NDA 20-610

AUG - 3 1998

Salix Pharmaceuticals, Inc.
Attention: David Kashiwase
3600 W. Bayshore Road
Palo Alto, CA 94303

Dear Mr. Kashiwase:

Please refer to your new drug application (NDA) for balsalazide disodium Capsules.

We also refer to the July 24, 1998 telephone conversation between Ms. Debra Hathaway, Regulatory Affairs, of Salix and Ms. Melodi McNeil, Regulatory Health Project Manager, of this Agency, in which you requested a copy of the Medical Officer's review of the application referenced above.

The review is enclosed for your convenience.

If you have any questions, contact Melodi McNeil, Regulatory Health Project Manager, at (301) 443-0483.

Sincerely,

/S/ 8/3/98

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: May 20, 1998 Clinical review

cc:
Archival NDA 20-610
HFD-180/Div. Files
HFD-180/M.McNeil
DISTRICT OFFICE

Drafted by: mm/August 3, 1998
final: August 3, 1998
filename: c:\mydocuments\cso\n\20610808.DOC
GENERAL CORRESPONDENCE

C30/McNeil

MEMORANDUM OF TELECON

DATE: July 28, 1998

APPLICATION NUMBER: NDA 20-610; balsalazide disodium Capsules

BETWEEN:

Name: Dr. David Boyle, Executive Vice-President

Dr. Ping Hsu, Data Management
Dr. Don Jung, Pharmacokinetics
Ms. Debra Hathaway, Regulatory Affairs
Phone: (650) 849-5908
Representing: Salix Pharmaceuticals, Inc.

AND

Name: Ms. Melodi McNeil, Regulatory Health Project Manager
Dr. Lilia Talarico, Division Director
Dr. Hugo Gallo-Torres, Medical Team Leader
Dr. Robert Prizont, Medical Reviewer
Dr. Carol Cronenberger, Biopharmaceutics Reviewer
Mr. John Hunt, Biopharmaceutics Team Leader
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Discussion of Pharmacokinetics Study, Requested in June 15, 1998 Approvable Letter

BACKGROUND: NDA 20-610 was submitted June 23, 1997 by Salix Pharmaceuticals, Inc. to market balsalazide disodium 750 mg Capsules, at a dose of 2.25 gm tid, for the treatment of mildly to moderately active ulcerative colitis. The application was approvable, pending (among other things) a multiple-dose pharmacokinetic study in the target patient population using the formulation of the drug that is proposed for marketing.

In a June 26, 1998 submission, the firm requested a teleconference with the Division to clarify the type of pharmacokinetic study that is required for approval. The request included a list of questions which are reproduced below. (Note: The firm's questions are in regular print; the Agency's responses are in bold print).

TODAY'S PHONE CALL:

1. Confirm that the proposed pharmacokinetic study will be conducted with one drug product lot at one dose level, balsalazide disodium 6.75 g (3 x 750 mg capsules to be taken three times a day).

The firm was informed that this proposal is acceptable, however, Agency representatives reiterated that the study should be carried out in the target patient population (patients with acute [active] ulcerative colitis) and that, in general, the drug should be administered in the same manner it is expected to be given in clinical practice (e.g., three times daily, instead of every eight hours around the clock; to patients of both genders and of a wide age range; etc.). Although not required for approval, the Agency suggested that the effect of fasting vs. fed state on balsalazide pharmacokinetics be assessed, since balsalazide is likely to be administered with meals in clinical practice.

2. Clarify whether the purpose of the multiple-dose pharmacokinetic study is to evaluate the plasma pharmacokinetics and metabolites of balsalazide disodium at steady-state, or the potential accumulation and elimination.

   Agency representatives said the purpose of the study is to evaluate the pharmacokinetics, accumulation, and elimination of balsalazide disodium (the parent compound) and each of its three metabolites and added that there should be sufficient numbers of patients to ensure an accurate assessment of these characteristics. Also, since ulcerative colitis can affect absorption from the gastrointestinal tract, the firm was advised to assess whether there is a relationship between balsalazide pharmacokinetics and patients' disease state.

3. Clarify the length of treatment to be followed in the multiple-dose pharmacokinetic study.

   Agency representatives said the study duration should be eight weeks, to ensure that the pharmacokinetics of balsalazide are accurately characterized.

4. Salix would like to discuss use of a smaller batch size for the proposed study. Since the product is not commercialized in the US, the drug product manufacturer's batch size is approximately —, of the proposed commercial scale (—).

   The firm was informed that the use of a smaller batch size is acceptable, provided its size is greater than or equal to 10% of a full scale batch.

