



DEC 28 2007

Food and Drug Administration
Rockville MD 20857

Stephen D. Celestini
William P. Forbes, Pharm D.
Salix Pharmaceuticals, Inc.
1700 Perimeter Park Drive
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Re: Docket No. 2005P-0146/CP1, SUP 1, SUP 2, SUP 3, & SUP 4

Dear Mr. Celestini and Mr. Forbes,

This letter responds to your citizen petition dated April 13, 2005 (Petition), and related supplements dated July 14, 2006 (Supplement 1), November 14, 2006 (Supplement 2), June 14, 2007 (Supplement 3), and September 27, 2007 (Supplement 4). In the Petition and Supplements, you request that the Food and Drug Administration (FDA) establish guidance or regulations providing bioequivalence standards for oral, locally acting gastrointestinal (GI) drug products prior to approval of any abbreviated new drug applications (ANDAs) for these products. Specifically with regard to balsalazide disodium drug products, in the Petition and Supplements 1, 3,¹ and 4 you request that any ANDA for an oral formulation of these products include safety and effectiveness evidence from appropriately designed comparative clinical studies. In Supplement 2, you request such studies only for assessment of clinical efficacy. In Supplement 4, you also request comparative clinical trials in pediatric patients.² You also request that:

- FDA's Office of Generic Drugs (OGD) withdraw recommendations contained in a March 24, 2006, letter to a third party regarding bioequivalence measures for these products (Supplement 1)
- Any in vivo bioequivalence studies use ulcerative colitis patients in remission instead of normal healthy subjects (Supplements 1, 2, and 3)
- Any in vivo bioequivalence studies include measurement of N-Acetyl-5-Aminosalicylic acid (N-Acetyl-5-ASA) in plasma in addition to balsalazide and mesalamine (5-Aminosalicylic acid (5-ASA)) (Supplements 1, 2, and 3)

¹ Even though you request safety and effectiveness evidence from comparative clinical studies in the "Action Requested" section of Supplement 3, in the "Conclusion" section of this supplement, you request only that such studies assess clinical efficacy.

² We note that your requests in Supplement 4 pertaining to the pediatric population are based on information that you previously provided to the Agency on June 19, 2006. This pediatric information was included in the approved labeling for balsalazide disodium in December 2006. You have not provided any new information in the supplement to support your pediatric-related requests.

2005P-0146

PDN 1

- Any in vivo bioequivalence studies require a fed study and a sprinkling study in addition to a fasting study (Supplements 2 and 3)
- Any in vitro dissolution studies include conditions that more closely mimic the in vivo conditions to which balsalazide is exposed (Supplements 1 and 3)
- Any in vivo bioequivalence studies should include pharmacokinetic studies in the pediatric population that measure plasma levels of balsalazide, mesalamine, and N-Acetyl-5-ASA (Supplement 4)

For the reasons described below, we deny your Petition and Supplements 1 and 4 and we grant Supplements 2 and 3 in part with respect to recommending a fed study to demonstrate in vivo bioequivalence, but deny them in all other respects.

I. BACKGROUND

Colazal (new drug application (NDA) 20-610) was initially approved by FDA in July 2000. It is available as a 750-milligram (mg) immediate-release capsule containing balsalazide disodium. FDA has designated Colazal as the reference listed drug³ for balsalazide disodium capsules. Balsalazide disodium is a prodrug⁴ that is delivered intact to the colon, where it is cleaved by bacterial azoreduction to release equimolar quantities of mesalamine, the therapeutic active portion of the molecule, and 4-aminobenzole-B-alanine (4-ABA). The 4-ABA carrier moiety is only minimally absorbed and largely inert.

Colazal is approved for treatment of mildly to moderately active ulcerative colitis. Ulcerative colitis is an idiopathic chronic inflammatory disease of the colon and rectum requiring both acute and long-term medical therapy to induce and maintain remission. The oral mesalamine formulations (Asacol, Pentasa), prodrugs (sulfasalazine, olasalazine, balsalazide), and rectal preparations are the first line therapies in patients with mild to moderate ulcerative colitis. All of these agents have been deemed to be safe and effective in treating ulcerative colitis despite different routes of administration and varied sites of GI contact and action. Although mesalamine has been available worldwide for the treatment of ulcerative colitis for more than 20 years and used as the active component in sulfasalazine for more than 50 years, its precise mode of action remains unknown.

³ A *reference listed drug* or RLD is "the listed [i.e., approved] drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application" (21 CFR 314.3). Reference listed drugs are identified in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book).

⁴ A prodrug is a pharmacologically inactive derivative of a parent drug molecule that requires spontaneous or enzymatic transformation in vivo to release the active drug. See Sinha VR and Kumria R. Review Article: Colonic Drug Delivery: Prodrug Approach. *Pharmaceutical Research* 2001; 557-564.

Available data suggest that mesalamine acts locally rather than systemically.⁵ It is known, however, that small quantities of mesalamine are absorbed systemically.⁶ Thus, one cannot exclude the contribution of systemically absorbed mesalamine to the pharmacological action of balsalazide. To date, there is no clinical evidence to support this hypothesis.

II. STATUTORY AND REGULATORY STANDARDS

The Federal Food, Drug, and Cosmetic Act (the Act) generally requires an ANDA applicant to provide, among other things, information to show that the generic drug⁷ is bioequivalent⁸ to the reference listed drug (section 505(j)(2)(A)(iv)). FDA must approve an ANDA unless the information submitted in the ANDA is insufficient to meet the requirements delineated in section 505(j)(4) of the Act, including a demonstration of bioequivalence. If the generic drug and reference listed drug are both bioequivalent and pharmaceutically equivalent,⁹ they are therapeutically equivalent and may be substituted for each other.

⁵ Kane SV and Bjorkman DJ. The efficacy of oral 5-ASAs in the treatment of active ulcerative colitis: a systemic review. *Reviews in Gastroenterological Disorders* 2003; 3:210-218.

⁶ Prakash A and Spencer CM. Balsalazide. *Drugs* 1998; 56:83-89.

⁷ For purposes of this response, the term *generic drug* refers to a new drug product for which approval is sought in an ANDA submitted under section 505(j) of the Act (21 U.S.C. 355(j)).

⁸ Section 505(j)(8)(B) of the Act provides that a generic drug shall be considered to be bioequivalent to the listed drug if

- (i) the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses; or
- (ii) the extent of absorption of the drug does not show a significant difference from the extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses and the difference from the listed drug in the rate of absorption of the drug is intentional, is reflected in its proposed labeling, is not essential to the attainment of effective body drug concentrations on the chronic use, and is considered medically insignificant for the drug.

Section 505(j)(8)(C) further provides:

For a drug that is not intended to be absorbed into the bloodstream, the Secretary may establish alternative, scientifically valid methods to show bioequivalence if the alternative methods are expected to detect a significant difference between the drug and the listed drug in safety and therapeutic effect.

⁹ Pharmaceutically equivalent drug products have identical dosage forms and contain identical amounts of the identical active ingredient, and meet the identical compendial or other applicable standard of identity, strength, quality, and purity. They do not necessarily contain the same inactive ingredients and may also differ in characteristics such as shape, scoring, release mechanism, and, within certain limits, labeling. See 21 CFR 320.1; Orange Book, 26th Ed., at v-vi.

