



**HAND DELIVERY - RETURN RECEIPT REQUESTED**

April 13, 2005

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

CITIZEN PETITION

The undersigned, Salix Pharmaceuticals, Inc. ("Salix"), is submitting this petition in accordance with § 505(j) of the Federal Food Drug and Cosmetic Act ("FFDCA"), as well as 21 C.F.R. §§10.20, 10.30, and 320, and respectfully requesting that the Commissioner of Food and Drugs establish guidance or regulations providing bioequivalence requirements for oral locally-acting gastrointestinal ("GI") drug products prior to approval of any generic versions of such drugs. Furthermore, Salix respectfully requests that specific bioequivalence requirements, *i.e.*, comparative clinical trials, be required as a condition of approval for oral drug products containing balsalazide disodium because of several unique aspects of these drug products and because of known bioequivalence issues with prodrugs in the mesalamine family in general, including: (A) low absorption in the GI tract;<sup>1</sup> (B) topical pharmacological effect in the lower GI tract;<sup>2</sup> (C) certain aspects of balsalazide disodium containing drug products that present "evidence of actual or potential bioequivalence problems";<sup>3</sup> (D) disease states for which

<sup>1</sup> Green JB Gastroenterology 1999;117:1513-1514.

<sup>2</sup> Frieri G, Giacomelli R, Pimpo M. et al. Gut 2000;47:410-414.

<sup>3</sup> 21 C.F.R. § 320.33.

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balsalazide disodium is indicated have a dramatic impact on intersubject and intrasubject variability;<sup>4</sup> and (E) a high degree of interaction with normal concurrent therapy such as mercaptopurine therapies.<sup>5</sup> We submit that these factors must be considered against the established scientific and regulatory requirement for bioequivalence, *i.e.*, "the absence of a significant difference in the rate and extent to which the active ingredient ... becomes available *at the site of drug action* when administered at the same molar dose under similar conditions in an appropriately designed study" (emphasis added).<sup>6</sup> Once these considerations are made, we believe the only logical and scientifically responsible conclusion possible is that traditional *in vivo* pharmacokinetics in normal healthy subjects and *in vitro* dissolution measures are not, by themselves, sufficient to ensure bioequivalence of any generic version of balsalazide disodium.

The Food and Drug Administration ("FDA") in the October 20, 2004 meeting of the Advisory Committee for Pharmaceutical Science recognized that orally administered, locally-acting, GI drugs present significant difficulties in demonstrating bioequivalence using traditional and scientifically acceptable pharmacokinetic methods. Balsalazide disodium, a prodrug of the oral locally-acting GI drug compound 5-aminosalicylic acid ("5-ASA"), is in the mesalamine drug family that was specifically examined as an example of oral GI drugs that present bioequivalence problems. The Committee was not able to resolve the question of what types of studies are necessary to establish bioequivalence for these drugs. Further, FDA has not established any formal guidance for bioequivalence in orally administered, locally-acting drugs.

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<sup>4</sup> Pruitt R, Hanson J, Safdi M, et al. *Am. J. Gastroenterol* 2002 ;97:3078-3086.

<sup>5</sup> Lowry PW, Franklin CL, Weaver AL et al. *Gut* 2001;49:656-664.

<sup>6</sup> 21 C.F.R. § 320.1(e).

Because of the significant scientific and regulatory bioequivalence issues with these drugs, combined with the lack of clear guidance from FDA and its Pharmaceutical Science Advisory Committee, the bioequivalence standards necessary for approval of an abbreviated new drug application ("ANDA") for generic versions of oral mesalamine drug products generally, and oral balsalazide disodium drug products specifically, are not clearly established. The lack of a rigorous bioequivalence standard has created confusion in the approval requirements for generic balsalazide disodium drug products. And because safety and efficacy problems could arise if a drug product is approved without adequate assurance of bioequivalence, Salix requests the following to ensure bioequivalence.

#### **A. ACTION REQUESTED**

The Drug Price Competition and Patent Term Restoration Act of 1994 (the "Hatch-Waxman Amendments") created § 505(j) of the FFDCA. This section provides an ANDA sponsor the opportunity to receive FDA approval to market a new drug that is the same<sup>7</sup> as a previously approved drug without submitting substantial evidence of the drug product's safety and efficacy. Instead, the ANDA relies upon the FDA's prior finding that the reference listed drug ("RLD") is safe and effective and upon evidence showing that the ANDA drug is bioequivalent to the RLD. In addition to providing an approval mechanism, the statute also provides that ANDA drugs that are found to be bioequivalent, and that are the same in all other relevant respects (e.g., active ingredient, route of administration, strength, labeling, dosage form, etc.) are therapeutically equivalent and therefore generally substitutable under state law.