In addition, the Agency requested that the firm evaluate patient symptoms during the study, and other endpoints such as endoscopy scores or flexible sigmoidoscopy findings. In response to a question, the Agency said that patients could be enrolled from multiple sites, provided that plasma levels are analyzed using a standard, accurate assay at a single location. Agency representatives also said that there was no need to have a washout period for patients who are taking other medications prior to their enrollment in this study. The firm was requested to submit the protocol for the pharmacokinetic study to the Agency for review and comment, prior to its execution.

The firm was asked to verify that the formulation of Asacol used in the pivotal clinical trials (as an active comparator) is the same formulation as what is approved in the US. The firm agreed to provide the requested information. Agency representatives commented that if a non-US formulation of Asacol was used in the clinical trials, all references to "Asacol" will have to be deleted from the labeling. The call was then concluded.

/S/ 9/8/98

Melodi McNeil
Regulatory Health Project Manager

/S/ mo 9-8-98

cc: Original NDA 20-610
HFD-180/Div. File
HFD-180/Melodi McNeil
HFD-180/Prizont
HFD-180/Gallo-Torres
HFD-870/Hunt
HFD-870/Cronenberger
HFD-870/Chen

RD Init: CCronenberger 8/28/98
HGallo-Torres 9/1/98
RPrizont 9/1/98
LTalarico 9/2/98
Final 09/08/98

TELECON

MEMORANDUM OF TELECON

DATE: May 20, 1998

APPLICATION NUMBER: NDA 20-610; Colazide (balsalazide disodium) Capsules

BETWEEN:

Name: Mary Ketchum, Regulatory Affairs
Phone: (650) 849-5905
Representing: Salix Pharmaceuticals, Inc.

AND

Name: Melodi McNeil, Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Proposed Trade Name

BACKGROUND: In an October 3, 1997 letter, the firm was informed that their proposed trade name, Colazide, was unacceptable (based on a review by the Center's Labeling and Nomenclature Committee [LNC]). In response, the sponsor provided a March 11, 1998 correspondence, which proposed the following trade names: ——— (first choice), ——— (second choice), ——— (third choice), and ——— (fourth choice).

TODAY'S PHONE CALL: Based on the LNC's review of the four trade names listed above, I called the firm and informed them that the committee recommended against the use of the firm's first three choices but considered ——— acceptable for use. In response to a question, I indicated that this decision could be appealed if the firm chose to do so and the call was concluded.

/S/ 5/27/98
Melodi McNeil
Regulatory Health Project Manager

cc: Original NDA 20-610
HFD-180/Div. File
HFD-180/MMcNeil

TELECON

MEMORANDUM OF TELECON

DATE: May 20, 1998

APPLICATION NUMBER: NDA 20-610; Colazide (balsalazide disodium) Capsules

BETWEEN:

Name: Ms. Mary Ketchum, Regulatory Affairs
Phone: (650)849-5908
Representing: Salix Pharmaceuticals, Inc.

AND

Name: Melodi McNeil, Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Pediatric Development Plans

BACKGROUND: This application was submitted June 23, 1997 by Salix Pharmaceuticals, Inc. to market Colazide 750 mg Capsules, at a dose of 2.25 gm tid, for the treatment of mildly to moderately active ulcerative colitis.

TODAY'S PHONE CALL: I called the firm to inquire about their pediatric development plans. In response to my question, Ms. Ketchum said that the firm does not have any plans to develop Colazide for use in the pediatric population at this time. She indicated, however, that the firm would welcome Agency advice on this subject.

/S/ 5/20/98
Melodi McNeil
Regulatory Health Project Manager

cc: Original NDA 20-610
HFD-180/Div. File
HFD-180/MMcNeil

TELECON

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MAR 4 1998

20610

Lawrence D. Wruble, M.D.
80 Humphrey's Blvd STE220
Memphis, Tennessee 38103

Dear Dr. Wruble:

On December 8-10, 1997, Mr. George Flynn, representing the Food and Drug Administration (FDA), conducted an inspection of your conduct, as investigator of record, of a clinical study of the investigational drug Colazide, (protocol #CP099301) performed for Salix Pharmaceuticals. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From an evaluation of the inspection report and of the documents collected during the inspection, we conclude that there were no substantial departures from pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Mr. Flynn during the inspection.

Sincerely

/S/

Bette L. Barton, Ph.D., M.D.
Chief
Clinical Investigaitons Branch
Division of Scientific
Investigations
Office of Compliance
Center for Drug Evaluation
and Research

CFN: 1054247
Field classification:NAI
Headquarters classification:
_x_1)NAI
___2)VAI-no response required
___3)VAI-no response requested

cc.:
HFA-224
HFD-344
HFD-340
HFR-SE350
HFR-SE350
HFD-180 Review Div. Div. Dir/Doc.RM: NDA#20610
M.O. L.Talarico CSO M.McNeil
r/d:KM:2/24/98
corrected:slk:2/25/98

DEPARTMENT OF HEALTH & HUMAN SERVICES

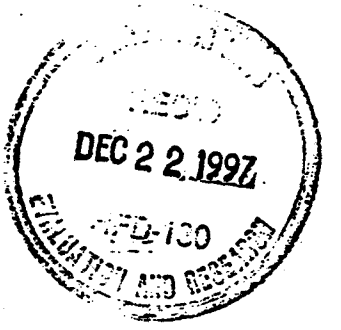
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

Division of Manufacturing and Product Quality, HFD-322
7520 Standish Place
Rockville, Maryland 20855-2737

TELEPHONE: (301) 594-0095
FAX: (301) 594-2202

DEC 19 1997



ate

We have completed our review of your additional response letter dated 26 November 1997 showing completion of corrective actions to the objectionable observations reported on the Inspectional Observations form, FDA 483, that followed an inspection of your laboratory testing operations dealing with pharmaceutical stability samples in [redacted] on August 27 - 28, 1997.

We conclude that these responses adequately addresses the deficiencies noted during the August 1997 inspection and the majority of the concerns raised in the October 23, 1997 Unapproved Letter.

Our office will recommend approval of any applications listing [redacted] as an acceptable contract laboratory of pharmaceutical products. However, we have requested a reinspection of your [redacted] stability testing laboratory within the next few months to verify implementation of corrections promised in your response.

Please contact me at the address shown above, if you have any questions or if I can be of further assistance.

Sincerely,

Edwin Melendez
Compliance Officer

Internal CC:

HFR-MA1505 David J. Hafner, Investigator

HFC-133	Associate Director, DEIO (Drugs) Schedule an accelerated reinspection within 6/98 to verify corrections
HFC-240	DMPQA CFN:9614387 Profile Class: NEC Acceptable
HFD-205	FOI
HFA-224	
HFD-180	NDA 20-610
HFD-322	Reading file
HFD-322	FIT firm file
HFD-322	E. Melendez

Draft: E. Melendez: 12/12/97
Concur: John M. Dietrick 12/10/97

WP: pen_phar.end

MC Mail

NDA 20-610

Salix Pharmaceuticals, Inc.
Attention: David Kashiwase
3600 W. Bayshore Road
Palo Alto, CA 94303

DEC 15 1997

Dear Mr. Kashiwase:

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

To continue our review of the chemistry, manufacturing, and controls section of your submission, we request the following:

I. Regarding Drug Substance:

A. Equivalency of Drug Substances:

We have identified several differences in the reported properties and physicochemical data, such as color and solubility, for drug substance (balsalazide disodium dihydrate) manufactured by ——— as compared to that manufactured at

1. Please provide a comparison of the solubility profiles from both suppliers. Include the same solvents and temperature conditions for both.

2. Please provide the melting points of the drug substance from both suppliers.

3. Please explain the pH range difference observed between the ——— (pH 8.2-8.3) and the ——— product (pH 7.7-8.3) when dissolved in water.

4. Please provide the partition coefficient for each drug substance.

5. Please explain the difference in the ——— data. The major peak appears to be Above 200° C for the ——— drug substance and approximately 190° C for balsalazide manufactured by ———

6. Please clarify the residual solvent testing each manufacturer performs. Describe the methods, and state the established specifications.

7. According to Table 3A4d-1 (Vol. 1.3, page 197), the amount of residual ethanol in the ——— batches (although within specifications), is almost three times higher than for the ——— Please provide an explanation for this difference.

To evaluate the equivalence of drug substance from both sources, data which have been obtained in the same laboratory using the same test methods are needed. Alternatively, provide cross validation of methods demonstrating equivalence.

B. Specifications:

1. In the "Release specifications" for the drug substance (Vol. 1.3, page 11), please indicate the origin of the reference standard that was used and include its lot number. In addition, indicate whether these specifications and methods are for both drug substance manufacturers.

2. Please clarify why there is a difference between the total 4-aminobenzoyl alanine and 4-hydroxybenzoyl alanine on the certificate of analysis (COA) from [redacted] and for release specifications [redacted]

C. Methodology:

1. Please provide the lot number(s) for drug substance used to obtain the IR spectra shown in Vol. 1.3, pages 039 and 041 and indicate whether they are reference standards.

2. Explain whether samples from the same lot were used for the [redacted] and for the [redacted] tests, and provide the lot number(s).

3. Please provide [redacted] chromatograms which are clearly labeled and readable.

D. Manufacturing Process:

Please completely describe the drug substance manufacturing process or reference the DMF, by volume and page number, where this information can be found for both drug substance sources.

E. Reference Standards:

1. A single primary balsalazide disodium dihydrate reference standard should be used from which secondary standards are qualified. Please identify all reference standards used. Your response should clearly link each reference standard to data which has already been submitted.

2. Please explain why the balsalazide reference standard tested appears to be the free di-acid and not the disodium salt (Vol 1.3, page 200). Also, indicate whether the di-acid and the disodium salt are used interchangeably.

3. Please submit the COA from [redacted] balsalazide disodium Lot # BSA/5/84 reference standard and include the following: heavy metals, balsalazide assay, identity by [redacted]

4. Please provide a range for the drug substance water content specification and also specify solubility in mg/mL.

5. Please explain the differences between the [redacted] for the [redacted] balsalazide disodium reference standard (Vol 1.3, page 140) and that of [redacted] (Vol 1.3 page 145).

6. Please provide a readable copy of the [redacted] ^{1}H NMR spectrum (Vol. 1.3, page 141) for the reference standard. Also, please provide spectra of both [redacted] reference standards obtained in the same solvent and concentration. Clearly notate the spectra to facilitate comparison. Please provide the same for the [redacted]

7. The HPLC chromatogram (Vol. 1.3, page 143) indicates that the [redacted] reference standard is 3B1507, however this does not correspond to the reference standard lot number provided in Vol. 1.003, page 055, section 3.A.1.d.1. Please explain this discrepancy. In addition, the major peak for the [redacted] reference standard appears at 1.5 minutes, however, the major peak in the [redacted] reference standard is at 1.8 minutes. Please provide chromatograms which have been run under the same conditions so it is possible to compare relative times.

F. Stability:

1. Please explain why the [redacted] drug substance has not tested for photostability.

2. Water Content:

   a. Please explain why water content data, although specified in the protocol, were not provided for the samples tested under photostability test conditions at three months. If these data are available, please provide them.

   b. Please explain why water content data were not provided at 12 month and 24 month stations for Lots numbered E6832.7D04, E6832.7D05, E6832.7D06, and 516. Also, please explain the cause of the failing value at 18 months for Lot E6832.7D05 (See Vol. 1.3, pages 241-242).

c. Lots numbered 6162001 and 6162003 failed the water content specification at 3 months. Please explain what action was taken after observation of the failing results.

II. Regarding Drug Product:

Manufacturing:

1. Please clarify whether drug substance is acceptance tested for release by the drug product manufacturer, or whether it is accepted based upon a certificate of analysis from the manufacturer.

2. Please provide copies of COAs for any drug substance lots which were ultimately manufactured into drug product used in any pharmacological, toxicological, biopharmaceutical, stability, or clinical studies. Your response should clearly indicate exactly which lots of drug substance were used in each study.

3. Specify the operating parameters [redacted] step (Vol. 1.4, page 017).

4. In the evaluation of roller compaction and size reduction, (Vol. 1.4 page 029), the results for hardness of compacted [redacted] drug substance for capsules Batch R6289R01 are quite different from the compacted [redacted] drug substance for manufacture of drug product batches M627R04 and N6289G02. Please provide an explanation for the difference(s) and discuss what this could indicate, as well as its impact, if any, on drug product performance. Also, please provide a description of the test method.

5. The tapped density at [redacted] for lot R6289R01 is lower than that observed for the other two lots validated. Please provide an explanation for the difference(s) and discuss what this could indicate as well its impact, if any, on drug product performance. Please also explain why the tapped density for Lot R6289RO1 was not determined at intervals until it reached a plateau for three consecutive readings. Refer to Vol. 1.004, page 030.

6. Please provide the particle size distribution data obtained for Batches M6272R04 and N6289GO2.

7. Please indicate why the capsules composite assay is expressed as a percent in 45 minutes and explain the method.

8. Please state whether any reprocessing is done, and if so, fully describe the process.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact Melodi McNeil, Regulatory Health Project Manager, at (301) 443-0483.

Sincerely yours,

/S/ 12/12/97

Eric P. Duffy, Ph.D.
Chemistry Team Leader
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Original NDA 20-610
HFD-180/Div. Files
HFD-180/CSO/M.McNeil
HFD-180/Ysern
HFD-180/Prizont
HFD-180/Robie-Suh
HFD-870/Chen
HFD-870/Kaus
HFD-870/Cronenberger
HFD-820/ONDC Division Director (only for CMC related issues)

Drafted by: mm/December 9, 1997/c:\wpfiles\cso\n\20610712.ir
Initialed by: EDuffy 12/11/97, 12/12/97
MYsern 12/12/97
final: December 12, 1997

INFORMATION REQUEST (IR)

NDA 20-610

NOV 21 [illegible]

Salix Pharmaceuticals, Inc.
Attention: David Kashiwase
3600 W. Bayshore Road
Palo Alto, CA 94303

Dear Mr. Kashiwase:

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

We also refer to your amendment dated October 10, 1997, submitted in response to our August 8, 1997 letter requesting additional clinical and biopharmaceutics information.