FDA's regulation at 21 CFR 320.24(b) lists the in vivo and in vitro methods of determining bioavailability or bioequivalence for a drug product. Applicants must use the most accurate, sensitive, and reproducible method available (21 CFR 320.24(a)). In descending order of accuracy, sensitivity, and reproducibility, the methods for establishing bioequivalence include the following:

- An in vivo test in humans in which the concentration of the active ingredient or active moiety, and, when appropriate, its active metabolite(s), in whole blood, plasma, serum, or other appropriate biological fluid is measured as a function of time
- An in vitro test that has been correlated with and is predictive of human in vivo bioavailability data
- An in vivo test in humans in which the urinary excretion of the active ingredient or active moiety, and, when appropriate, its active metabolite(s), is measured as a function of time
- An in vivo test in humans in which an appropriate acute pharmacological effect of the active moiety, and, when appropriate, its active metabolite(s), is measured as a function of time if such effect can be measured with sufficient accuracy, sensitivity, and reproducibility
- Well-controlled clinical trials that establish the safety and effectiveness of the drug product, for purposes of measuring bioavailability, or appropriately designed comparative clinical trials, for purposes of demonstrating bioequivalence

For in vivo pharmacokinetic tests, FDA generally considers two products to be bioequivalent when the 90 percent confidence intervals for the ratios of the pharmacokinetic parameters (area under the plasma concentration vs. time curve (AUC) and maximum drug concentration (C_{max})) are entirely within an 80 to 125 percent acceptance interval. The use of an 80 to 125 percent acceptance interval is a scientific judgment about the best statistical practices for bioequivalence determinations and reflects decades of scientific data on the variability of product characteristics within and between batches, as well as biological variability in patients. Because the mean of the study data lies in the center of the 90 percent confidence interval, the mean of the data is usually close to 100 percent (a test/reference ratio of 1).¹⁰

FDA's guidance for industry on *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations* (BA/BE guidance) (March 2003) provides, among other things, recommendations concerning the measurement of the active drug ingredient or its active moiety in the administered dosage form (parent drug) and its active metabolite(s).¹¹ For bioequivalence studies, the BA/BE guidance generally recommends measurement of only the parent drug (the moiety released from the dosage form), rather than the metabolite. The basis for this recommendation is that the "concentration-time profile of the parent drug is more sensitive to changes in

¹⁰ FDA guidance for industry on *Statistical Approaches to Establishing Bioequivalence*, January 2001; Orange Book, 26th Ed., at viii.

¹¹ See pp. 17-18 of the BA/BE guidance.

formulation performance than a metabolite, which is more reflective of metabolite formation, distribution, and elimination.” The BA/BE guidance describes two situations when the general recommendation (i.e., measuring the parent drug only) does not apply:

- When the parent drug levels are too low to allow reliable analytical measurement in blood, plasma, or serum for an adequate length of time, or
- When a metabolite may be formed as a result of gut wall or other presystemic metabolism. If the metabolite contributes meaningfully to safety and/or efficacy, the metabolite and the parent drug should be measured. If 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. The parent drug measured in these bioequivalence studies should be analyzed using a confidence interval approach. The metabolite data can be used to provide supportive evidence of comparable therapeutic outcome.

III. DISCUSSION

A. **The Request That FDA Issue Guidance or Regulations Specifying Bioequivalence Standards for Oral, Locally Acting GI Drug Products Before Approval of ANDAs Is Not Warranted**

You request that FDA issue guidance or regulations specifying bioequivalence standards for oral, locally acting GI drug products because these products present significant and complex issues (Petition at 4-5, see also Supplement 1 at 1 and Supplement 2 at 1). You claim that traditional pharmacokinetic studies in normal healthy subjects are problematic for these drug products because there is a lack of correlation between systemic plasma concentrations of the drug and the active drug ingredient available at the site of action (Petition at 5). You also claim that in vitro dissolution testing is inadequate for these drug products because bioavailability to the intended site of action is based on passage of the drug through many varied conditions present in the GI tract (Petition at 5-6).

You note that FDA has not issued a specific detailed guidance on this topic and only includes limited information on oral, locally acting GI drug products in the BA/BE guidance (Petition at 15). You state that in this guidance, FDA suggests that products that produce local effects in the GI tract could be evaluated for bioequivalence by suitably designed and validated in vitro or pharmacokinetic studies, but that FDA does not suggest how such studies should be designed (Petition at 15-16, 20-21). You mention that FDA issued a draft guidance for industry entitled *Bioequivalence Recommendations for Specific Products* (BE Recommendation Process guidance) in May 2007, but did not include recommendations for balsalazide disodium (Supplement 3 at 1). You claim that in the BE Recommendation Process guidance, FDA’s recommendations for bioequivalence testing of mesalamine-containing products are not aligned nor consistent (Supplement 3 at 12-13).

You indicate that FDA has acted on a case-by-case basis when assessing the bioequivalence of oral, locally acting GI drug products and that 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) (Petition at 6). You claim that a lack of a rigorous bioequivalence standard has created confusion in the approval requirements for generic balsalazide disodium drug products that could result in safety and efficacy problems if these products are approved without adequate assurance of bioequivalence (Petition at 3).

FDA decides whether it may approve a new generic drug based on evaluation of the scientific information provided in the ANDA for the drug. In assessing whether an ANDA sponsor has provided sufficient evidence in its application to establish that the proposed drug is bioequivalent to the reference listed drug, the agency applies the requirements of the Act and FDA's regulations, as discussed above at section II, and relies upon its scientific experience and judgment. FDA need not have published category- or product-specific bioequivalence guidance prior to evaluating or approving ANDAs. If an ANDA includes sufficient evidence to show bioequivalence, the agency may approve the application.

Although it may be useful to the public for FDA to provide guidance specifying how bioequivalence may be established for a particular type of drug product, the category of oral, locally acting GI drug products is so diverse that a single bioequivalence recommendation would not be appropriate. Locally acting GI drug products use a variety of release mechanisms to target different locations within the GI tract. Immediate release products such as cholestyramine make drug available throughout the small intestine, while delayed release mesalamine formulations (Asacol) release at regions with a particular intestinal pH, and prodrugs such as balsalazide release the active ingredient in the colon. Some locally acting GI products, such as balsalazide, sulfasalazine, and olsalazine, are partially absorbed, while others, for example cholestyramine and sucralfate, show no measurable absorption. Thus, we are considering bioequivalence testing of these products on a case-by-case basis. Some of the factors that we are basing our determinations on include:

- Drug characteristics such as solubility
- Mechanism of release of the product
- Ability to measure plasma concentrations and the relation of plasma concentrations to drug release at the site of action
- Sensitivity of clinical studies to detect differences in product performance.

Therefore, your request that FDA issue guidance specifying bioequivalence standards for oral, locally acting GI drug products prior to approval of ANDAs is denied.

With regard to providing product-specific bioequivalence recommendations for balsalazide disodium, as you pointed out, in May 2007, we issued the BE

Recommendation Process guidance. This draft guidance describes FDA's process for making available to the public FDA guidance on how to design BE studies for specific drug products to support ANDAs. At the same time, we issued draft guidance for industry entitled, *Individual Product Bioequivalence Recommendations* (Individual Product BE guidance) which contained an initial group of draft bioequivalence guidances for specific products. Since then, we have issued additional draft bioequivalence guidances for other products. We have not included recommendations for balsalazide disodium because we have been reviewing the issues raised in your pending citizen petition, and did not believe that publication of a draft guidance for the drug was necessary or appropriate at that point.¹² We may publish product-specific bioequivalence recommendations for balsalazide disodium in the future. With regard to other mesalamine products for which we have issued bioequivalence recommendations, we have provided recommendations similar to balsalazide disodium for those products that rely on a diazo-bond reduction to release mesalamine in the colon. As for other mesalamine products that use different release mechanisms or routes of administration, we are treating them individually.

B. The Request That ANDAs for Oral Drug Products Containing Balsalazide Disodium Include Appropriately Designed Comparative Clinical Studies Is Not Warranted

You request that FDA require that ANDAs for oral drug products containing balsalazide disodium include safety and effectiveness evidence from appropriately designed comparative clinical studies because of several unique aspects of these drug products and because of known bioequivalence issues with prodrugs in the mesalamine family in general, including:

- Low absorption in the GI tract
- Topical pharmacological effect in the lower GI tract
- Certain aspects of balsalazide disodium-containing drug products that present "evidence of actual or potential bioequivalence problems"
- Disease states for which balsalazide disodium is indicated have a dramatic impact on intersubject and intrasubject variability
- A high degree of interaction with normal concurrent therapy such as mercaptopurine therapies

(Petition at 1-2, see also Supplement 1 at 2, 10). You believe that these factors must be considered in applying the established scientific and regulatory requirements 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

¹² Whether FDA will include publication of a draft guidance as part of the process for identifying appropriate bioequivalence methodologies for a drug product will depend upon a number of factors, including the specific characteristics of the drug at issue, the applicability of related agency bioequivalence guidance, and the opportunities already provided for the agency to obtain expert advice on the issue (for example, advisory committee meetings, citizen petition dockets, comments on related guidances).

administered at the same molar dose under similar conditions in an appropriately designed study”¹³). You maintain that once these factors are considered, traditional in vivo pharmacokinetic or bioavailability testing in normal healthy subjects and in vitro dissolution assessments will not, by themselves, be sufficient to ensure bioequivalence of any generic version of balsalazide disodium (Petition at 2, 4). You assert that clinical trials are the best measure for assessing the bioequivalence of these drug products even though you acknowledge that many variables exist with regard to the use of clinical trials to establish bioequivalence (Petition at 8).

In Supplement 2, you limit your request for comparative clinical studies to assessment of clinical efficacy (Supplement 2 at 1). You state that while pharmacokinetic bioequivalence studies used as a measure of safety may be required as a condition of approval for oral drug products containing balsalazide disodium, comparative measures of pharmacokinetic bioequivalence are inadequate as a substitute for clinical efficacy (Supplement 2 at 1). You assert that the comparative clinical studies are needed because balsalazide disodium’s efficacy, as stated in Colazal’s labeling,¹⁴ is presumed to be primarily due to the local effects of mesalamine on the colonic mucosa (Supplement 2 at 1).

You further state that at the October 20, 2004, meeting of the Advisory Committee for Pharmaceutical Science (advisory committee), FDA recognized the difficulties in demonstrating bioequivalence for oral, locally acting GI drug products and that the advisory committee was not able to resolve the question of what types of studies are necessary to establish bioequivalence for these drugs (Petition at 2). In contrast, later in your Petition, you state that at the 2004 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 (Petition at 17, 19). You note that the possibility of implementing detailed and realistic dissolution testing as a mechanism for determining bioequivalence for these drugs was proposed, but you indicate that the panel determined, and FDA agreed, that such an approach required considerably more work and study before it could be implemented (Petition at 17). You state that FDA, nonetheless, concluded in its minutes from the meeting that while the advisory committee agreed it was difficult to reach a consensus, in order to prove bioequivalence, in vitro dissolution along with pharmacokinetics should be acceptable¹⁵ (Petition at 17). You claim that FDA’s summary conclusion is not accurate because of the five Committee members that took an active part in the conversation, none endorsed the view that pharmacokinetics and dissolution testing, as it is currently performed, can adequately demonstrate bioequivalence for oral, locally acting GI drug products (Petition at 17-18).

¹³ See 21 CFR 320.1(e).

¹⁴ See the Absorption subsection of the CLINICAL PHARMACOLOGY section of Colazal’s labeling (approved December 2006).

¹⁵ November 11, 2004, minutes of the October 19-20, 2004, Pharmaceutical Science Advisory Committee meeting (2004 advisory committee meeting).

You state that clinical trials have been required or recommended for other oral, locally acting drug products (Petition at 20). You note that in 2000, the advisory committee recommended that clinical trials, in addition to dissolution and pharmacokinetic studies, be conducted for locally acting nasal or inhaled drug products¹⁶ (Petition at 20). You also note that FDA has required clinical studies for demonstration of bioequivalence for certain locally acting oral drugs such as sucralfate¹⁷ (Petition at 20).

In Supplement 4, you request conduct of comparative clinical trials in pediatric patients to ensure the safety and effectiveness of a new formulation of balsalazide disodium (Supplement 4 at 2). You assert that these clinical trials are necessary because, as is demonstrated in the approved labeling for Colazal, pediatric patients absorb balsalazide disodium very differently than adult patients (Supplement 4 at 2).

In the BA/BE guidance,¹⁸ we state:

Where there are no other means, well-controlled clinical trials in humans can be useful to provide supportive evidence of bioavailability or bioequivalence. However, we recommend that the use of comparative clinical trials as an approach to demonstrate bioequivalence generally be considered insensitive and be avoided where possible (21 CFR 320.24). The use of bioequivalence studies with clinical trial endpoints can be appropriate to demonstrate bioequivalence for orally administered drug products when measurement of the active ingredients or active moieties in an accessible biological fluid (pharmacokinetic approach) or pharmacodynamic approach is infeasible.

Despite balsalazide disodium's unique properties (discussed separately in sections III.B.1 to III.B.6 of this response), we have determined that comparative clinical trials are not required to demonstrate bioequivalence of these drug products. On February 22, 2005, FDA convened a group of scientists and physicians from its Center for Drug Evaluation and Research (CDER) to recommend approaches for bioequivalence assessment of locally active drug products that deliver mesalamine to the GI tract. This group concluded that the following data are expected to be needed to determine if a generic formulation of balsalazide disodium is bioequivalent to the reference listed drug, Colazal: (1) equivalent dissolution of the generic formulation and the reference listed drug in multiple media and (2) equivalent pharmacokinetic parameters for the generic formulation and the reference listed drug in an acceptable in vivo bioequivalence study.

Because balsalazide disodium acts locally in the lower GI tract rather than systemically, evaluation of the dissolution of the drug product in the GI tract is important in assessing the rate and extent to which balsalazide disodium is delivered to the site of action. We

¹⁶ November 5, 2000, minutes of the April 26, 2000, Pharmaceutical Science Advisory Committee meeting.

¹⁷ Sucralfate Tablets USP 1 g, ANDA 74-415.

¹⁸ See pp. 9-10 of the BA/BE guidance.

determined that extensive in vitro dissolution testing, using conditions that mimic those in the GI tract, is an appropriate surrogate for in vivo dissolution and that this test is important for comparison of the generic formulation to the reference listed drug.

Although in vitro dissolution testing of balsalazide disodium is very informative, we decided that additional assurance of in vivo bioequivalence is needed. Because balsalazide disodium and the active moiety, mesalamine, can be quantitated in plasma (see section III.B.1 of this response), we decided that an in vivo bioequivalence study with pharmacokinetic endpoints also needs to be conducted comparing the generic formulation and the reference listed drug. As noted in section II of this response, this type of study is the most accurate, sensitive, and reproducible approach for determining bioequivalence of a systemically acting drug product.

For the in vivo bioequivalence study, we decided that plasma levels of both balsalazide and mesalamine should be measured. Plasma levels of balsalazide should be measured because, as stated earlier (see section II of this response), plasma concentrations of a parent drug are sensitive to changes in formulation performance. Plasma levels of mesalamine should also be measured because balsalazide is delivered intact to the colon, the intended site of drug action, where it is cleaved into mesalamine and other inactive metabolites, and mesalamine's pharmacokinetics reflect its absorption from the colon, which is relevant to its availability at the site of activity. The 90 percent confidence intervals of the test/reference geometric mean ratios for the pharmacokinetic parameters, AUC and Cmax, of both balsalazide and mesalamine should fall within the range of 0.8 to 1.25. Our recommendation that plasma levels of mesalamine be measured, in addition to balsalazide, is consistent with our BA/BE guidance because mesalamine is formed presystemically and contributes meaningfully to efficacy.¹⁹ Our recommendation that a confidence interval approach be used for balsalazide is also consistent with our BA/BE guidance.²⁰ However, our recommendation that a confidence interval approach be used for mesalamine goes beyond what is recommended in our BA/BE guidance.²¹ In the guidance, we indicate that metabolite data can be used to provide supportive evidence of comparable therapeutic outcome. For the case of balsalazide, because it is a prodrug that releases a locally acting drug, FDA determined that to demonstrate bioequivalence between a generic product and the reference listed drug evaluating the mesalamine data using the confidence interval approach was needed to ensure that balsalazide reaches the colon and is converted to the active moiety, mesalamine.

Thus, we concluded that a combination of comparative tests for in vivo pharmacokinetics (measure of the rate and extent of systemic exposure) and in vitro dissolution (surrogate of in vivo drug release in the GI tract) should be conducted to establish bioequivalence for balsalazide disodium drug products. Although measures of dissolution and pharmacokinetics in the blood stream each, individually, only partially reflect

¹⁹ See page 18 of the BA/BE guidance.

²⁰ See page 18 of the BA/BE guidance.

²¹ See page 18 of the BA/BE guidance.

mesalamine appearance at the local site(s) of action, assessment of both provides us with assurance of formulation performance to support a determination of bioequivalence. Demonstration of equivalence in comparative in vitro dissolution testing assures us that both the generic formulation and the reference listed drug release balsalazide disodium at the same rate under the range of conditions that occur in the GI tract. Demonstration of equivalent pharmacokinetic parameters of balsalazide disodium assures us that the absorption of balsalazide disodium from the generic formulation and the reference listed drug is equivalent in vivo. Finally, demonstration of equivalent pharmacokinetic parameters of mesalamine assures us that balsalazide disodium reaches the colon and is converted to mesalamine at an equivalent rate for both the generic formulation and the reference listed drug.

Our recommendation for balsalazide disodium drug products is consistent with the Agency's approval of a generic application for sulfasalazine (Azulfidine), a prodrug similar to Colazal. The approval of Azulfidine was based on comparative in vitro dissolution and in vivo bioequivalence data.²²

With regard to your assessment of the 2004 advisory committee meeting, we do not agree with some of your comments. In particular, your comment that there was agreement that clinical effectiveness testing was the only currently effective way to demonstrate bioequivalence for locally acting GI drugs. Even the one member who advocated comparative clinical testing said that, given the understanding we have about GI dissolution and GI absorption, he was comfortable "not making the clinical gold standard a requirement."²³ Instead, most of the discussion at the meeting focused on use of in vitro dissolution testing as a surrogate for in vivo dissolution and whether or not a pharmacokinetic study was needed.²⁴ Various opinions were presented regarding these tests without a definitive recommendation, most likely because bioequivalence testing of these products should be considered on a case-by-case basis since their pharmacology and metabolism varies. Nonetheless, overall, it appeared that committee members felt that in vitro dissolution testing was a desired approach for these products, with some expressing the need for conducting these tests over a range of physiological pH. It also appeared that some sort of in vivo pharmacokinetic study would be desirable.

With regard to conduct of clinical trials in pediatric patients, it is not necessary to conduct such trials for approval of an ANDA. Our bioequivalence recommendations ensure that the performance of the generic formulation and the reference listed drug is bioequivalent. Even though there are differences in exposure to balsalazide disodium between children and adults, as described in Colazal's approved labeling, if two products are bioequivalent in healthy adult subjects, then they will be bioequivalent in populations such as pediatric patients. We, therefore, do not recommend that clinical studies be conducted in pediatric

²² See approval package for sulfasalazine available on the Internet at <http://www.fda.gov/cder/foi/nda/2002/40349.pdf>

²³ Transcript of the 2004 advisory committee meeting, p. 337.

²⁴ Transcript of the 2004 advisory committee meeting, pp. 273-341.

patients. This approach is consistent with our desire to avoid unnecessary human testing, particularly with respect to pediatric populations.

We respond, as follows, to specific issues related to balsalazide disodium that you identify in your petition as justification for conduct of comparative clinical studies:

1. *Low Absorption and Toxicity of Balsalazide*

You claim that balsalazide disodium has been demonstrated to have low absorption and toxicity of both the carrier, 4-ABA, and active moiety, mesalamine, as compared with the prodrugs, sulfasalazine and olsalazine.^{25, 26} For example, you argue that about 10-15 percent of the prodrug sulfasalazine can be reproducibly measured in the plasma, while less than 1 percent of the prodrug balsalazide is absorbed.²⁷ As a result, there are low levels of both 4-ABA and mesalamine in the bloodstream, making bioequivalence determinations for balsalazide based on traditional blood level measurements scientifically unsupported.²⁸ You state that this is in contrast to sulfasalazine for which the parent and carrier plasma levels can be readily measured and represent a significant portion of the oral dose, thus permitting bioequivalence determinations for approval of generic sulfasalazine drug products. (See Petition at 6-7 and 10-11.)

We disagree that low absorption of balsalazide distinguishes balsalazide disodium from other prodrugs in the mesalamine family. Recent literature reports have demonstrated that the systemic exposure to total mesalamine, as measured by urinary and fecal excretion of mesalamine and N-Acetyl-5-ASA, is comparable for all oral mesalamine formulations (Asacol, Salofalk, Mesasal, Claversal, and Pentasa) and prodrugs (sulfasalazine, olsalazine, and balsalazide).^{29, 30} In particular, the relative bioavailability of total mesalamine following oral administration of sulfasalazine (mean 11-33 percent;

²⁵ Green JRB. Balsalazide and azathioprine or 6-mercaptopurine. *Gastroenterology* 1999; 117:1513-1514.

²⁶ NDA 20-610 Volume 1.047, page 75-Volume 1.053, page 228.

²⁷ Green JRB. Balsalazide and azathioprine or 6-mercaptopurine. *Gastroenterology* 1999; 117:1513-1514.

²⁸ See transcript for 2004 advisory committee meeting, discussion regarding blood levels of locally acting GI drugs (available at <http://www.fda.gov/ohrms/dockets/ac/cder04.html#PharmScience>).

²⁹ Sandborn WJ and Hanauer SB. Systemic review: The pharmacokinetic profiles of oral mesalazine formulations and mesalazine pro-drugs used in the management of ulcerative colitis. *Alimentary Pharmacology and Therapeutics* 2003; 17(1):29-42.

³⁰ Sandborn WJ, Hanauer SB, and Buch A. Comparative pharmacokinetics of equimolar doses of 5-aminosalicylate administered as oral mesalamine (Asacol) and balsalazide: a randomized, single-dose, crossover study in healthy volunteers. *Alimentary Pharmacology and Therapeutics* 2004; 19(10): 1089-1098.

median 22 percent) was similar to that following administration of balsalazide (mean 12-35 percent; median 20 percent).³¹

Further, while balsalazide is extensively metabolized by azoreductases in the colon, data provided in the approved labeling for Colazal indicate that a fraction of orally administered balsalazide and the active moiety, mesalamine, are bioavailable, resulting in systemic levels that are quantifiable.³² Thus, in vivo pharmacokinetic studies are appropriate to help establish bioequivalence for balsalazide disodium drug products. For these studies, we recommend, as previously described, that plasma concentrations of both balsalazide and mesalamine be measured.

2. *Local Action of Balsalazide in Lower GI Tract*

You claim that balsalazide disodium's primary pharmacological effect appears to be through topical action in the lower GI tract.³³ This is because the active moiety, mesalamine, which is released from balsalazide disodium at the site of intended action, is believed to provide all the pharmacological activity by contact or absorption at that site only. You state that a correlation of blood levels or other biopharmaceutical measurements with clinical effect are the foundation of Agency decisions on bioequivalence (21 CFR 320.1). You claim that there is no evidence of any correlation between blood levels of the active moiety, mesalamine, and clinical effect.³⁴ To support this claim, you provide data from your NDA (Study CP069101 and Study CP099301) that demonstrate the lack of concurrence between plasma concentrations of mesalamine and symptom relief as measured by the 12-point Sutherland Disease Activity Index (SDAI), where a lower score is reflective of less active ulcerative colitis symptoms. You further claim that the labeling of September 2006 for Colazal corroborates that plasma concentration data are not correlated with efficacy, because the labeling states

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

³¹ Sandborn WJ and Hanauer SB. Systemic Review: The pharmacokinetic profiles of oral mesalazine formulations and mesalazine pro-drugs used in the management of ulcerative colitis. *Alimentary Pharmacology and Therapeutics* 2003; 17(1):29-42.

³² See the Absorption subsection of the CLINICAL PHARMACOLOGY section of Colazal's labeling (approved December 2006).

³³ Frieri G, Giacomelli R, Pimpo M et al. Mucosal 5-aminosalicylic acid concentration inversely correlates with severity of colonic inflammation in patients with ulcerative colitis. *Gut* 2000; 47:410-414.

³⁴ Levine DS, Riff DS, Pruitt R et al. A randomized, double blind, dose-response comparison of balsalazide (6.75 g), balsalazide (2.25 g), and mesalamine (2.4 g) in the treatment of active, mild-to-moderate ulcerative colitis. *American Journal of Gastroenterology* 2002; 97:1398-1407.

You submit that since the labeling explicitly says that no inference can be made as to the clinical efficacy under different dosing conditions, the same logic should apply to different formulations. (See Petition at 7 and 9-11 and Supplement 2 at 6-8.)

The specific mechanism of action of mesalamine products has never been fully characterized, but is thought to be primarily through local action within the GI tract. We cannot exclude, however, the contribution of systemically absorbed mesalamine to its pharmacological action because systemically absorbed drug will be distributed into tissues including the GI tract. To date, there is no clinical evidence to support this hypothesis.

