



June 14, 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-0146

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, and November 14, 2006. This Supplement addresses issues concerning the dissolution testing proposed within the bioequivalence recommendations of the Food and Drug Administration's ("FDA's") Office of Generic Drugs ("OGD"), listed in a letter dated March 24, 2006. Salix asserts, that the proposed dissolution studies do not adequately mimic *in vivo* conditions; and, consequently fail to capture critical data predictive of the equivalence of a generic balsalazide disodium in *in vivo* conditions, to the reference listed drug (RLD) Colazal®. In addition, the proposed *in vivo* clinical bioequivalence studies proposed by FDA fail to measure the key metabolite, N-acetyl-5-amino salicylic acid, which is present at 10 to 100-fold the concentration of the proposed 5-ASA analyte and which possess and exerts beneficial pharmacological activity. Thus, adequate efficacy and safety assurance, cannot be predicted from such recommendations lacking adequate scientific rigor.

I. ACTION REQUESTED

Salix continues to support the actions requested in its April 13, 2005, Citizen Petition and its July 14, 2006, and November 14, 2006, 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. The FDA has recently released a "Draft Guidance for Industry: Bioequivalence Recommendations for Specific Products" which issued in May 2007.¹ The Draft Guidance lists selected Draft Guidances for certain products; however, it does not include balsalazide.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.

¹ FDA, *Guidance for Industry: Bioequivalence Recommendations for Specific Products* (May 2007), available at: <http://www.fda.gov/cder/guidance/6772dft.pdf>.

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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.

In this Supplement, Salix demonstrates that OGD's proposed dissolution testing does not mimic *in vivo* dissolution and presents evidence that data obtained through OGD's recommended dissolution testing differs from data obtained through dissolution testing that more closely mimics *in vivo* conditions. This new data adds further support to Salix's previous arguments that OGD has failed to consider measurement of an important component of the therapeutic treatment regimen for all oral 5-ASA-containing compounds, N-acetyl-5-aminosalicylic acid. The lack of profiling of this analyte for balsalazide-containing formulations, coupled with the lower than expected dissolution of balsalazide capsules described herein under "*in vivo*-like" conditions raises additional serious safety and equivalency concerns regarding generic balsalazide products.

II. STATEMENT OF GROUNDS

A. Background

1. OGD Public Statement Regarding Bioequivalence Testing

Representatives from OGD have on several occasions presented the Office's general concept of the role of *in vitro* dissolution and *in vivo* bioequivalence testing in the generic approval process. This concept is shown below in **Figure 1**:²

² Figure 1 is reproduced from a slide deck presented at a May 2007 "Workshop on BE, BCS and Beyond" which was co-sponsored by FDA and the American Association of Pharmaceutical Scientists. See www.aapspharmaceutica.com/meetings/meeting.asp?id=90.

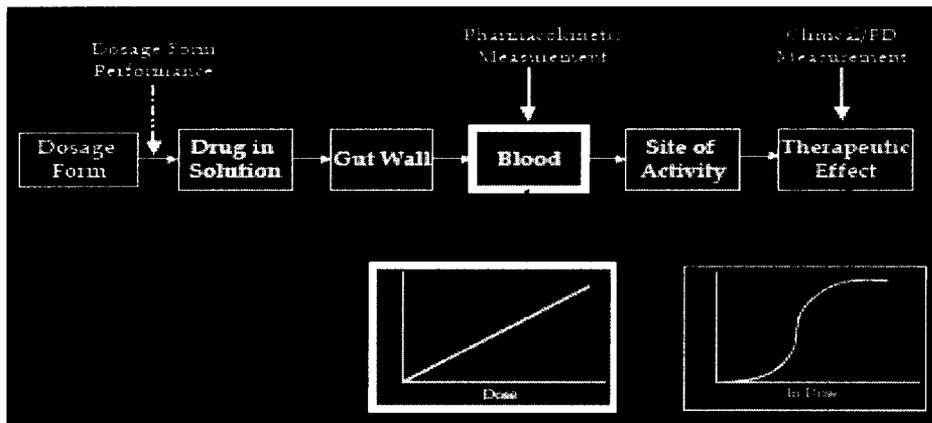


Figure 1. OGD Schematic Diagram of Relationship Between Pharmacokinetic Bioequivalence and Therapeutic Effect for Systemically Acting Drugs

Two critical points of measurement are: 1) **dosage form performance** which should correlate with the solubility of the drug *in vivo*, and 2) **the pharmacokinetic measurement in blood** which should correlate with the concentration of drug reaching the site of activity. These are well accepted principles on which the approval of generic drugs is based.

However, the situation of locally acting oral GI drugs is entirely different as shown schematically in **Figure 2** below. First, ***in vivo* dissolution** is critical as dissolution is the first and only step required prior to appearance of the drug at the site of action. There is no intermediate step of absorption into the blood where an *in vivo* measure can monitor the level of released drug prior to its arrival at the site of action. Measurement of drug at the site of action is the only true measure of formulation performance.

Secondly, measurement of blood levels of the therapeutic agent and its relevant metabolites are important safety determinants. If no measurement of delivered drug is made at the site of activity, the blood levels become even more important, if they can also give some clue regarding the level of the therapeutic agent reaching the target tissue. However, since the blood levels are only a surrogate measure of formulation performance, made **after** the drug has left the therapeutic site of action, it is important to take into account both the active drug substance; and, its known metabolite if the metabolite is also a marker for the interaction of the drug with the site of activity.

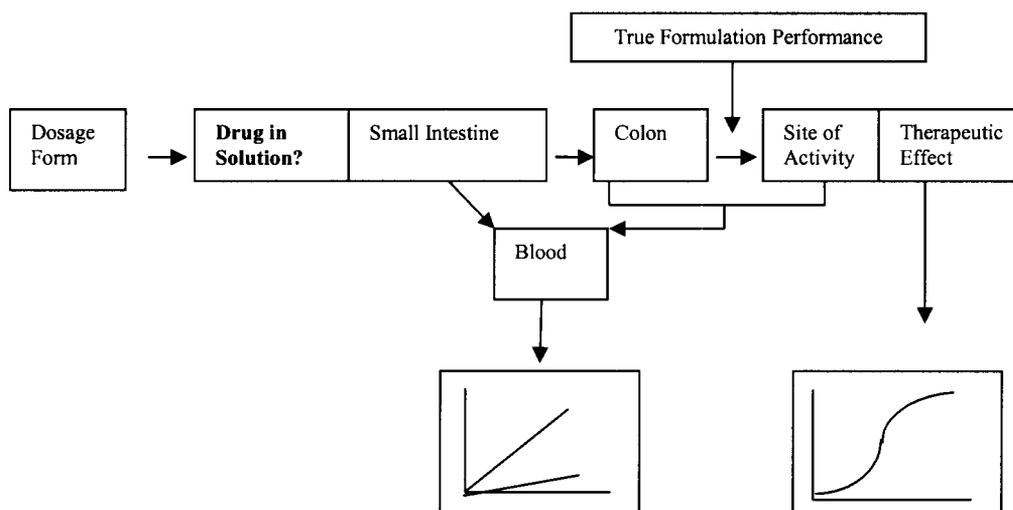


Figure 2. Schematic Diagram of Relationship Between Pharmacokinetic Bioequivalence and Therapeutic Effect for Local GI Acting Drugs (Adapted from Figure 1.)

The following discussion focuses on these two most important steps in determining the bioequivalence of the locally acting GI drug balsalazide disodium, *in vivo* dissolution and *in vivo* bioequivalence of the most relevant analytes, 5-ASA and N-acetyl-5-ASA.

2. Low Solubility and Permeability of Balsalazide Disodium

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. 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.

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, and November 14, 2006. These supplements were submitted by Salix in response to bioequivalence recommendations that OGD provided for balsalazide-containing drug products.³ Specifically, the July supplement reviewed the scientific inadequacies of the *in vitro* dissolution and *in vivo* bioequivalence approach being considered by OGD. The November 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: 1) fail to require *in vitro* and *in vivo* data demonstrating 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.

In the present supplement, Salix provides some experimental data showing that FDA's *in vitro* dissolution protocol does not correlate with actual *in vivo* performance; and, hence fails to provide a basis for comparing even relative formulation performance under physiological conditions.