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<sup>7</sup> Statutory requirements for determining whether a drug is the "same" as a previously approved drug are found in FFDCA § 505(j)(2)(A).

As we explain below, the unique properties and site of action of balsalazide disodium drug products create a situation in which the conventional dissolution, pharmacokinetic and bioavailability methods in normal healthy subjects do not adequately establish bioequivalence to support approval of an ANDA. The recognized bioequivalence problems regarding oral, locally-acting GI drugs as a class are exacerbated by these unique properties of balsalazide disodium.

Therefore, we respectfully request that FDA take steps to ensure the bioequivalence and thus the safety and effectiveness of any generic balsalazide disodium drug products by:

- a) Establishing precise bioequivalence requirements for generic drug products containing balsalazide disodium to address the issues associated with the unique properties of the drug. Specifically, ANDAs for balsalazide disodium must include safety and effectiveness evidence from appropriately designed comparative clinical studies to address the bioequivalence issues. These problems cannot be adequately addressed with traditional in vitro dissolution or in vivo, pharmacokinetic or bioavailability testing in normal healthy subjects.
- b) Preparing and issuing guidance or regulations specifying how bioequivalence of oral, locally-acting GI drug products may be established.

## B. STATEMENT OF GROUNDS

### I. Introduction

#### A. Bioequivalence issues with oral locally-acting GI drug products

Determination of bioequivalence for oral locally-acting GI drug products presents significant and complex issues. FDA regulations define bioequivalence as the absence of difference in the rate and extent of the active drug ingredient at the site of drug action.<sup>8</sup> Most oral dosage forms have either systemic action or systemic delivery to the site of action. Therefore, blood plasma concentrations of the active drug ingredient are directly related to the amount of that drug ingredient that is presented to the site of action. Blood plasma concentrations as measured by traditional pharmacokinetic studies in normal healthy subjects are a logical and well accepted surrogate for rate and extent of drug ingredient at the site of action. However, with oral locally-acting GI drugs, there is no correlation between systemic plasma concentrations and active drug ingredient available at the site of action. Systemic absorption is not involved in the delivery of drug to the site of action, and such absorption can, in some cases, reduce the amount of active drug ingredient that is available to the site of action. Variations in absorption, dissolution rate, excipients, and other factors can result in drugs that have similar in vivo plasma drug concentrations, but significantly different drug levels at the site of action.

In vitro dissolution testing is also unproven and problematic for drugs in this category. Currently accepted dissolution testing procedures have limited utility. The tests are relatively simplistic, and they are not suitable for modeling the complex conditions present throughout the

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<sup>8</sup> 21 C.F.R. § 320.1(e).

entire GI tract. The current methods are suitable for determining the bioequivalence of some immediate release dosage forms, and they may be helpful in evaluating the bioequivalence of other systemic orally administered dosage forms. But, dissolution testing is clearly inadequate in determining the bioequivalence of drugs where bioavailability to the intended site of action is based on passage of the drug through the many varied conditions present in the GI tract.

FDA has acted on a case by case basis when assessing the bioequivalence of oral locally-acting GI drug products. Such an ad hoc approach is contrary to the Agency's general policy of establishing scientific and regulatory principles that can apply to a class of products, *e.g.*, aerosols for asthma, topicals for inflammation, and intranasal products. A rigorous and systematic approach is necessary. As shown by the discussion at the October Advisory Committee meeting, only comparative clinical trials currently meet this standard. Furthermore, only this approach is consistent with FDA's regulations establishing the types of evidence required to measure bioavailability or establish bioequivalence.<sup>9</sup>

B. Bioequivalence issues with balsalazide disodium

In addition to the general bioequivalence issues associated with oral locally-acting GI drugs as a class, oral balsalazide disodium drug products have unique properties that present further complicating factors. These unique properties can be summarized as follows:

- A. Balsalazide disodium is a unique 5-ASA prodrug. It has been demonstrated to have low absorption and toxicity of both the carrier and

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<sup>9</sup> 21 C.F.R. § 320.24.

the active moiety. Further, the release of the active moiety (5-ASA) is not random but occurs at the site of intended action.