We have the following requests:

1. Clinical:

   We reiterate our request, previously conveyed in the August 8, 1997 letter for an intention to treat (ITT) analysis for all randomized patients in **Study CP099301.** You indicated that this information can be found in Volume 1.070, pages 126-159 of the NDA, however, the referenced text does not account for patients who were randomized, but who did not receive study medication or who otherwise failed to complete the study. For each parameter in these patients, the last available value (if necessary, baseline) should be carried forward to subsequent visits, i.e. Last Observation Carried Forward (LOCF). For example, a patient who was randomized and administered a few capsules of study medication, then discontinued at baseline (or shortly thereafter) without being healed should be carried forward as a treatment failure to each one of the subsequent visits, as well as the final study visit.

2. Biopharmaceutics:

   a. The October 10, 1997 submission contains the results of dissolution testing performed on lots used in the pharmacokinetic and clinical studies. Please indicate who performed the studies, provide the lot# of the reference standard that was used, and explain why ——— rather than a buffer.

   b. As noted above, —— was used as a medium for dissolution testing. Please indicate whether the pH changed as the drug product dissolved and specify the initial pH of the water.

To continue our review of the clinical statistical section, we request the following information:

1. Please perform a subgroup analysis by gender (M/F), age (geriatric/young), and race (W/B/O). This analysis should include response rates and 95% confidence interval for Colazide by subgroup and by study (all pivotal and supportive studies). The analysis should also include overall subgroup differences (meta analysis with study as strata). Please provide the report, data and SAS code of analysis. Your response should be submitted as SAS diskettes as 6.11 files (extension .sd2).

2. Please provide a justification for Asacol's use as the active control in the pivotal studies. Your response should include historical data to show the consistency of Asacol's effect versus placebo.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact Melodi McNeil, Regulatory Health Project Manager, at (301) 443-0483.

Sincerely yours,

11-21-97 /S/ 11/21/97

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Original NDA 20-610
HFD-180/Div. Files
HFD-180/CSO/M.McNeil
HFD-180/Prizont
HFD-180/Robie-Suh
HFD-720/Tsong
HFD-870/Kaus
HFD-870/Cronenberger
HFD-870/Chen

Drafted by: mm/November 18, 1997/c:\wpfiles\cso\n\20610711.ir
Initialed by: CCronenberger 11/19/97
LTalarico 11/20/97
YTsong 11/4/97
final: November 21, 1997

INFORMATION REQUEST (IR)

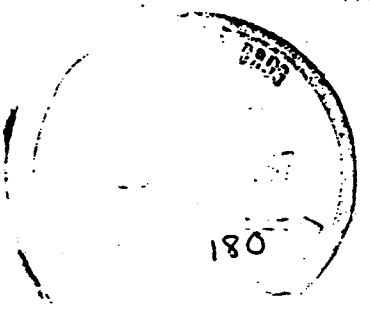
McNeil

DEPARTMENT OF HEALTH & HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION CENTER FOR DRUG EVALUATION AND RESEARCH

Division of Manufacturing and Product Quality
Foreign Inspection Team, HFD-322
7520 Standish Place
Rockville, Maryland 20855-2737

TELEPHONE: (301) 594-0095
FAX: (301) 594-2202

OCT 23 1997



This is regarding an inspection of your pharmaceutical testing laboratory in ——— by Investigator David Hafner of the United States Food and Drug Administration (FDA) on August 27 and 28, 1997. The inspection revealed significant deviations from Current Good Manufacturing Practices (CGMPs) in your laboratory testing operations dealing with pharmaceutical stability samples. The deviations were presented to ———, on an FDA-483, Inspectional Observations form, at the close of the inspection. These CGMP deviations cause pharmaceutical products tested by your facility to be unacceptable for use in the United States, since under United States law, the CGMP deviations make these products adulterated within the meaning of Section 501(a) (2) (B) of the Federal Food, Drug and Cosmetic Act (the Act).

We have reviewed the written response submitted by your company dated, September 23, 1997, and signed by ———. We conclude that this response lacks sufficient detail, explanations, or documentation to adequately address the deviations noted during the August 1997 inspection. Our comments regarding the most significant observations for the stability testing program are shown:

1. There was no investigation report assessing the cause of the initial Out Of Specification (OOS) results of the stability samples for Balsalazide Disodium active pharmaceutical ingredient as follows:

   Three samples (DS150/25-IS626; DS150/30-IS627; and DS152/30-IS633) initially failed specifications for water moisture content at the three month test interval. These results were retested and only the passing results of the retests were reported to the sponsor. There is no documentation to explain disregarding the failing results.

Two samples (DS150-IS653 and DS151-IS654) initially failed specifications for water moisture content under exposure to light at the three month test interval. These results were retested and found acceptable, however, neither the passing nor the failing results were provided to the sponsor.