B. OGD Recommended Dissolution Studies

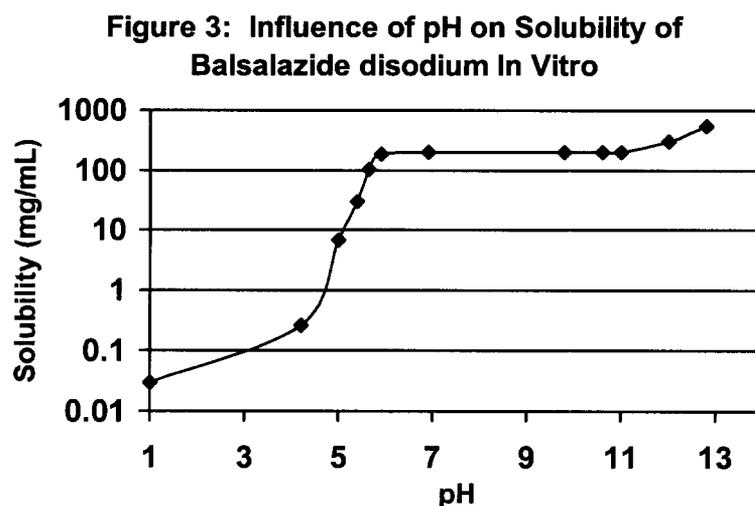
The Office of Generic Drugs has recommended certain studies to demonstrate bioequivalence of a potential generic version of the reference listed drug, Colazal (balsalazide disodium) capsules 750mg. OGD has reasoned that dissolution of the drug substance *in vivo* is the determining factor in performance of the drug product formulation. Thus, OGD has stated that *in vitro* dissolution, coupled with limited *in vivo* pharmacokinetic evaluations, is sufficient to confirm bioequivalence of two different balsalazide containing formulations. OGD put forth this recommendation even though neither balsalazide nor its therapeutically active metabolites, 5-ASA and NASA, exert their efficacy within the systemic circulating compartment. OGD has recommended no studies that directly address the issue of *in vivo* dissolution. OGD has also not recommended studies that directly measure the drug at the site of action or a surrogate marker for the drug having acted at the site of action, although both of these measurements are scientifically valid and experimentally possible. Such experiments would yield valuable information about the local GI bioequivalence of two different balsalazide formulations.

The OGD 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.” The recommendations propose a comparative dissolution test to fulfill this function. OGD recommends 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

³ On February 5, 2007, 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.

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 profiling is insufficiently discriminatory to detect differences in formulation performance. Balsalazide has very limited solubility at pH 1.0-4.0, but this increases 1000-fold as the range rises between pH 4.5-7.4. This is demonstrated in **Figure 3** below for balsalazide disodium powder *in vitro*:⁴



Because balsalazide rapidly goes into solution above pH 4.0, 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 the average 24 hour pH is well below pH 4.5.⁵ 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. Thus, the sequential exposure experience *in vivo* is not reflected in the recommended *in vitro* study.

The failure of OGD's recommended studies to replicate *in vivo* dissolution is significant because it is not known where in the GI tract *in vivo* dissolution takes place. As

⁴ Open Part to OmniChem DMF 12287 (1996), page 22.

⁵ Merki HS, Fimmel, CP, Walt, RP *et al.* (1988). Pattern of 24 hour intra-gastric acidity in active duodenal ulcer disease and in healthy controls. *Gut* 29: 1583.

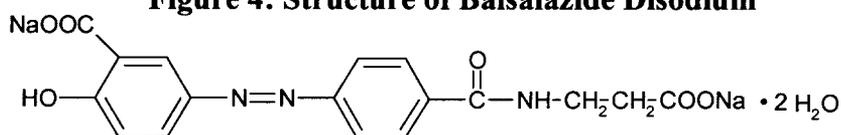
outlined below, less than 1% of the balsalazide dose is absorbed systemically and this absorption generally occurs within an hour of dosing. The cause of this limited absorption is unknown; it may be due to either low solubility or low permeability in the small intestine, or some combination of both.