- B. The primary pharmacological effect of oral balsalazide drugs appears to be through topical action in the lower GI tract. All pharmacological activity is believed to be provided by contact or absorption at that site only. Blood levels have not been shown to be a relevant measure of clinical effect.<sup>10</sup>
- C. Balsalazide disodium meets the regulatory definition of a drug product that presents evidence of actual or potential bioequivalence problems that may result in efficacy and safety issues.<sup>11</sup>
- D. The disease state treated by balsalazide disodium has a dramatic impact on intersubject and intrasubject variation in trial subjects, which further complicates clinical outcome comparisons.<sup>12</sup>
- E. Recent evidence indicated that balsalazide disodium has a high and measurable degree of interaction with normal concurrent therapies such as mercaptopurine therapies. The interaction with mercaptopurine is directly related to the amount of active drug absorbed (characteristic of the drug). This activity is not an issue of balsalazide disodium efficacy, but an issue

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<sup>10</sup> Prakash A. Spencer CM. *Drugs* 1998;56:83-89.

<sup>11</sup> 21 C.F.R. § 320.33.

<sup>12</sup> Pruitt R, Hanson J, Safdi M, et al *Am. J. Gastroenterol* 2002;97:3078-3086.

of side effects and safety of mercaptopurine, and thus is indirectly related to bioequivalency.<sup>13</sup>

As a result of the above, traditional in vitro measures of bioequivalence (*i.e.*, blood level measurements of Area Under the Curve ("AUC"), the maximum blood concentration ("C<sub>max</sub>"), the time to the maximum blood concentration ("T<sub>max</sub>"), and in vitro dissolution) are even less relevant than they are for oral locally-acting GI drugs generally. Demonstration of bioequivalence for balsalazide drug products requires specific equivalence requirements that address the foregoing issues. Such requirements must include clinical data demonstrating comparable effects or similar active drug ingredient concentrations at the site of action. Many variables exist with regard to the use of clinical trials to establish bioequivalence; consequently, the results of such studies may be inconclusive, like the results of many clinical trials. Nevertheless, such trials are the best measure for assessing the bioequivalence of these drug products. Accordingly, comparative clinical trials data should be required to establish the bioequivalence of different versions of oral balsalazide drug products. Only this approach is consistent with FDA's regulations.<sup>14</sup>

## **II. The Balsalazide Drug Product**

Balsalazide disodium is the drug substance of the reference branded drug, COLAZAL<sup>®</sup>. COLAZAL is indicated for the treatment of mildly to moderately active ulcerative colitis. Balsalazide is a prodrug containing 5-ASA, linked to 4-amino benzoyl-β-alanine ("4-ABA") by

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<sup>13</sup> Lowry PW, Franklin CL, Weaver AL et al. Gut 2001;49:656-664.

<sup>14</sup> 21 C.F.R. §§ 320.24, 320.33.

an azo-bond. The drug product, COLAZAL, contains 750mg of balsalazide disodium in a hard gelatin capsule for oral delivery. When taken orally, 99% of the prodrug balsalazide reaches the colon, where the presence of colonic bacterial azo-reductase enzyme reduces or “cleaves” the azo-bond, thereby liberating the 5-ASA for topical activity in the colon.<sup>15</sup> The released 4-ABA carrier component is poorly absorbed and largely eliminated in the feces.<sup>16</sup> The local presence of 5-ASA is the basis for the effectiveness of this class of drugs generally.<sup>17</sup> The actual mechanism of action of 5-ASA is not completely understood. Nevertheless, the clinical evidence and in vivo evidence show that clinical effectiveness is unrelated to blood levels of the drugs and the historic FDA criteria for measurement of bioequivalence, *i.e.*, AUC, T<sub>max</sub> and C<sub>max</sub>. A correlation of blood levels or other biopharmaceutical measurements with clinical effect are the foundation of Agency decisions on bioequivalence.<sup>18</sup> No such correlations exist for balsalazide or for this class of oral locally-acting GI drugs in general.

### **III. Balsalazide Bioequivalence Issues**

A number of factors distinguish balsalazide from other drug products generally, and from other oral 5-ASA drugs more specifically. These factors (discussed below) all have a significant role in creating the problems in demonstrating bioequivalence between oral balsalazide drug products.

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<sup>15</sup> Colazal® (balsalazide disodium) Capsules 750mg Package Insert 0004.1/July 2000.

<sup>16</sup> Rangunath K and Williams JG. *Aliment Pharmacol. Ther.* 2001;15:1549-1554.

<sup>17</sup> Frieri G, Giacomelli R, Pimpo M. et al. *Gut* 2000;47:410-414.

<sup>18</sup> 21 CFR § 320.1.

A. Balsalazide appears to act locally in the lower GI tract

The primary pharmacological effect of oral balsalazide drugs appears to be through topical action in the lower GI tract. To be effective, the active moiety of the drug must be delivered through the GI tract with minimal, if any, absorption. Thus, absorption into the bloodstream is very low and cannot be correlated to clinical effect.<sup>19</sup> Additionally, the azo-bond linkage, which is reduced by the presence of colonic bacterial azo-reductase, is a confounding factor in any in vitro dissolution testing.

B. Balsalazide is significantly different from other 5-ASA prodrugs

Like many drug products formulated to deliver 5-ASA to the lower GI tract, balsalazide is a prodrug; however, it is significantly different from the other 5-ASA prodrugs, sulfasalazine and olsalazine. The carrier for balsalazide, 4-ABA, has demonstrated lower absorption and toxicity than the carrier of sulfasalazine.<sup>20</sup> Furthermore, this carrier provides more specific delivery of 5-ASA to the site of intended action, the lower GI tract.<sup>21</sup> As a result, there are lower levels of both the carrier and active drug moiety in the bloodstream than with sulfasalazine.<sup>22</sup>

Balsalazide utilizes the azo-bond and the specificity of the colonic azo-reductase enzyme to reduce the azo-bond link to the 4-ABA and 5-ASA, thereby delivering the anti-inflammatory 5-ASA to the colon. Unlike sulfasalazine where 10-15% of the parent prodrug can be reproducibly measured in the plasma, less than 1% of the balsalazide (parent) prodrug is absorbed.<sup>22</sup> This limited amount of absorption is thought to occur prior to reaching the colon.

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<sup>19</sup> Prakash A. Spencer CM. *Drugs* 1998;56:83-89.

<sup>20</sup> NDA 20,610 Volume 1.047, page 75 – Volume 1.053, page 228.

<sup>21</sup> 21 CFR § 320.33.

<sup>22</sup> Green JB *Gastroenterology* 1999;117:1513-1514.

Because the sulfasalazine parent and carrier plasma levels can be readily measured, and represent a significant portion of the oral dose, pharmacokinetic studies have been allowed for establishing the bioequivalence of generic sulfasalazine to the RLD, Azulfidine®. In marked contrast, the extremely low levels of absorption for both carrier and active drug components, and the resulting extremely low percentage of absorbed drug in the blood, create significant difficulties in any such measurement for balsalazide, making any such bioequivalence determination based on traditional blood level measurements scientifically unsupportable.<sup>23</sup> Furthermore, no evidence shows any correlation between blood levels of the active moiety, 5-ASA, and clinical effect, which is the cornerstone for findings of bioequivalence,<sup>24</sup> and balsalazide is a bioproblem drug in part based on this issue.<sup>25</sup>

C. Balsalazide meets FDA's criteria for bioproblem drugs

The site of action, delivery, and absorption issues that create the difficulties in bioavailability and bioequivalence are magnified because certain aspects of balsalazide containing drug products meet the regulatory criteria for drugs which may present actual or potential bioequivalence problems. These include the following pharmacokinetic factors: 1) the lack of significant systemic absorption of the (parent) balsalazide molecule; 2) the release of active and inactive molecular moieties for action in the large intestine; 3) the metabolism by the gut wall, prior to limited systemic availability; and 4) the instability of the therapeutic moiety in

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<sup>23</sup> See transcript for October 20, 2004 Advisory Committee for Pharmaceutical Science, discussion regarding blood levels of locally-acting GI drugs (available at <http://www.fda.gov/ohrms/dockets/ac/cder04.html#PharmScience>).

<sup>24</sup> Levine DS, Riff DS, Pruitt R et al. Am. J. Gastroenterol. 2002;9:1398-1407.

<sup>25</sup> See, e.g., 21 CFR § 321.33(f).

specific portions of the GI tract.<sup>26</sup> These factors are further supported by other factors that identify bioproblem drugs and apply to balsalazide.<sup>27</sup> Well-controlled clinical trials and controlled clinical observations in patients show that analogous drug products do not necessarily give comparable therapeutic effects. Leading practitioners in the GI area believe that a lack of bioequivalence could have a serious adverse effect on the treatment of the disease for which balsalazide is indicated.<sup>28</sup> FDA has recognized the significance of these bioequivalence issues for 30 years, and we are unaware of any scientific basis for disregarding these principles in this situation.

D. The disease extent and history have a significant impact on the pharmacological effect

Balsalazide is indicated for the treatment of mildly to moderately active ulcerative colitis. The concerns of practitioners that a lack of bioequivalence would have a serious adverse effect in the treatment of the disease are further magnified by the significant inter and intra-subject variability in clinical response to this drug. Such variability has been demonstrated in well-controlled studies.<sup>29</sup> Due to this variability, any pharmaceutical variation between different balsalazide drug products may be exacerbated. For these reasons, care must be taken in designing comparative clinical and non-clinical studies between different balsalazide drug products.

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<sup>26</sup> Allgayer H, Ahnfelt NO, Kruis W et al Gastroenterology. 1989;97:38-41.

<sup>27</sup> 21 CFR § 320.33(f).

<sup>28</sup> Forbes A, Cartwright A, Marchant S et al. Aliment. Pharmacol. Ther 2003;17:1207-1214.

<sup>29</sup> NDA 20,610 Volume 1.067, page 218 – Volume 1.074, page 327.

In efficacy studies for this indication, patients did not demonstrate a uniformly equivalent response to balsalazide. Factors contributing to the response were found to be related to the extent of disease (*i.e.*, the extent of colonic inflammation) and to previous disease duration.<sup>30</sup> Patients divided into different sub-groups based on extent and history of their disease had significantly different responses to the drug treatment.<sup>31</sup> It is therefore necessary for any comparative efficacy study of two balsalazide-containing drug products to be sufficiently powered such that the randomization can equally assign patients into the relevant sub-groups based on disease extent and disease history. Failure to power the study adequately and control for the contribution of patient sub-types will result in an outcome that is not indicative of the efficacy achieved in the overall patient population.

Other parameters that can influence the outcome of an efficacy study in this patient population are the duration or the presence of relapse, symptom severity at the time of randomization, concomitant medications and time since withdrawal of prior medications.<sup>32</sup> All of these potentially confounding variables must be adequately controlled during the patient selection, screening and randomization process.

E. Balsalazide has a high degree of interaction with a normal concurrent therapy, mercaptopurine

The mercaptopurine products, 6-mercaptopurine and its prodrug, azathioprine, are immunosuppressive drugs that are commonly used concomitantly with mesalamine products for

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<sup>30</sup> Green JR, Lobo AJ, Holdsworth CD et al. *Gastroenterology* 1998;114:15-22.

<sup>31</sup> Pruitt R, Hanson J, Safdi M, et al. *Am. J. Gastroenterol* 2002;97:3078-3086.

<sup>32</sup> Lim WC, Hanauer SB. *Rev. Gastroenterol. Disord.* 2004;4:104-117.

the treatment of inflammatory bowel diseases. The mercaptopurines are metabolized ultimately to 6-thioguanine nucleotides (“6TGN”) that inhibit DNA synthesis of immune-progenitor cells and also bone marrow cells that can lead to leucopenia.

A key component of this pathway is the enzyme, thiopurine methyl transferase (“TPMT”). TPMT has recently been determined to be inhibited by both 5-ASA and the prodrugs sulfasalazine, olsalazine, and balsalazide. Thus, when the mercaptopurines and mesalamine products are used concomitantly, the potential exists for a serious drug-drug interaction that can lead to leukopenia.