The response to item 1 of the FDA-483 did not provide, the investigation explaining the cause of the OOS results. Typically, failing results happen for three reasons: analytical error, human error, or manufacturing problem. Please provide the results of your investigation and whether the sponsor was notified of these events.

2. Failure to comply with stability study protocol commitments. Stability protocol DS001-003 for samples of Balsalazide Disodium active pharmaceutical ingredient was not followed in that there are no reports indicating analysis for the required moisture content under light at the three month test interval and moisture content at the 12 and 24 month test intervals for lots E6832.7D-05 and E6832.7D-07.

The response to item 2 of the FDA-483 failed to address the corrective measures that would ensure complying with stability commitments. Please provide documentary evidence of corrections. Your response indicates that a new study has been started using commercial lots of Balsalazide Disodium. Please indicate the relationship between the stability sample lots described above (missing moisture test) and the commercial lots you propose to use for testing.

3. Failure to have an appropriate scheduled preventive maintenance program to maintain the required equipment in adequate operating conditions so that the stability samples are tested and stored as required by stability commitments. For example:

The water content for studies DS011-003 were not determined due to the failure of the ——— at the three, twelve, and twenty fourth month test intervals.

The stability chambers log book indicates several entry dates where malfunctions in chamber temperature and humidity were due to faulty equipment caused by water filter blockage and lack of water.

Your response failed to address and provide documentation with corrective measures for establishing an appropriate scheduled preventive maintenance program for equipment involved in stability studies. Furthermore, please indicate why the ——— was not corrected after it failed at the third month test interval in order to prevent repeated failures during the twelfth and twenty fourth month test intervals.

The CGMP deviations identified above and on the FDA-483 issued to your firm are not to be considered an all inclusive list of the deficiencies at your facility. FDA inspections are audits which are not intended to determine all deviations from CGMPs that exist at a firm. We recommend that you continually evaluate your facility on an overall basis for CGMP compliance.

Until FDA has confirmed that your firm is in CGMP compliance, we will not recommend approval of any applications listing your firm as the testing laboratory of any pharmaceutical products.

You may contact me at the address and telephone numbers shown above if you have any questions, written response or concerns regarding this decision. Please include your Central File Number "9614387" in any correspondence with this office.

Sincerely,

/S/

Edwin Melendez
Compliance Officer

APPEARS THIS WAY
ON ORIGINAL

Internal cc's:

HFR-MA1505 David J. Hafner, Investigator
HRR-MA150 DIB
HFC-133 Associate Director (Drug Inspections)
DO NOT RESCHEDULE W/O HFD-322 CONCURRENCE

HFC-240 DMPQA CFN: 9614387 Profile Class: NEC Unacceptable

HFA-224

HFD-205 FOI
HFD-320 R/F
HFD-322 Reading file
HFD-322 Edwin Melendez
HFD-322 Foreign Firm File

HFD-180 M. Ysern, NDA 20-610 Balsalazide Disodium for 750 mg capsule

Drafted: E.Melendez 10/23/97
Concur: J.Dietrick 10/23/97

CONTROL # 322-97-09-14
WP:

APPEARS THIS WAY
ON ORIGINAL

McNeil

NDA 20-610

Salix Pharmaceuticals, Inc.
Attention: David Kashiwase
3600 W. Bayshore Road
Palo Alto, CA 94303

OCT - 3 1997

Dear Mr. Kashiwase:

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

We have completed our review of your proposed trade name, Colazide Capsules and note the following look-alike/sound-alike conflicts: Corazide, Capozide, and Dyazide. At this time, our position is that there is a high potential for confusion between your proposed trade name and that of the products referenced above. In addition, we are also concerned that the suffix "-azide" is widely associated with thiazide diuretics. For these reasons, we recommend against the use of the name Colazide.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact Melodi McNeil, Regulatory Health Project Manager, at (301) 443-0483.

Sincerely yours,

LT 10-2-97

mm 10/2/97

cc:
Original NDA 20-610
HFD-180/Div. Files
HFD-180/CSO/M.McNeil
HFD-180/Duffy
HFD-180/Ysern
HFD-820/ONDC Division Director (only for CMC related issues)

Lilia Talarico, M.D.
Acting Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Drafted by: mm/September 30, 1997/c:\wpfiles\cso\n\20610709.ir
Initialed by: KJohnson 9/30/97
final: October 2, 1997

INFORMATION REQUEST (IR)

NDA 20-610

AUG - 8 1997

Salix Pharmaceuticals, Inc.
Attention: Mary Ketchum
3600 Bayshore Road
Palo Alto, CA 94303

Dear Ms. Ketchum:

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

To continue our review of the biopharmaceutics and clinical sections your submission, we request the following:

1. Biopharmaceutics:

   a. Please provide a side by side comparison of the [redacted], used in the food effect study (**#500301**), and the formulation proposed to be marketed. The comparison should include the manufacturer, location and dates of manufacture, manufacturing processes, lot numbers, and batch sizes. Further, please provide a discussion of how the results from the [redacted] food effect study can be extrapolated to the current capsule formulation.

   b. Please specify whether patients in the clinical studies received Colazide with or without food.

   c. Please describe the composition of meals used in the pharmacokinetic studies with respect to kcal., protein, fat, and carbohydrates.

   d. In Volume 44, pg. 26 you indicate that "....metabolism of 4-ABA is independent of acetylation phenotype." Please send information to support this statement.

   e. Indicate whether you cross-validated biological samples with the different assay methodologies.

   f. Pharmacokinetic study **#20061** lists C_{max} values below the limits of quantitation of the assay used. Please confirm/refute this information.

   g. Pharmacokinetic studies **#GLY01/93** and **#0500242** list C_{max} values which exceed the calibration range of the assays used. Please confirm/refute this information.

   h. Please provide the method used in the dissolution testing studies performed on the formulations used in the clinical and pharmacokinetic studies, along with data from individual studies.

2. Clinical:

   a. Please provide complete composition data for the dummy capsules given in the two pivotal studies, **CP099301** and **57-3001**, and for the placebo used in Study **CP069101**.

   b. An intention to treat (ITT) analysis for all randomized patients in Study **CP099301** could not be located. Please either provide this information, or indicate, by volume and page number, where it can be found.

We would appreciate your prompt written response so we can continue our evaluation of your NDA. Your response should be submitted in triplicate (Archival [blue], Biopharmaceutics [orange], and Clinical [tan]).

If you have any questions, please contact Melodi McNeil, Regulatory Health Project Manager, at (301) 443-0483.

Sincerely yours,

/S/ 8/8/97

Lilia Talarico, M.D.
Acting Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Original NDA 20-610
HFD-180/Div. Files
HFD-180/CSO/M.McNeil
HFD-720/Cronenberger
HFD-720/Kaus
HFD-720/Chen

Drafted by: mm/August 6, 1997/c:\wpfiles\cso\n\20610708.ir
Initialed by: CCronenberger 8/8/97
RPrizont 8/8/97
final: August 8, 1997

INFORMATION REQUEST (IR)

NDA 20-610

Salix Pharmaceuticals, Inc.
Attention: Margie Nemcik-Cruz
3600 W. Bayshore Road, Suite 205
Palo Alto, CA 94303

JUL - 8 1997

Dear Ms. Nemcik-Cruz:

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

To continue our review of the statistical section of your submission, we request that you provide the following information on SAS diskettes as 6.11 files (extension .sd2) for each of the pivotal clinical studies:

1. Study #
2. Patient #
3. Center # [give names in a separate file]
3b. Country code if multinational study
4. Treatment code
5. Is patient randomized but excluded from ITT analysis (yes/no)?
6. If yes, give reason (1=, 2=, ...). [define codes in a separate file]
7. Is patient evaluable (yes/no)?
8. If no, give reason (1=, 2=....). [define codes in a separate file]
9. Date for baseline evaluation
10. Date patient began treatment after randomization
11. Baseline and demographic evaluations [separate field for each item]
12. Date for the given post baseline evaluation
13. Each efficacy endpoint value for the given post baseline evaluation [separate field for each efficacy endpoint]
14. Repeat 12-13 for each post baseline evaluation (if multiple post baseline evaluations)
15. Did the patient discontinue before completing the study (yes/no)?
16. If yes, reason for discontinuation (1=, 2=, ...) [define codes in a separate file]
17. Date for discontinuation

In addition, please include any other information (e.g., compliance, concomitant medication, patient included in an interim analysis [with date]).

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact Melodi McNeil, Regulatory Health Project Manager, at (301) 443-0483.

Sincerely yours,

/S/ 7/7/97

Lilia Talarico, M.D.
Acting Director
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Original NDA 20-610
HFD-180/Div. Files
HFD-180/CSO/M.McNeil
HFD-720/Huque

Drafted by: mm/July 3, 1997/c:\wpfiles\cso\n\20610707.ir
Initialed by: MHuque 7/7/97
final: July 3, 1997

INFORMATION REQUEST (IR)

APPEARS THIS WAY
ON ORIGINAL

M.McNeil

NDA 20-610

Salix Pharmaceuticals, Inc.
Attention: Margie Nemcik-Cruz
3600 W. Bayshore Road, Suite 205
Palo Alto, CA 94303

JUL 2 0 1997

Dear Ms. Nemcik-Cruz:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Colazide (balsalazide disodium) Capsules

Therapeutic Classification: Standard

Date of Application: June 23, 1997

Date of Receipt: June 23, 1997

Our Reference Number: 20-610

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on August 22, 1997 in accordance with 21 CFR 314.101(a).