Given these characteristics of balsalazide, formulation performance as tested by the recommended *in vitro* conditions, cannot be used as a surrogate for the complexities of *in vivo* dissolution. The dissolution testing proposal is even more questionable given the possible change in crystalline structure that can occur at pH < 4.0 in the stomach, 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, Salix has argued and continues to believe that *in vitro* dissolution is only appropriate for use as a release specification, not as a bioequivalence measure.

C. Influence of pH on Crystalline Structure

The chemical structure of balsalazide and the characteristics of its constituent chemical groups is relevant to its dissolution *in vivo*. Shown below in **Figure 4** is the chemical structure of balsalazide disodium, as displayed in the Colзал Package Insert.

Figure 4: Structure of Balsalazide Disodium



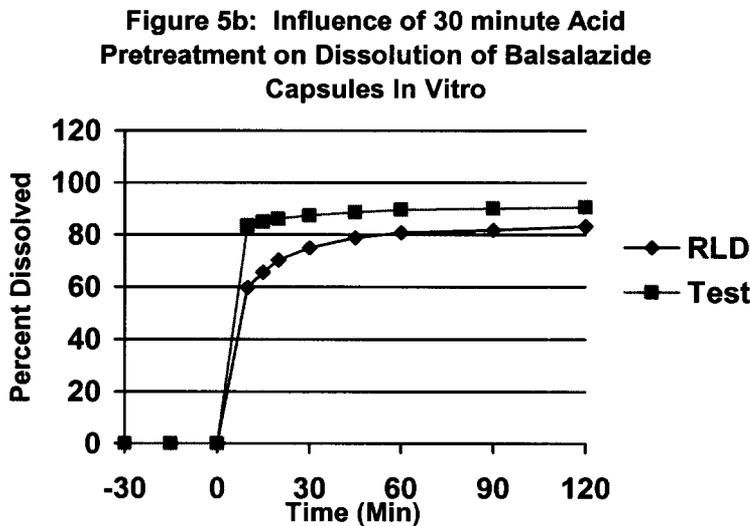
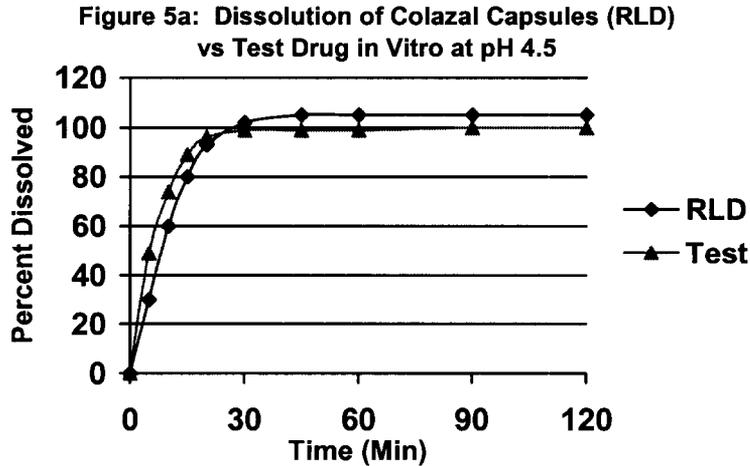
The molecule has three ionizable groups that influence the solubility of the compound at various pH. In the powder form of the Colзал capsule, two of these groups (the C-terminal carboxyl of β -alanine and the 3-carboxyl group of 5-ASA are presented as the sodium salt. These have pK values of 5.1 and 5.3 respectively, while the remaining ionizable group (the 2-hydroxyl group of 5-ASA) has a pK of 10.8.⁶ The disodium salt is therefore soluble at pH greater than 4.0.

The import of this structure is that when the capsule contents are exposed to acid conditions of 0.1N HCL in gastric fluid, the sodium salt form is rapidly converted to the protonated acid form, which has been shown experimentally to be insoluble. The subsequent solubility of the free acid form of balsalazide is then the determining factor of *in vivo* dissolution. However, the OGD recommended *in vitro* dissolution tests do not address this issue and propose only to test dissolution of the sodium salt.

Salix has therefore performed tests to determine whether balsalazide disodium as formulated in Colзал capsules quantitatively dissolves after exposure to 0.1N HCL, conditions which mimic the *in vivo* conditions of gastric fluid. For comparison, samples of balsalazide disodium capsules from a different manufacturer were also tested. As shown in

⁶ Colзал NDA 20-610, Volume 1.003, page 0038.

Figure 5 below (see reference⁷ for methods), both the RLD and the Test drug dissolve completely in pH 4.5 buffer under the OGD recommended conditions. The f2 metric comparison between these two dissolution profiles is $f_2 = 50$, which is not strong but an acceptable correlation.



However, as shown in **Figure 5b**, the RLD and the Test drug do not display identical dissolution profiles when first exposed to 0.1N HCL for 30 minutes, and then

⁷ Apparatus: paddles with sinkers (USP Apparatus 2), Temperature: 37 +/- 0.5 degrees C, Paddle Speed: 50 rpm, Volume: 900 mL, Sample Volume: 10 mL, Buffer: 22 mM Acetate, pH 4.5, Method of Detection: UV, Sample Size: 12 capsules. For two-tiered dissolution, first condition was 0.1N HCL for 30 min, followed by direct addition of buffer to raise the pH to 4.5. Starting and final pH of each vessel was confirmed by direct pH measurement at each time point.

shifted to pH 4.5 buffer to assess dissolution. While a large percentage of both the RLD and Test drug rapidly dissolve in 5 minutes after the acid pretreatment, there is a residual amount of drug substance that fails to dissolve out to 120 minutes. For the RLD this fraction is approximately 20% of the dose. Thus, while the Test drug would pass the *in vitro* dissolution specification set forth by OGD, under more simulated “*in vivo*” conditions its dissolution differs from the RLD.

These data demonstrate Salix’s contention that the proposed *in vitro* dissolution conditions lack sufficient scientific rigor to be used as a surrogate for actual dissolution *in vivo*. The influence of acid could be due to interaction of crystalline balsalazide with the solubilized gelatin capsule shell. Alternatively, differences in particle size, formulation, and formulation processing, such as blend time, may influence this crystalline transition that occurs upon exposure of balsalazide-containing capsules to acid. Salix is continuing to experimentally address these possibilities.

Consistent with these possible interactions, Salix has used dissolution testing only in connection with a full physical and chemical characterization of the drug, including both the API and the manufacturing process, so as to ensure adequate understanding of formulation performance within the context of the RLD.⁸ By comparison, the *in vitro* dissolution conditions proposed in the guidelines for comparing an entirely different drug product to the RLD do not (and cannot) provide for any such underlying basis for comparison and, as suggested by the testing set forth above, lack sufficient scientific rigor to be used as a surrogate for actual dissolution *in vivo*.

D. OGD Recommended Dissolution Testing *In Vitro* Is Not Discriminatory

The OGD recommendations for *in vitro* dissolution testing do not reflect the *in vivo* conditions to which balsalazide is exposed. As shown in **Figure 5a**, two different balsalazide-containing formulations can show acceptable or identical dissolution profiles when tested directly under pH conditions where balsalazide is soluble (i.e. pH > 4.0). However, under simulated *in vivo* conditions, the two different balsalazide-containing formulations show differences that are relevant *in vivo* and influence the quantity of drug substance that ultimately reaches the intended site of action in the colon. These differences will not be detected using the *in vitro* conditions currently proposed by OGD for generic balsalazide formulations. Thus, a key missing piece of information in OGD’s recommendations is the direct testing of *in vivo* vs. *in vitro* dissolution.

OGD has not yet proposed an acceptable, validated, *in vivo* test that either measures dissolution in the upper GI tract or measures the amount of active drug reaching the intended site of action in the colon. Indeed, the *in vivo* bioequivalence tests proposed by OGD only measure analytes in plasma that account for 3% of the oral dose.⁹ However, the dissolution test results reported here identify a fraction of balsalazide (up to 20%), with a

⁸ Colazal NDA 20-610, Supplement 002: Action date February 7, 2002.

⁹ Colazal Package Insert: **Elimination**. September 21, 2006.

dissolution profile that differs after exposure to conditions present in the gastric compartment. There can, therefore, be no assurance that any of the testing proposed by OGD can discriminate between two formulations whose performance may truly differ markedly *in vivo* but may not appear to differ *in vitro*.