This drug-drug interaction has been experimentally examined, and a correlation does appear to exist between mesalamine and prodrug plasma levels and white blood cell counts.<sup>33</sup> These data demonstrated that the plasma levels of both 5-ASA and the parent azo-compounds can contribute to the level of leucopenia observed when patients are concomitantly treated with mesalamine products and 6-mercaptopurine containing products. It is also apparent that balsalazide has a lower potential for this drug-drug interaction because the plasma concentrations of its components (5-ASA and 4-ABA) are an order of magnitude lower than plasma concentrations for other drug products in this category.<sup>34</sup> Nonetheless, it is also clear that changes in the absorption of either of these components could lead to significant differences in the safety of a balsalazide-containing drug product from the standpoint of leucopenia resulting from this drug-drug interaction. It is therefore imperative that any balsalazide containing drug product exhibit equivalent absorption characteristics to the reference listed drug in order to

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<sup>33</sup> Lowry PW, Franklin CL, Weaver AL et al. Gut 2001;49:656-664.

<sup>34</sup> Green JB Gastroenterology 1999;117:1513-1514.

ensure overall patient safety with respect to co-administered drugs. Accordingly, the issue of drug interaction between balsalazide and mercaptopurine drug products cannot be adequately investigated until the other bioequivalence issues for balsalazide are addressed.

#### **IV. FDA Standards Regarding the Bioequivalence For Oral Locally-Acting GI Drug Products**

Traditional bioequivalence standards for in vivo bioavailability were developed for systemically absorbed drugs where systemic blood levels are indicative of the therapeutic dose delivered to the intended site of action. For most drugs, the dose is delivered to the site of action by the blood, so the absorbed dose has a direct correlation to effect.<sup>35</sup> As noted above, with oral locally-acting GI drugs such as balsalazide disodium, blood levels have little or no relevance to dose received at the site of local action. In some cases, blood levels of such drugs may actually increase without changing the dose received at the site of local action.<sup>36</sup>

Bioequivalence determinations for oral, locally-acting GI drugs have been recognized by FDA as a complex topic that has no easy answers. No specific, detailed guidelines exist for defining the bioequivalence of orally administered drugs that exert their activity through topical action in the GI tract. Some guidance is given in the Guidance Document issued March 2003, entitled "Guidance for Industry - Bioavailability and Bioequivalence Studies for Orally Administered Drug Products". Section VI(E) of that document, entitled "Orally Administered Drugs Intended for Local Action", provides:

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<sup>35</sup> 21 CFR § 320.1.

<sup>36</sup> Hussain FN, Ajjan RA, Riley SA. Br. J. Clin. Pharmacol. 2000;49:323-330.

“Documentation of product quality BA for NDAs where the drug substance produces its effects by local action in the gastrointestinal tract can be achieved using clinical efficacy and safety studies and/or suitably designed and validated in vitro studies. Similarly, documentation of BE for ANDAs, and for both NDAs and ANDAs in the presence of certain post approval changes can be achieved using BE studies with clinical efficacy and safety endpoints and/or suitably designed and validated in vitro studies if the latter studies are either reflective of important clinical effects or are more sensitive to changes in product performance compared to a clinical study. To ensure comparable safety, additional studies with and without food may help understand the degree of systemic exposure that occurs following administration of a drug product intended for local action in the gastrointestinal tract.”<sup>37</sup>

This guidance reflects the difficulties in establishing bioequivalence for oral, locally-acting GI drugs. Although the guidance suggests that products that produce local effects in the GI tract can be evaluated for bioequivalence by clinical studies or suitably designed and validated in vitro studies, the guidance does not suggest how such nonclinical studies should be designed.

FDA also recognizes the possible existence of bioequivalence issues with locally-acting drugs in the preface to its Approved Drug Products with Therapeutic Equivalence Evaluations ("Orange Book") where it states that where traditional bioequivalence methods "are not

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<sup>37</sup> Food and Drug Administration, Center for Drug Evaluation and Research, Guidance—"Guidance for Industry - Bioavailability and Bioequivalence Studies for Orally Administered Drug Products" March 2003.

applicable (e.g., for drug products that are not intended to be absorbed into the bloodstream), other *in vivo* or *in vitro* test methods to demonstrate bioequivalence may be appropriate."<sup>38</sup>

The Agency's questions about establishing bioequivalence criteria for such products were the subject of a recent meeting of its Advisory Committee for Pharmaceutical Science. This October 20, 2004 meeting specifically addressed the issue of locally-acting GI drug bioequivalence. During this meeting, it was generally agreed that the only currently effective way to demonstrate bioequivalence for locally-acting GI drugs is through clinical effectiveness testing, possibly in combination with other *in vitro* and *in vivo* testing. The possibility of implementing detailed and realistic dissolution testing as a mechanism for determining bioequivalence for these drugs was proposed; however, the panel determined, and FDA agreed, that such an approach required considerably more work and study before it could be implemented. After considerable discussion, no conclusions were reached on this difficult issue, except that further work is necessary.