You cite 21 CFR 320.1 regarding use of correlation of blood levels or other pharmaceutical measurements with clinical effect as the basis for Agency decisions on bioequivalence. This provision of our regulations, which provides definitions for bioavailability and other terms related to bioequivalence, does not mention the need for establishing correlations between plasma levels and clinical response. We do not require that generic drug companies establish a correlation between plasma levels and clinical effect as justification for the use of pharmacokinetic parameters (AUC and Cmax) in bioequivalence studies. The purpose of determining pharmacokinetic parameters in bioequivalence studies is to compare the generic drug's formulation to the reference listed drug's formulation to identify any significant differences in the rate and extent to which the active moiety or active ingredient becomes available at the site of drug action. As previously described, in vivo pharmacokinetic studies, together with in vitro dissolution data, can readily accomplish this comparison for balsalazide disodium.

The data that you provide from your NDA are not relevant to the evaluation of a bioequivalence method because such information indicates the variability between different people. For instance, one person might have a low plasma concentration and low efficacy while another may have a high plasma concentration and low efficacy. The variability among individuals is due to numerous potential factors such as sex, weight, genetics, disease severity, and diet. In a bioequivalence study, much of this variability is removed by testing both the test and reference products in the same person.

With regard to the statement that you quote from the labeling for Colazal, this language reflects the fact that there is no evidence that the different dosing conditions for balsalazide (i.e., effect of food) have any impact on the clinical effectiveness of the product. In fact, the data from the food-effect study described in Colazal's labeling supports our conclusion that in vivo pharmacokinetic studies, which are part of FDA's evaluation of equivalence, are able to detect smaller differences in the performance of the generic formulation and the reference listed drug than can be detected clinically. Thus, in vivo pharmacokinetic studies are superior to clinical studies of effectiveness for assessment of the bioequivalence of balsalazide disodium drug products.

3. *Balsalazide's Azo-Bond Linkage and In Vitro Dissolution Testing*

You claim that balsalazide disodium's azo-bond linkage, which is reduced by the presence of colonic bacterial azo-reductase, is a confounding factor in any in vitro dissolution testing (Petition at 10).

Approved oral, locally acting GI drug products have validated dissolution methods that are routinely used for quality control of production lots and can be used for the approval of qualifying pre- and postapproval changes in lieu of a bioequivalence study. For example, dissolution testing has been used to examine the similarity between different formulations of mesalamine. In 1999, you submitted to us comparative in vitro dissolution data using the Asacol formulation employed in some of your clinical studies (a United Kingdom-approved formulation) and the U.S. formulation.³⁵ In another example pertaining to Pentasa, another oral mesalamine formulation, a level A in vitro/in vivo correlation was established.³⁶ The study entailed a correlation between systemic exposure to mesalamine and drug release in vitro. This approach was used by the sponsor to link Pentasa formulations of different composition in lieu of conducting comparative clinical efficacy trials.

We have not encountered any problems with the dissolution methodology used for these products. Furthermore, you have not submitted any data, nor are we aware of any, that would substantiate your concern.

4. *Actual or Potential Bioequivalence Problems Associated With Balsalazide*

You claim that 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.³⁷ These include the following pharmacokinetic factors: (1) the lack of significant systemic absorption of the prodrug, balsalazide, (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 specific portions of the GI tract.³⁸ These factors are further supported by other factors that identify bioproblem drugs and apply to balsalazide.³⁹ A

³⁵ See NDA 20-610, Clinical Pharmacology and Biopharmaceutics Review, Response to FDA Letters Dated 6/15/98, 1/9/98, and 3/16/99.

³⁶ See NDA 20-049, Clinical Pharmacology and Biopharmaceutics Review, Appendix I, Study 1.

³⁷ 21 CFR 320.33.

³⁸ Allgayer H, Ahnfelt NO, Krus W et al. Colonic N-acetylation of 5-aminosalicylic acid in inflammatory bowel disease. *Gastroenterology* 1989; 97:38-41.

³⁹ 21 CFR 320.33(f).

lack of bioequivalence could have a serious effect on the treatment of the disease for which balsalazide is indicated.⁴⁰ (See Petition at 7 and 11-12.)

Although balsalazide has some of the characteristics listed in 21 CFR 320.33, this section of the regulations is relevant only to drugs that are not subject to section 505(j) of the Act (i.e., drugs approved prior to 1962).⁴¹ These characteristics are used to determine when a bioequivalence study should be requested for drugs not subject to section 505(j) of the Act. No such determination is needed for generic drug products that are subject to section 505(j) of the Act, such as balsalazide disodium, because section 505(j) of the Act establishes bioequivalence requirements for generic drugs. In fact, by its terms, 21 CFR 320.32 — which sets forth conditions in accordance with which FDA may seek to establish bioequivalence requirements — applies only to “a product not subject to section 505(j) of the [A]ct.”

In any event, the fact that balsalazide disodium possesses some of the characteristics detailed in 21 CFR 320.33 does not mean that bioequivalence may not be established between a generic formulation of balsalazide disodium and the reference listed drug, as you claim. Drugs that exhibit the properties in 21 CFR 320.33 may be deemed bioequivalent if they meet an appropriate bioequivalence standard. If a generic formulation of balsalazide disodium fails to meet requirements for demonstrating bioequivalence, the product will not be approved.

5. *Inter- and Intrasubject Variability in Clinical Response to Balsalazide*

You claim that well-controlled studies of balsalazide disodium have demonstrated significant inter- and intrasubject variability in clinical response to the drug.⁴² 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.⁴³ Patients divided into different subgroups based on extent and history of their disease had significantly different responses to the drug treatment.⁴⁴ Because of this variability, any pharmaceutical variation between different balsalazide drug products may be exacerbated. Therefore, it is necessary for any comparative efficacy study of two balsalazide-containing drug products to be sufficiently powered such that the randomization can equally assign

⁴⁰ Forbes A, Cartwright A, Marchant S et al. Review article: oral, modified-release mesalazine formulations — proprietary versus generic. *Alimentary Pharmacology and Therapeutics* 2003; 17:1207-1214.

⁴¹ 21 CFR 320.32.

⁴² NDA 20-160 Vol. 1.067, p. 218-Vol. 1.074, p. 327.

⁴³ Green JRB, Lobo AJ, Holdsworth CD et al. Balsalazide is more effective and better tolerated than mesalamine in the treatment of acute ulcerative colitis. *Gastroenterology* 1998; 114:15-22.

⁴⁴ Pruitt R, Hanson J, Safdi M et al. Balsalazide is superior to mesalamine in the time to improvement of signs and symptoms of acute mild-to-moderate ulcerative colitis. *American Journal of Gastroenterology* 2002; 97:3078-3086.

patients into the relevant subgroups based on disease extent and disease history. Failure to power the study adequately and control for the contribution of patient subtypes 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 presence of relapse, symptom severity at the time of randomization, concomitant medications, and time since withdrawal of prior medications. All of these potentially confounding variables must be adequately controlled during patient selection, screening, and randomization process. (See Petition at 7, and 12-13.)

For the reasons previously described, comparative efficacy studies are not warranted to demonstrate bioequivalence of balsalazide disodium drug products. For pharmacokinetic bioequivalence studies, healthy subjects are generally used because the disease state of patients greatly influences the sensitivity of the test due to within subject, as well as between subject, variability. The lower variability associated with use of healthy subjects provides greater sensitivity for the detection of small differences in the bioavailability of pharmaceutically equivalent formulations. Therefore, the use of patients as subjects in bioequivalence studies for balsalazide disodium drug products is not appropriate and your arguments are not relevant.

6. *Interaction of Balsalazide With Normal Concurrent Therapies*

You claim that balsalazide disodium has a high and measurable degree of interaction with normal concurrent therapies such as mercaptopurine therapies. When these products are used concomitantly, the potential exists for a serious drug-drug interaction that can lead to leucopenia. Data demonstrate that the plasma levels of both mesalamine 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. Balsalazide has a lower potential for this drug-drug interaction because the plasma concentrations of its components (mesalamine and 4-ABA) are an order of magnitude lower than plasma concentrations for other drug products in this category. Nonetheless, you claim it is 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. This activity is not an issue of balsalazide disodium efficacy, but an issue of side effects and safety of mercaptopurine, and this is indirectly related to bioequivalency. You conclude that it is therefore imperative that any balsalazide-containing drug product exhibit equivalent absorption characteristics to the reference listed drug in order to ensure overall patient safety with respect to co-administered drugs. (See Petition at 7-8, and 13-15.)

As long as a generic product is shown to be bioequivalent to its reference listed drug, the drug-drug interaction profile for both drug products would be expected to be the same. In a bioequivalence study, the generic drug's formulation is compared, as previously described, with the reference listed drug's formulation to identify any significant differences in the rate and extent to which the active moiety or active ingredient becomes available at the site of drug action (see section III.B.2 of this response). If two drug

products containing the same active ingredient are shown to be bioequivalent, their interaction with a concomitant medication would be equivalent. In this case, if a generic balsalazide disodium drug product is bioequivalent to Colazal, the reference listed drug, its drug interaction with mercaptopurine would be equivalent to the interaction between Colazal and mercaptopurine.

C. The Request that FDA's OGD Withdraw Recommendations Regarding Bioequivalence Measures for Balsalazide Disodium Outlined in a March 24, 2006, Letter to a Third Party Is Not Warranted

You indicate that you are aware of a letter dated March 24, 2006, provided to a third party by FDA that discusses a possible approach, combining in vitro dissolution and in vivo bioequivalence measures for balsalazide-containing drug products (Supplement 1 at 2). You claim that these recommendations require a series of tests that are not proven equivalency measures and therefore will not ensure the safe interchangeability of balsalazide disodium products (Supplement 1 at 2). You further submit that FDA's recommendations do not reflect changes to the approved labeling for Colazal that may occur as a result of your submission of phase 4 study results from pharmacokinetic studies in ulcerative colitis patients with active disease, a food-effect study and a pediatric study (Supplement 1 at 9). Thus, you claim that it is not possible at this time for OGD to provide a recommendation for bioequivalence that fully accounts for the scientific data available on the dissolution and absorption of balsalazide-containing products and request that OGD withdraw the recommendations described in the letter (Supplement 1 at 1-2, 9). Instead, you suggest that a better measure would be a more appropriate in vitro dissolution test coupled with a study of bioequivalence in ulcerative colitis patients in remission that measures the bioequivalence of balsalazide, mesalamine and N-Acetyl-5-ASA (Supplement 1 at 2, 9). Even if such an approach is used, you still maintain that comparative measures of therapeutic outcomes in patients is the best method for balsalazide-containing products because of the low and variable absorption of the drug and the influence of disease activity, food, and age on this absorption (Supplement 1 at 2, 9-10).

Our recommendations for bioequivalence studies for balsalazide disodium drug products in the March 24, 2006, letter were based on the labeling for Colazal and information available to us at that time. Since then, the labeling for Colazal has been revised to reflect new data from a food study and a pediatric study.⁴⁵ As a result of the food study, we have revised our recommendations to include a fed study in addition to the studies that were previously recommended (see section III.C.2.a of this response). It is not necessary to withdraw any of the other recommendations that were provided in the letter of March 24, 2006. It is our practice to modify our recommendations for bioequivalence testing, as necessary, if new studies provide additional relevant information or changes to the approved labeling for the reference listed drug are made. In the future, we may also post our bioequivalence recommendations on our Web site in accordance with our BE

⁴⁵ The labeling for Colazal was revised in September 2006 to reflect data from a food-effect study and revised again in December 2006 to reflect data from a pediatric study.

Recommendations Process guidance. In addition, this citizen petition response contains a description of our bioequivalence recommendations for balsalazide disodium products.

We respond, as follows, to specific issues pertaining to bioequivalence measures for balsalazide disodium drug products that you identified in Supplements 1, 2, 3, and 4:

1. *In Vitro Dissolution Testing*

You submit that FDA's recommended pH levels for the dissolution testing (i.e., 0.1 N HCl, pH 4.5, pH 6.8, and pH 7.4) are insufficiently discriminatory to detect differences in formulation because balsalazide is insoluble in 0.1 N HCl and rapidly solubilizes in pH levels above 4.5 (Supplement 1 at 3 and Supplement 3 at 6). You claim that a pH condition needs to be added that yields some level of intermediate dissolution rate (Supplement 1 at 3 and Supplement 3 at 6).

You also claim that the dissolution testing needs to include a pretreatment with acid (e.g., 30 minutes with 0.1 N HCl) to more closely mimic in vivo conditions (Supplement 3 at 7). You explain that when balsalazide disodium is exposed to acid conditions of 0.1 N HCl in gastric fluid, the sodium salt form is rapidly converted to the protonated acid form, which has been shown experimentally to be insoluble. You submit that the subsequent solubility of the free acid form of balsalazide is then the determining factor of in vivo dissolution and that FDA, which recommends dissolution testing of the sodium salt only, does not address this issue. You provide data you claim supports this approach (Supplement 3 at 7-9). In your study, you compare in vitro dissolution of the reference listed drug and the test drug at pH 4.5 and also at pH 4.5 after pretreatment with 0.1 N HCl for 30 minutes. In this study, the reference listed drug and test drug showed the same dissolution profile when tested at pH 4.5, but not when they were first pretreated with 0.1 N HCl and then tested at pH 4.5. In addition, you note that while a large percentage of both the reference listed drug and test drug rapidly dissolve in 5 minutes after pretreatment, there is a residual amount of drug substance that fails to dissolve out to 120 minutes. For the reference listed drug, you state that the undissolved fraction is approximately 20 percent of the dose. You claim that the differences observed with acid pretreatment are relevant in vivo, influence the quantity of drug substance that ultimately reaches the intended site of action in the colon, and indicate that FDA's in vitro dissolution tests lack sufficient scientific rigor to be used as a surrogate for actual dissolution in vivo.

You submit that in vitro dissolution is only appropriate for use as a release specification and not as a bioequivalence measure because the recommended in vitro conditions do not approximate the sequential exposure of balsalazide to varying pH conditions in vivo (Supplement 1 at 4 and Supplement 3 at 6-7). You claim that this factor is significant because it is not known where in the GI tract in vivo dissolution takes place (Supplement 1 at 4 and Supplement 3 at 6).

The availability of balsalazide in the colon is contingent on its dissolution in the GI tract. Our recommended pH range for in vitro dissolution testing, which includes pH values

representative of conditions that would be encountered in the GI tract, is appropriate for balsalazide disodium. Balsalazide disodium only briefly encounters pH values between 1 and 4.5 in vivo (see Appendix A enclosed); therefore, additional testing between these two points is not relevant to the expected in vivo performance. Further, you have not submitted any data to substantiate your claim. We note that the dissolution method that you have used with respect to the Colazal NDA does not include either a pH between 1 and 4.5 or a sequential exposure to varying pH.

With regard to pretreatment of balsalazide disodium with acid prior to dissolution testing, such a test may give different results than separate dissolution tests in multiple media as we recommend for balsalazide disodium. However, a determination of which of these dissolution conditions is more discriminatory is not possible because you did not provide dissolution data of the reference listed drug and test drug with pretreatment with acid using all of our recommended dissolution conditions. Because of the high solubility of balsalazide disodium at higher pHs and balsalazide's extended exposure to pH 6.8 in the small intestine (approximately 3 hour small intestine transit time before balsalazide reaches the colon), it is important to evaluate dissolution of balsalazide disodium at higher pH levels as part of the overall bioequivalence assessment. Such an assessment would detect differences between the reference listed drug and the test drug that would result in differences in the availability of balsalazide at its site of action in the colon.

Furthermore, your selection of pH 4.5 for your in vitro dissolution testing does not reflect true in vivo conditions. Balsalazide is only exposed to pH 4.5 for a short period of time and, as noted previously, is exposed to pH 6.8 for an extended period of time (several hours). Thus, an in vivo relevant dissolution test would include in vitro dissolution testing for least 1 hour at pH 6.8. In this case, we would not expect to see differences in the dissolution profile of the reference listed drug and the test drug.

2. *In Vivo Bioequivalence Study*

a. Fed Study

You submit that, as a phase 4 commitment, you assessed the effect of food on the absorption of balsalazide disodium and the results of your study showed that feeding influences the bioavailability of balsalazide (Supplement 2 at 3-5). You note that, as a result of this study, the labeling for Colazal was revised in September 2006 (Supplement 2 at 5). You further submit that, in accordance with FDA's food-effect studies guidance,⁴⁶ if bioequivalence studies are used to establish safe interchangeability of drug products containing balsalazide disodium, a food-effect study is required (Supplement 2 at 8-10, see also Supplement 3 at 2 and 14). You also note that FDA required a food-effect study for another mesalamine product, Asacol, because it is a delayed-release drug product (Supplement 2 at 9). You request that FDA apply the same logic for Colazal, which also acts like a delayed-release product because of negligible gastric solubility,

⁴⁶ FDA guidance for industry on *Food-Effect Bioavailability and Fed Bioequivalence Studies* (food-effect studies guidance), December 2002, pp. 3-4.

low permeability and resultant bioavailability of the prodrug (balsalazide), and the delayed mechanism by which the prodrug releases the active therapeutic moiety in the colon (Supplement 2 at 9).