It therefore becomes even more important scientifically to account for the maximum possible percentage of the oral dose reaching the site of activity. As discussed below, OGD's failure to recommend measurement of the key analyte, N-acetyl-5-ASA, further compromises the scientific validity of the recommended equivalence testing, in light of the newly presented dissolution data.

E. Systemic Levels of 5-ASA Cannot Be Used to Assess Formulation Performance

The data presented in **Figure 5** show that *in vivo* formulation performance cannot be predicted from *in vitro* dissolution. Further, the recommended bioequivalence measurement of systemic 5-ASA does not reflect the level of therapeutically active agent(s) at the site of activity (the inflamed colonic mucosa). Upon receiving a single dose of the RLD Colazal, only 0.2-3% of the dose as 5-ASA of the balsalazide parent compound is ultimately absorbed into the systemic circulation. It is possible that 0.2-3% of the dose would still appear in the systemic circulation if only 80% of the dose was exposed to the colonic mucosa (i.e. if 20% of the dose failed to dissolve). Furthermore, there is no scientific evidence that the 5-ASA appearing in plasma, has in fact acted in the colonic mucosa.

Given these complications and the difficulty of predicting formulation performance through *in vitro* dissolution, it is surprising that OGD does not recommend the measurement of the primary metabolite of 5-ASA, N-acetyl-5-ASA (NASA). Salix has previously presented the scientific rationale for measuring NASA in any BE assessment of an oral mesalamine product. Unlike 5-ASA, NASA is formed in the colonic mucosa and is reflective of the appearance of 5-ASA, at the site of activity. Its measurement in the systemic circulation could be used as a surrogate indicator of formulation performance.

There are situations where FDA recommends measurement of a primary metabolite in a BE study, as found in the FDA Guidance for Industry, "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products"¹⁰ which states:

For BE studies, measurement of only the parent drug released from the dosage form, rather than the metabolite, is generally recommended. The rationale for this recommendation is that the concentration-time profile of the parent drug is more sensitive to changes in formulation performance than a metabolite, which is more reflective of metabolite formation,

¹⁰ FDA, *Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations*, VI(B)(2), p. 18 (March 2003), available at: <http://www.fda.gov/cder/guidance/5356fml.pdf>.

distribution, and elimination. The following are exceptions to this general approach.

- Measurement of a metabolite may be preferred when parent drug levels are too low to allow reliable analytical measurement in blood, plasma, or serum for an adequate length of time . . .
- . . . If the metabolite contributes meaningfully to safety and/or efficacy, we also recommend that the metabolite and the parent drug should be measured. When the relative activity of the metabolite is low and does not contribute meaningfully to safety and/or efficacy, it does not have to be measured

For the present drug product both of the exceptions put forth by FDA apply, as seen below.

1. Measurement of a metabolite may be preferred when parent drug levels are too low to allow reliable analytical measurement

In light of the unexpected dissolution results described herein, where up to 20% of the parent drug dose may not dissolve *in vivo*, it is of utmost importance to focus analysis on the analyte that yields the most precise measure. While NASA is a metabolite of 5-ASA, its systemic appearance does not kinetically lag the appearance of 5-ASA in plasma. At the earliest time points there is quantitative conversion of 5-ASA to NASA until the acetylation system becomes saturated.¹¹ It can therefore be argued that the detection of NASA in plasma is more (not less) sensitive to formulation performance than measurement of 5-ASA. Ultimately, the systemic exposure to NASA is 10-100-fold greater (20-25% of the dose) than the parent 5-ASA (0.2-2% of the dose).¹²

Both balsalazide and 5-ASA are considered highly variable, critical analytes based on the FDA-defined systemic exposure metrics (i.e., within Subject CV >30% and a non-narrow Therapeutic Index).¹³ However, for NASA, the inter-subject variability for the three primary metrics (C_{max}, AUC_T, and AUC_{inf}) are 32, 21 and 26%, respectively. Thus measurement of NASA adds an increased measure of precision to the RLD and Test drug comparison.

¹¹ *Colazal: Pharmacology and Biopharmaceutics Review*, NDA 20,610, p. 9, para 4. May 19, 2000.

¹² *Colazal Package Insert: Elimination*. September 21, 2006.

¹³ FDA, *Draft Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations*, p.7 (Oct. 2000), available at: <http://www.fda.gov/cder/guidance/3615f1.pdf>. The March 2003 final guidance is available at: <http://www.fda.gov/cder/guidance/5356f1.pdf>.

2. If the metabolite contributes meaningfully to safety and/or efficacy, the metabolite and the parent drug should be measured.

NASA does contribute to the overall efficacy of mesalamine therapy. Acetylation occurs primarily in the mucosa and in colonic homogenates was 370nmol/g versus 13 nmol/g in fecal bacteria.¹⁴ Acetylation is therefore a pre-systemic event and directly reflects the interaction of the released 5-ASA with the inflamed mucosa. In addition, NASA has been shown to exert anti-inflammatory activity. Early studies using NASA containing enemas to treat distal ulcerative colitis demonstrated improvement of clinical symptoms as well as sigmoidoscopic and histological improvement in significantly more patients than placebo enemas.¹⁵ While this activity was later confirmed to be lower (by about half) on a molar basis than 5-ASA,¹⁶ it is noted that in mucosal biopsies from patients treated with oral mesalamine the ratio of NASA to 5-ASA is >1.0.¹⁷ It is therefore likely that mucosal NASA also is a significant contributor to the overall efficacy of mesalamine products.

NASA also has its own safety profile. Given the high plasma concentrations of NASA and its known pharmacological activity, it is necessary from a safety standpoint to confirm that any balsalazide containing formulation is shown to be bioequivalent with respect to the plasma NASA concentration delivered. Obviously, the safety profile discussed in the approved package insert is a summary of those events that are reported due to the combined plasma levels of balsalazide, NASA and 5-ASA. Since NASA represents by far the greatest level of these absorbed components (10-100-fold greater), it is necessary to confirm that it remains within the described safety limits.

F. Guidance for Other Mesalamine Formulations Are Not Aligned or Consistent

Salix notes that the OGD guidance for BE testing of mesalamine containing products are not aligned nor consistent.¹⁸ OGD has indicated that when the site of drug

¹⁴ Allgayer H, Ahnfelt NO, Kruis W, Klotz U, Frank-Holmberg K, Soderberg HN, Paumgartner G. (1989). Colonic N-acetylation of 5-aminosalicylic acid in inflammatory bowel disease. *Gastroenterology*. 1989 Jul;97(1):38-41.

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

¹⁶ van Hogezaand RA, van Hees PA, van Gorp JP, van Lier HJ, Bakker JH, (1988). Double-blind comparison of 5-aminosalicylic acid and acetyl-5-aminosalicylic acid suppositories in patients with idiopathic proctitis. *Aliment Pharmacol Ther*. Feb; 2(1):33-40.

¹⁷ Hussain FN, Ajjan RA, Riley SA. (2000). Dose loading with delayed-release mesalazine: a study of tissue drug concentrations and standard pharmacokinetic parameters. *Br J Clin Pharmacol*. Apr;49(4):323-30.

¹⁸ FDA, *Guidance for Industry: Bioequivalence Recommendations for Specific Products* (May 2007), available at: <http://www.fda.gov/cder/guidance/6772dft.pdf>.

release **cannot** be reliably predicted, BE studies with clinical endpoints are required. Thus, Pentasa® which is mesalamine formulated in a slow release matrix, releases mesalamine throughout the upper GI tract. However, since the precise location is unknown, OGD has indicated that a BE study with clinical endpoints is required. Similarly, Sponsors submitting ANDAs for mesalamine rectal suppositories, whose dissolution *in vivo* cannot be quantitatively predicted by melting studies *in vitro*, are guided to perform a BE study with clinical endpoints. In contrast, sponsors submitting ANDAs for pH-dependent release mesalamine (Asacol®), diazo-bonded olsalazine (Dipentum®) and diazo-bonded balsalazide (Colazal®) are guided to test BE only, without clinical endpoints.

It is reasonable that OGD should recommend product specific testing. However, in the case of the RLD Colazal, based on data provided herein, it appears impossible to predict where in the GI tract quantitative dissolution of the formulation takes place. The recommended *in vitro* dissolution testing does not predict *in vivo* formulation performance, where as much as 20% of the dose may not be available for release at the site of activity. Furthermore, the recommended *in vivo* BE testing only measures the equivalent of at most 3% of the dose. This is certainly a smaller quantity of active drug than that accounted for in the use of mesalamine rectal suppositories (about 40% bioavailability)¹⁹ where the dosage form is manually placed directly at the site of activity. This shows OGD's inconsistent use of scientific rationale for the recommendation of testing required for approval of mesalamine-containing products.

Figure 6, below summarizes the data presented herein in relation to measurements recommended by OGD for approval of an ANDA for balsalazide-containing compounds. The numbered steps below refer to the numbers (1,2,3) in the figure.

1. The *in vitro* dissolution measures are unable to account for as much as 20% of the dose when more appropriate “*in vivo-like*” conditions are used.
2. Profiling the absorbed balsalazide by blood-based BE is next used to confirm *in vivo* dissolution by examining only 0.1% of the dose in the blood compartment.
3. Profiling only the absorbed 5-ASA and not the NASA by blood-based BE is next used to confirm the presence of the drug at the site of action by examining only 0.2-3% of the dose, while ignoring another 20-25% of the dose in the systemic compartment.

Approving an ANDA for a balsalazide-containing formulation following the proposed recommendations, will base bioequivalence on a measure of formulation performance that assesses analytes representing only 3% of the original oral dose, even though measurements made, *in vivo*, at the site of activity (true formulation performance) is

¹⁹ Aumais G, Lefebvre M, Tremblay C, Bitton A, Martin F, Giard A, Madi M, Spenard J. (2003) Rectal tissue, plasma and urine concentrations of mesalazine after single and multiple administrations of 500 mg suppositories to healthy volunteers and ulcerative proctitis patients. *Aliment Pharmacol Ther.* 17(1):93-7.

scientifically feasible and would assess the bioavailability of the remaining 97% of the original oral dose.

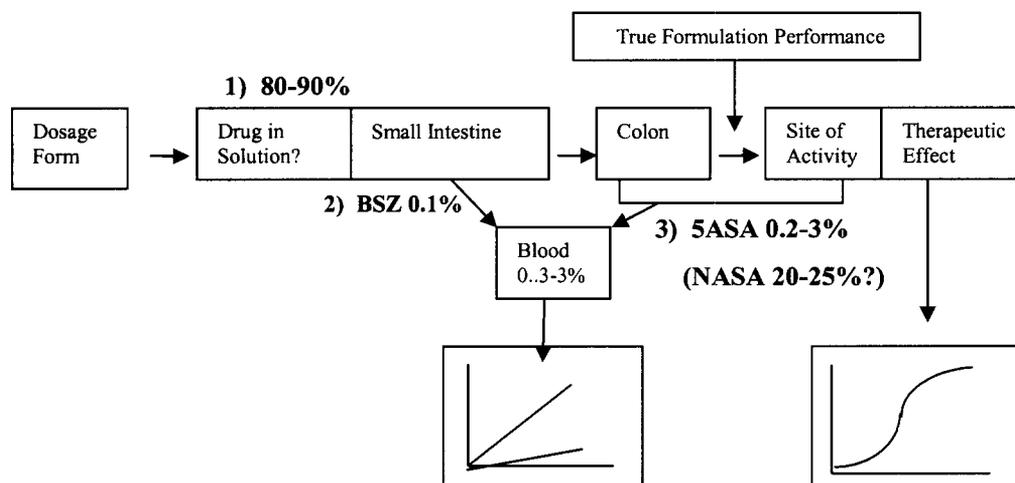


Figure 6. Schematic diagram of measurement points recommended by OGD for approval of an ANDA for balsalazide-containing compounds (Adapted from Figure 1)

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®.

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 effectiveness of a new formulation of balsalazide is to conduct a clinical efficacy trial. *In vitro* dissolution testing and pharmacokinetic studies are only valuable in assessing equivalence in relation to the safe use of balsalazide.

As is demonstrated in this Supplement, if dissolution testing is used, dissolution studies should be designed to mimic *in vivo* conditions. Furthermore, as was demonstrated in previous Supplements, if an *in vivo* pharmacokinetic study is used 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). The study should also be conducted using ulcerative colitis patients in remission, because of the increased absorption of all analytes over that seen with healthy volunteers.

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.

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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