FDA has recently made available minutes of the October 20 meeting. In summarizing the Committee's conclusion regarding the bioequivalence requirements for oral locally-acting GI drugs, the minutes state: "In conclusion, the Committee agreed that it was difficult to reach a consensus, but that in order to prove bioequivalence *in vitro* dissolution along with pharmacokinetics should be acceptable."<sup>39</sup> This summary conclusion is not an accurate reflection of the actual conclusion of the Committee. Of the five Committee members that took an active part in the conversation, none endorsed the view that pharmacokinetics and dissolution

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<sup>38</sup> Food and Drug Administration, Center for Drug Evaluation and Research, *Approved Drug Products with Therapeutic Equivalence Evaluations*, 24th Edition.

<sup>39</sup> November 11, 2004 minutes of the October 19-20, 2004 Pharmaceutical Science Advisory Committee meeting.

testing, as it is currently performed, can adequately demonstrate bioequivalence for oral locally-acting GI drug products.

The strongest proponent for use of dissolution testing was Dr. Gordon Amidon.<sup>40</sup> Dr. Amidon supported the use of enhanced dissolution testing in the demonstration of bioequivalence. This view is consistent with his opinion that enhanced dissolution testing is a sufficient, if not preferred, method for demonstration of bioequivalence for all or almost all oral dosage forms. However, the dissolution testing advocated by Dr. Amidon is not the sort of testing that is currently practiced in standard dissolution testing methods. Instead, Dr. Amidon is a proponent of developing highly realistic dissolution models that closely simulate physiological conditions throughout the digestive system. Such testing could involve hundreds of different test systems (with varying pH, stir rates, surfactants, etc...) <sup>41</sup> in which the test products must be shown to exhibit similar dissolution characteristics. To simply state that Dr. Amidon is in favor of the conclusion that in vitro dissolution and in vivo pharmacokinetic testing are adequate for demonstration of bioequivalence is not supported by his actual statements at the meeting.

Dr. Kenneth Morris<sup>42</sup> and Dr. Marvin Meyer<sup>43</sup> also supported the idea that some sort of enhanced dissolution testing of the type proposed by Dr. Amidon might also be acceptable if properly developed. However, both also acknowledged that such methods are not currently available, and that much work and discussion was needed before such methods would be usable.

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<sup>40</sup> Gordon Amidon, Ph.D., M.A. Voting Advisory Committee member. Dr. Amidon also made a presentation supporting the use of enhanced dissolution testing at the October 20 meeting.

<sup>41</sup> Not discussed at the meeting, but critical to the bioequivalence determinations of oral locally-acting GI drug products is the effect of GI flora on dissolution. In vitro dissolution testing that does not take into account degradation and dissolution of drugs, including the release of prodrug active ingredients, does not provide a accurate surrogate for actual in vivo drug activity.

<sup>42</sup> Kenneth Morris, Ph.D. Voting Advisory Committee member.

<sup>43</sup> Marvin Meyer, Ph.D. Voting Advisory Committee member.

Dr. Paul Fackler<sup>44</sup> did not offer a clear opinion on what should be required to demonstrate bioequivalence. He only noted that clinical trials, on their own, can be somewhat indiscriminate with regards to bioequivalence.

Dr. Jurgen Vinitz<sup>45</sup> strongly supported the use of clinical trials in addition to other bioequivalence measures for locally-acting oral drugs. He noted that previous Advisory Committees had supported the requirement for a combination of clinical, dissolution, and pharmacokinetic studies in the demonstration of bioequivalence for other categories of locally-acting drug products, nasal sprays, and oral inhalation drugs.

The views of these experts in no way endorsed the use of current in vitro dissolution and in vivo pharmacokinetic methods as adequate to demonstrate bioequivalence in oral locally-acting GI drug products.

The views expressed in the Guidance and at the Advisory Committee meeting support Salix's view that bioequivalence determinations for oral balsalazide disodium products cannot be adequately made on the basis of current dissolution or pharmacokinetic studies. Therefore, comparative clinical efficacy testing must be the basis for proof of bioequivalence. Other in vitro and in vivo tests, such as absorption and dissolution, may be useful supporting studies, but until well thought out and validated alternatives are developed, the determination of bioequivalence for locally-acting GI drugs must be based on carefully controlled clinical, efficacy, and toxicity testing through comparative clinical trials. For balsalazide disodium, this is the only approach that is consistent with FDA's historical science-based consideration of these issues.