We concur with your request. As a result of changes to Colazal's labeling in September 2006, pertaining to the effects of food on absorption of balsalazide disodium, we revised our recommendations for bioequivalence studies to include both fasting and fed studies. This change is consistent, as you noted, with our food-effect studies guidance, which recommends both fed and fasting bioequivalence studies when the labeling for the reference listed drug mentions an effect of food.

b. Sprinkling Study

You submit that FDA's food-effect studies guidance on demonstrating bioequivalence in products labeled for dosing in sprinkles requires a single dose crossover sprinkle study, because in the guidance we state:⁴⁷

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

(Supplement 2 at 10). You state that the food-effect studies guidance contains no exceptions to the requirement that bioequivalence comparisons of a test product to a reference listed drug product with a label that describes sprinkling also test sprinkles. You further state that there is no justification for carving the sprinkling instructions out of the label and that the sprinkling instructions are not specific to any particular patient population (e.g., elderly patients or patients with difficulties in swallowing). Thus, you claim that a sprinkle study is needed for the directions of use for all patients (Supplement 2 at 10, see also Supplement 3 at 2 and 14). To support these sprinkle instructions, you request that a sprinkle bioequivalence study as well as a sprinkle (applesauce) stability study be required (Supplement 2 at 10).

With regard to your quote from the food-effect studies guidance (Supplement 2 at 10), you have misinterpreted our intent. The language that you quote describes how to conduct a sprinkle bioequivalence study for an ANDA, but does not indicate when FDA would request such a study. The food-effect studies guidance is silent with respect to when a sprinkle bioequivalence study would be requested for an ANDA. Nonetheless, FDA generally requests an in vivo bioequivalence study in which the test and reference products are opened and the component beads sprinkled on applesauce (or other soft food mentioned in the labeling) and administered to the study subjects (sprinkle bioequivalence study) for modified-release capsule products containing beads. The coating of beads used to fill modified-release capsules generally contains excipients that control the rate of drug release, and applesauce or other soft food may disrupt the

⁴⁷ Food-effect studies guidance, p. 8.

mechanism of release for such products. However, we generally do not request sprinkled bioequivalence studies for immediate-release capsules because there are no release-controlling excipients present. Colazal is an immediate-release capsule that does not contain any release controlling excipients; thus, we are not requesting sprinkled bioequivalence studies for balsalazide disodium drug products.

c. Patient Population

You submit that FDA's recommended pharmacokinetic study does not specify a particular subject population, which indicates that normal healthy subjects are suitable for the comparison of formulation performance (Supplement 1 at 5 and Supplement 2 at 11). You claim that such studies should use ulcerative colitis patients rather than normal healthy subjects because (1) the level of plasma absorption of balsalazide is barely detectable and subject to extreme variability and (2) greater absorption of balsalazide, mesalamine, and N-Acetyl-5-ASA has been observed in ulcerative colitis patients in remission than in normal healthy subjects⁴⁸ (Supplement 1 at 5-7 and Supplement 2 at 11; see also Supplement 3 at 2 and 14). You also claim that ulcerative colitis patients should be used for the pharmacokinetic studies because, given the new information on the effect of food on bioavailability of balsalazide (see section III.C.2.a of this response), it is not known how these profound changes in the mucosa architecture and intestinal environment will influence the in vivo dissolution and absorption of an alternative formulation of balsalazide (Supplement 2 at 11).

You also request that pharmacokinetic studies assess the absorption of balsalazide and its metabolites in the pediatric population (Supplement 4 at 2 and 7). You make this request because data that you include in Colazal's approved labeling demonstrate altered blood levels of balsalazide and its metabolites in pediatric ulcerative colitis patients as compared to adult patients (Supplement 4 at 3). You claim that the safe use of a generic formulation of balsalazide disodium can not be addressed by "carving out" this indication in the labeling (Supplement 4 at 2 and 7).

We disagree with your claim that greater absorption results in greater sensitivity at detecting formulation differences. Your claim does not take into account, as previously noted (see section III.B.5 of this response), the contribution of the disease state to within subject as well as between subject variability, which greatly impacts the sensitivity of the test. For this reason, bioequivalence studies are generally conducted in healthy subjects and use of patients as subjects in bioequivalence studies for balsalazide disodium drug products is not appropriate. Additional information about the effect of food does not change our conclusion; we have accounted for the effect of food by requesting that sponsors of ANDAs for balsalazide disodium drug products demonstrate that their products are bioequivalent to the reference listed drug when the products are given with food.

⁴⁸ See NDA 20-610, Clinical Pharmacology and Biopharmaceutics Review, pp. 17-18 and Absorption subsection of the CLINICAL PHARMACOLOGY section of Colazal's labeling (approved September 21, 2006).

With regard to conduct of pharmacokinetic studies in pediatric subjects, it is not necessary to conduct such studies for approval of an ANDA. As noted previously, if a generic formulation of a drug product is demonstrated in healthy adult subjects to be bioequivalent to a reference listed drug, then it will be bioequivalent in the pediatric population. We, therefore, do not recommend additional bioequivalence studies be conducted in pediatric subjects.

d. Measurement of Analytes

You submit that FDA's recommendation that the analytes balsalazide and mesalamine be measured in plasma is not sufficient because approval of a generic balsalazide would be based on a bioequivalence measurement resulting from less than 2 percent of the oral dose (Supplement 1 at 7). You claim that N-Acetyl-5-ASA must be measured also because:

- mesalamine is rapidly converted to N-Acetyl-5-ASA in the colonic mucosa prior to absorption (Supplement 1 at 8),
- N-Acetyl-5-ASA appears in plasma earlier than mesalamine and rises to a greater C_{max} and AUC (Supplement 1 at 8),⁴⁹
- N-Acetyl-5-ASA may have safety issues because of higher plasma concentrations of N-Acetyl-5-ASA relative to mesalamine (Supplement 3 at 12) and the possibility for renal toxicity (Supplement 1 at 8),
- FDA has previously required measurement of N-Acetyl-5-ASA for approval of generic pH-dependent mesalamine (i.e., Asacol) and for your phase 4 commitments for Colazal (Supplement 1 at 9),
- the food-effect study (see section III.C.2.a of this response) showed that N-Acetyl-5-ASA varies independently with different dosing conditions and may also vary independently with different formulations (Supplement 1 at 7-8; Supplement 2 at 10-11),
- the lower-than-expected in vitro dissolution of balsalazide that you observed (see section III.C.1 of this response) makes it of utmost importance to focus analysis on the analyte that yields the most precise measure (Supplement 3 at 10-11),
- N-Acetyl-5-ASA contributes to the efficacy of balsalazide, because studies have shown anti-inflammatory action of locally applied N-Acetyl-5-ASA (Supplement 3 at 12), and
- both balsalazide and mesalamine are considered highly variable analytes based on the FDA-defined systemic exposure metrics, while N-Acetyl-5-ASA results in measures of less variability and increased precision (Supplement 3 at 11).

You note that if a generic formulation of balsalazide yields greater systemic N-Acetyl-5-ASA, a safety concern is raised (Supplement 1 at 9). If, on the other hand, a generic

⁴⁹ See NDA 20-610, Clinical Pharmacology and Biopharmaceutics Review, p. 9.

formulation of balsalazide yields lower systemic N-Acetyl-5-ASA, you note that it may be indicative of a different release pattern of mesalamine in the colon and therefore represent an efficacy concern (Supplement 1 at 9).

As previously described, both balsalazide and mesalamine can be quantitated in plasma (see section III.B.1 of this response). We have determined that assessment of plasma levels of these two compounds is sufficient for bioequivalence studies of balsalazide disodium. We are requesting measurement of mesalamine and not N-Acetyl-5-ASA for the bioequivalence studies because N-Acetyl-5-ASA is a secondary metabolite formed from the primary metabolite, mesalamine, and measurement of mesalamine, as the primary metabolite, would be expected to be more sensitive to changes in formulation performance than N-Acetyl-5-ASA.⁵⁰ The fact that the AUC and Cmax of the metabolite, N-Acetyl-5-ASA, are greater than those of mesalamine is not relevant as long as it is possible to quantify mesalamine in plasma (see section III.B.1 of this response). Thus, any increased variability associated with measurements of mesalamine as compared to N-Acetyl-5-ASA is not relevant.

