NDA 20-610

Salix Pharmaceuticals, Inc.
Attention: Lorin Johnson, Ph.D.
Sr. Vice President Development and Chief Scientific Officer
9600 Bayshore Road, Suite 205
Palo Alto, CA 94303

Dear Dr. Johnson:

Please refer to your new drug application (NDA) dated June 23, 1997, received June 23, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Colazal (balsalazide disodium) Capsules.

We acknowledge receipt of your submissions dated April 28, May 23, June 21, and July 10, 2000. Your submission of May 23, 2000 constituted a complete response to our March 24, 2000 action letter.

We also refer to the June 21, 2000 teleconference in which you were informed that your proposed tradename, Colazal, is acceptable.

This new drug application provides for the use of Colazal (balsalazide disodium) Capsules for the treatment of mildly to moderately active ulcerative colitis.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert) with the following exception: Please modify Figure 1 in the package insert to include both the p values and sample sizes from the ITT-2 analysis (at eight weeks). This request was conveyed to you in our July 10, 2000 teleconference. In addition, the FPL must be identical to the immediate container and carton labels submitted July 10, 2000. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternately, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative purposes, this submission should be designated "FPL for approved NDA 20-610." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your Phase 4 commitments, in response to our June 15, 1998 letter, specified in your submissions dated October 13, 1999 and February 28, 2000. These commitments, along with any completion dates agreed upon, are listed below.

1. You have agreed to conduct a food-effect study in healthy subjects to assess the effect of food on the absorption of balsalazide.

2. You have agreed to conduct a multiple dose PK study. The final study report will be submitted to IND by the fourth quarter of 2000.

3. In the event that balsalazide plasma levels higher than are observed during the course of the multiple-dose PK study, you have committed to conducting an additional *in vitro* plasma binding study to cover the observed concentration range.

4. Regarding requested *in vitro* drug interaction studies, you have committed to conducting *in vitro* drug interaction studies to evaluate the potential for commonly co-administered drugs to interact with balsalazide.

5. With respect to requested *in vivo* drug interaction studies, based on the results of the *in vitro* drug interaction studies, you have agreed to conduct *in vivo* drug interaction studies in appropriate animal species and evaluate the PK (as deemed necessary). Based on the outcome of these studies, you will discuss with the Agency the need for any additional studies.

6. Regarding the requested renal impairment study, you have agreed to compare the PK data from the multiple-dose PK study to that obtained from literature on patients with varying degrees of renal impairment that are receiving mesalamine or related prodrugs. Based on the outcome of the analysis of the multiple-dose PK study, it will be decided whether an additional study is needed to assess PK of balsalazide in patients with varying degrees of renal impairment.

7. Regarding the hepatic impairment study, you have agreed to evaluate the PK of balsalazide in hepatically-impaired patients if clinically-relevant results are obtained in the renal impairment study.

8. You have agreed to conduct a study in the combined pediatric population of children and adolescents (2-18 years) to characterize PK of balsalazide in this age group. Please note that this will not fulfill the requirements of 21 CFR 314.55.

9. You have agreed to reanalyze the data from study GLY01/93 to examine the effect of gender on the disposition of balsalazide.

In addition, you have agreed to submit the study protocols prior to study initiation. Furthermore, the final protocols to for studies identified in items 1, 3, 4, and 8 will be submitted to the appropriate IND within one year of receiving the approval letter for NDA 20-610.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet any of your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.81(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). You have requested a pediatric waiver for both the neonate (birth-1 month) and infant (1 months-2 years) age groups. Review of this partial waiver request is pending. As noted above, you have not fulfilled the requirements of 21 CFR 314.55 (or 601.27). We are deferring submission of your pediatric studies until August 1, 2002. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR)

in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Gastrointestinal and Coagulation Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Melodi McNeil, Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

Florence Houn, M.D., M.P.H., F.A.C.P.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure