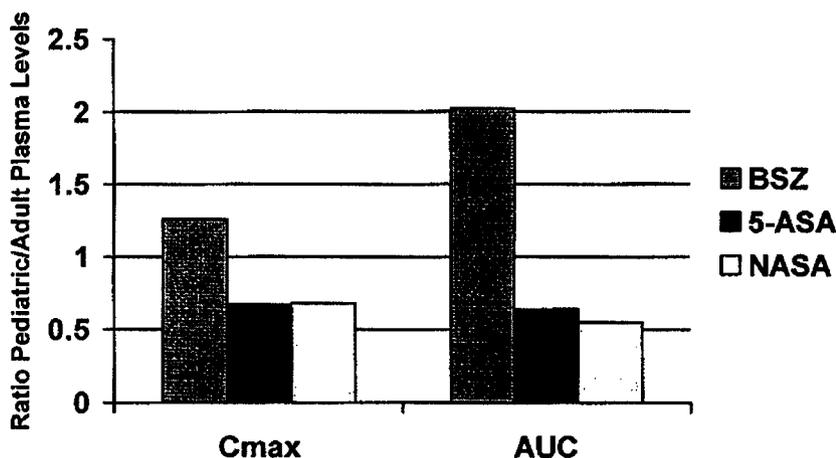
the pharmacokinetic and stability studies were submitted in an sNDA on March 26, 2006 and incorporated into the Colazal approved labeling on September 21, 2006.⁷

The results of the completed Phase IV requirements including PK, safety and efficacy studies in pediatric and adult ulcerative colitis patients coupled with the appropriate PK and stability studies on the sprinkle formulation have together contributed to the current approved labeling for Colazal. Thus, the current capsule formulation is both the adult and pediatric-appropriate formulation of the drug product.

D. Pediatric Patients have Different Blood Levels Than Adults

The approved labeling for Colazal includes information for physicians on the relative absorption levels of balsalazide and metabolites in both adult and pediatric ulcerative colitis patients. The approved labeling states that the plasma levels of the drug derived from Colazal are different in pediatric patients than those found in adult patients. Specifically, it is noted that balsalazide parent drug levels are higher in pediatric patients and that both 5-ASA and N-acetyl-5-ASA are lower in pediatric patients compared to adult patients.⁸ These data are shown graphically in Figure 1 below. Differences in C_{max} and AUC are both observed and there appears to be greater plasma levels of balsalazide (up to 2-times) in pediatric patients, and lower levels of 5-ASA and NASA (reduced by about one-half) in children relative to adults.

Figure 1: Comparison of Steady State Plasma Levels in Pediatric and Adult UC Patients⁸



⁷ Food effect approval letter, available at: <http://www.fda.gov/cder/foi/appletter/2006/020610s0141tr.pdf>.

⁸ Colazal Label, page 9.

E. Recommended Studies Do Not Predict Formulation Performance in the Pediatric Population

Salix has previously presented arguments describing the scientific inadequacies of the dissolution and bioequivalence studies recommended by OGD for the approval of generic formulations of the drug substance balsalazide disodium.⁹ Evidence has been presented showing that 1) the recommended *in vitro* dissolution studies do not predict formulation performance under more rigorous *in vivo* conditions, the 2) the recommended bioequivalence studies fail to measure all drug metabolites (5-ASA and NASA) and fail to use the most relevant subject population (patients) necessary to ensure safety, and that 3) the recommended bioequivalence studies are inconsistent with the approved labeling for the RLD Colazal by not requiring measurements in both fed and fasted conditions.

The reason for the differences seen in plasma profiles between pediatric and adult UC populations are not known. However, since the marketed formulation is the pediatric-appropriate formulation, a generic capsule product, once marketed, will be used in pediatric patients even though the performance of the generic formulation has not been shown to be bioequivalent to the RLD Colazal in this population. The concerns raised above regarding the scientific inadequacy of the recommended studies therefore become all the more critical because they will allow for pediatric use of a formulation whose plasma levels may not be within the range shown to be safe from the Colazal pediatric and pharmacokinetic studies.

II. 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®. Approval of a generic version of Colazal using the current recommended studies will allow its use in a patient population whose safety profile relies on a lower level of drug absorption than that known for the population targeted in the March 2006 bioequivalence recommendations.

As we have previously emphasized, Salix believes OGD's obligation is to ensure the safe and effective interchangeability of commercially available balsalazide, and that the only plausible manner to ensure the safe and effectiveness of a new formulation of balsalazide is to conduct clinical trials in the target population.

As is demonstrated in this Supplement, significant safety concerns are raised for the pediatric patient population if generic versions of the RLD Colazal are approved

⁹ FDA Docket No. 2005P-0146.

without proper scientific study. Furthermore, as was demonstrated in previous Supplements, if *in vivo* pharmacokinetic studies are used they must measure plasma concentrations under fasted and fed conditions and when balsalazide is sprinkled on applesauce, and the measurements should include all three key analytes (balsalazide, 5-ASA and N-Ac-5-ASA). The studies should also be conducted using ulcerative colitis patients in remission, because of the increased absorption of all analytes over that seen with healthy volunteers. They should at a minimum also assess absorption of the drug and metabolites in the pediatric population because the safe use of the generic formulation can not be addressed by "carving out" this indication in the labeling.

In the absence of suitable *in vivo* dissolution and pharmacokinetic measures, supported by scientific fact, we conclude at this time 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.

III. 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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