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<sup>44</sup> Paul Fackler, Ph.D. Voting Advisory Committee member.

<sup>45</sup> Jurgen Vinitz, M.D., Ph.D. Voting Advisory Committee member.

Salix notes that FDA has, for other locally-acting drugs, required comparative clinical effectiveness data for demonstration of bioequivalence. For example, in the past, FDA has required clinical studies for demonstration of bioequivalence for locally-acting oral drugs such as sucralfate.<sup>46</sup> Furthermore, the Advisory Committee for Pharmaceutical Science previously evaluated locally-acting dosage forms when it was asked by FDA to consider the requirements for establishing bioequivalence for locally-acting nasal or inhaled drug products.<sup>48</sup> At that Advisory Committee meeting, the Committee was asked to consider whether pharmacokinetic and dissolution testing would be adequate to demonstrate bioequivalence for these drug products. The Committee opined that clinical trials were needed in addition to dissolution and pharmacokinetic studies.<sup>47</sup>

Therefore, the inadequacy of current in vitro dissolution, in vivo pharmacokinetic methods and bioavailability studies has been shown in demonstrating the bioequivalence of oral locally-acting drug products. The scientific necessity of comparative clinical trials has been established, and this approach is consistent with FDA precedent as codified in its regulations.

### C. CONCLUSION

Based on the foregoing, there is currently no viable alternative to safety and effectiveness data from clinical trials to establish bioequivalence for balsalazide drug products. FDA has recognized that traditional bioavailability studies that compare  $C_{max}$ ,  $T_{max}$ , and AUC are problematic for locally-acting GI drug products. The Agency has suggested that properly

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<sup>46</sup> Sucralfate Tablets USP 1g, ANDA 74-415.

<sup>48</sup> April 26, 2000 Pharmaceutical Science Advisory Committee meeting.

<sup>47</sup> November 5, 2000 minutes of the April 26, 2000 Pharmaceutical Science Advisory Committee meeting.

designed and validated in vitro or pharmacokinetic studies might be useful, but it has not provided effective guidance on what such studies might entail. As was discussed at the recent Advisory Committee meeting, the development of alternative in vitro dissolution or in vivo pharmacokinetic methods has not progressed to a point where the Committee could recommend such an approach for the demonstration of bioequivalence for these drugs. Furthermore, balsalazide is a bioproblem drug with a myriad of additional, complicating factors that makes the use of traditional pharmacokinetic measures completely inappropriate for establishing bioequivalence. The record established by FDA shows that only safety and effectiveness data from well-controlled clinical trials can be used to prove bioequivalence of generic balsalazide drug products to COLAZAL<sup>®</sup>. This conclusion, and only this conclusion, is consistent with the Agency's past actions and its regulations.<sup>48</sup>

Salix recognizes the pressures facing the Agency to facilitate generic approvals, but the vagaries of the disease state in question and the complexities of the drug product itself mandate careful consideration of all the complex scientific issues involved. Furthermore, the opinions of the physician community treating these patients must also be considered in the scientific decision-making process concerning bioequivalence, not merely those of biopharmaceutical experts.

For the above listed reasons, Salix respectfully requests that the actions set forth in this petition, summarized below, be taken.

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<sup>48</sup> 21 C.F.R. § 320.24.

- a) Prior to approval of any ANDAs, FDA must establish precise bioequivalence requirements for generic drug products containing balsalazide disodium to address the issues associated with the unique properties of the drug. Specifically, ANDAs for balsalazide disodium must include safety and effectiveness evidence from appropriately designed comparative clinical studies to establish bioequivalence. These problems cannot be adequately addressed with traditional in vitro dissolution or in vivo pharmacokinetic or bioavailability testing.
- b) FDA must prepare and issue guidance or regulations specifying how bioequivalence of oral, locally-acting GI drug products may be established.

**D. ENVIRONMENTAL IMPACT**

In accordance with 21 C.F.R. § 25.31(g), an environmental impact analysis is not required.

**E. CERTIFICATION**

The undersigned certified, 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.

signature



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