The approved labeling for Colazal does not mention any safety issues associated with N-Acetyl-5-ASA.⁵¹ In addition, a higher plasma concentration does not in itself indicate that N-Acetyl-5-ASA contributes to the safety profile of balsalazide. There is no linkage of adverse events to exposure to N-Acetyl-5-ASA provided in your submissions or known to FDA. Thus, N-Acetyl-5-ASA does not have to be measured for bioequivalence studies, because, consistent with our BA/BE guidance,⁵² it does not contribute meaningfully to the safety of balsalazide disodium. Further, establishing bioequivalence between the test and reference listed drug with respect to mesalamine will ensure that there is no significant difference in the concentration of the metabolite, N-Acetyl-5-ASA, with these products and, thus, ensure equivalent safety respect to any possible N-Acetyl-5-ASA related toxicity.

In addition, the approved labeling of Colazal⁵³ indicates that the active ingredient in balsalazide disodium is mesalamine and does not indicate any contribution of N-Acetyl-5-ASA to efficacy.⁵⁴ The studies cited in your petition pertaining to efficacy of N-

⁵⁰ See the BA/BE guidance, pp. 17-18:

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 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, distribution, and elimination.

⁵¹ See Colazal labeling (approved December 2006).

⁵² See page 18 of the BA/BE guidance.

⁵³ See Colazal labeling (approved December 2006).

⁵⁴ In addition, the approved labeling for Dipentum (olsalazine sodium capsules) states that N-Acetyl-5-ASA is inactive (approved 2006). Like balsalazide, olsalazine is a prodrug that releases mesalamine upon metabolism by colonic bacteria.

Acetyl-5-ASA (anti-inflammatory activity) are not relevant to balsalazide disodium, because the studies evaluate direct delivery of N-Acetyl-5-ASA not via systemic exposure, while the metabolism of mesalamine to N-Acetyl-5-ASA occurs after mesalamine has been absorbed by the cells in the colon. All marketed mesalamine products are designed to provide local delivery to the site of action because, as noted previously, even though small quantities of mesalamine are absorbed systemically, there is no clinical evidence that any meaningful efficacy is provided by systemic exposure to mesalamine or its metabolites, including N-Acetyl-5-ASA. Furthermore, you assert that balsalazide disodium's pharmacological activity is through topical action in the lower GI tract and that blood levels have not been shown to be a relevant measure of clinical effect (Petition at 7 and 10). Thus, N-Acetyl-5-ASA is not recommended to be measured in bioequivalence studies, because, again consistent with our BA/BE guidance,⁵⁵ it does not contribute meaningfully to efficacy of balsalazide disodium.

Even though you were required to measure both mesalamine and N-Acetyl-5-ASA for your phase 4 studies to fully characterize balsalazide disodium, such studies are for evaluation of new drugs and are designed to answer different questions than for bioequivalence studies. In a bioequivalence study, we are comparing (as described in section III.B.2 of this response) a generic drug's formulation to the reference listed drug's formulation to identify any significant differences in the rate and extent to which the active moiety or active ingredient becomes available at the site of drug action, rather than trying to evaluate the safety or effectiveness of a product. Once we have established bioequivalence of the generic drug and reference listed drug, the safety and effectiveness of the reference listed drug applies to the generic drug.

With regard to measurement of N-Acetyl-5-ASA for approval of generic versions of Asacol, a modified release product, OGD's recommendations for bioequivalence of mesalamine-related products are product specific (see section III.A of this response). Thus, recommendations for balsalazide disodium drug products may be different from other mesalamine-containing products and reflect our current understanding of the biopharmaceutics of the product.

With regard to your claim that N-Acetyl-5-ASA varies independently with different dosing conditions, the data that you provide in Table 2 (page 5) of Supplement 2 do not support this claim. In this table, the changes in both AUC and C_{max} of mesalamine are always in the same direction as the change in N-Acetyl-5-ASA. When mesalamine decreases (ratio less than 1.0), N-Acetyl-5-ASA also decreases. When mesalamine increases (ratio greater than 1.0), N-Acetyl-5-ASA also increases. The change in mesalamine is also always greater than the change in N-Acetyl-5-ASA, thus mesalamine is more sensitive than N-Acetyl-5-ASA. For these reasons, we do not recommend measurement of N-Acetyl-5-ASA for bioequivalence determinations of balsalazide disodium drug products.

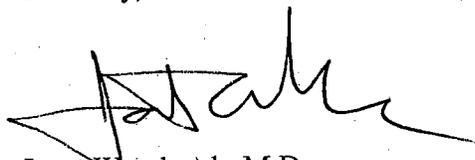
⁵⁵ See page 18 of the BA/BE guidance.

Further, we disagree with your claim that the lower-than-expected in vitro dissolution of balsalazide disodium that you observed necessitates measurement of N-Acetyl-5-ASA in the in vivo pharmacokinetic study. As previously noted, the rate of absorption of both balsalazide and mesalamine increases with the dose of balsalazide disodium (see section III.C.1 of this document). If the concentration of balsalazide disodium is reduced by 20 percent in the intestine, then the rate at which balsalazide and mesalamine are absorbed will be decreased and a decrease in their pharmacokinetic measures will be observed. It is not necessary to also include measurements of N-Acetyl-5-ASA.

IV. CONCLUSION

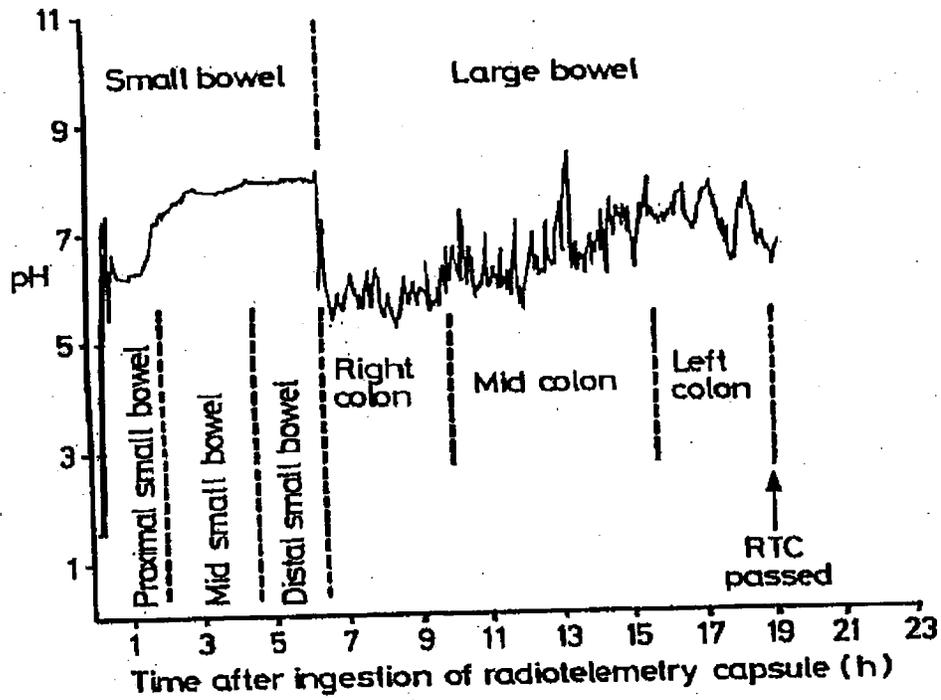
We concur with your request in Supplements 2 and 3 that, as a result of changes to Colazal's labeling in September 2006, both fasting and fed studies be conducted for bioequivalence determinations of balsalazide disodium drug products. For the reasons stated above, we deny your Petition, Supplements 1 and 4, and all other aspects of Supplements 2 and 3.

Sincerely,

A handwritten signature in black ink, appearing to read 'Janet Woodcock', with a stylized flourish at the end.

Janet Woodcock, M.D.
Acting Director
Center for Drug Evaluation and Research

Appendix A: GI pH Profile from a Normal Subject After Ingestion of a Radiotelemetry Capsule



Source: Evans DF, Pye G, Bramley R et al. Measurement of gastrointestinal pH profiles in normal ambulant human subjects. *Gut* 1988; 29, 1035-1041.