If you have any questions, please contact me at (301) 443-0483.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Original NDA 20-610
HFD-180/Div. Files
HFD-180/CSO/M.McNeil
HFD-180/Duffy
HFD-180/Gallo-Torres
HFD-870/Kaus
HFD-870/Chen
HFD-180/Choudary
HFD-720/Huque
DISTRICT OFFICE

Drafted by: mm/June 25, 1997/c:\wpfiles\cso\n\20610ltr.06
Final: June 25, 1997

Sincerely yours,

/S/ 6/25/97

Melodi McNeil
Regulatory Health Project Manager
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ACKNOWLEDGEMENT (AC)

MAY 12 1997

Salix Pharmaceuticals, Inc.
Attention: Margie Nemcik-Cruz
3600 West Bayshore Road, Suite 205
Palo Alto, CA 94303

Dear Ms. Nemcik-Cruz:

Please refer to your Investigational New Drug Application (IND) submitted pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act for Colazide (balsalazide) Capsules.

We also refer to the following amendments:

1. September 27, 1996, which contained a proposal for a 26-week oral gavage toxicity study (carcinogenicity study) of balsalazide, to be conducted in a transgenic mouse model, in lieu of repeating the 18-month mouse carcinogenicity study (1067/31) conducted by Biorex.

2. November 5, 1996, which contained a revised protocol for the 26-week oral gavage study, referenced above, in addition to a proposed protocol for the 4-week range-finding study in the p 53 +/- transgenic mouse that will be used to establish the doses for the 26-week study.

3. May 1, 1997, which seeks the Division's agreement with the use of the C57BL/6 strain in place of the p 53 transgenic mice in the 4-week dose-ranging study.

In these submissions, among other things, you requested Agency review and comment on the design of the proposed studies.

We have completed our review of your submissions and our discussion with the Center's Executive Carcinogenicity Assessment Committee and have the following comments:

Regarding the proposed protocol for a 4-week dose-ranging study:

1. Your proposal to use C57BL/6 mice in place of p 53 transgenic mice for the 4-week dose-ranging study is acceptable. It will also permit the use of sufficient number of animals for monitoring toxicokinetics.

2. We recommend that drug exposure be monitored, i.e. plasma AUC values for Colazide, 5-ASA, and 4-ABA at various dose levels. This information, together with the exposure levels at the maximum recommended dose in humans and comparative metabolism and protein binding data in humans and the rodent, would be useful for determining doses for the carcinogenicity study in the absence of any manifested toxicity in the dose-ranging study.

Regarding the proposed 26 week carcinogenicity study in p 53 +/- transgenic mice:

1. The overall study design/protocol is acceptable. However, the dose selection for this study should be based on the results of the proposed dose-ranging study. If the toxicity endpoints are needed for dose selection, the highest dose should be the maximum tolerated dose (MTD). If the pharmacokinetic endpoints are used for dose selection, please base it on the above suggested information regarding exposure levels, comparative metabolism, and protein binding.

2. Consider using p-cresidine (0.5% in the diet) as a positive control, instead of bromodichloromethane which has not been tested in p 53 heterogenous transgenic mice.

The appropriateness of your future dose selection for the proposed carcinogenicity study will be evaluated once the complete report of the four week dose-ranging study, along with the dose proposals, have been submitted.

If you have any questions, please contact:

Melodi McNeil
Regulatory Health Project Manager
(301) 443-0483

Sincerely yours,

5/7/97

/S/

Lilia Talarico, M.D.
Acting Director
Division of Gastrointestinal
and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:

HFD-180/Division Files
HFD-180/Choudary
HFD-180/CSO/MMcNeil
RD Init: KJohnson 5/2/97
JChoudary 5/4/97, 5/6/97
Final: May 7, 1997
MMcNeil/April 30, 1997
mm/April 30, 1997/c:\wpfiles

ADVICE

MCNeil

AUG 15 1996

Salix Pharmaceuticals
Attention: Margie Nemcik-Cruz
3600 W. Bayshore Road
Palo Alto, CA 94303

Dear Ms. Nemcik-Cruz:

Please refer to your Investigational New Drug Application (IND) submitted pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act for Colazide (balsalazide) Capsules.

We also refer to the following amendments:

1. August 21, 1995, annual report containing the final report of a 104 week dietary carcinogenicity study in rats (Report # 1067/6-1050)

2. August 31, 1995, containing:

   a. L5178Y $TK^{+/-}$ mouse lymphoma assay (Report # 1067/59-1052)

   b. Genotoxicity studies of 4-ABA ("carrier molecule"): L5178Y $TK^{+/-}$ mouse lymphoma assay and chromosomal aberration test in human lymphocytes (Reports # 1067/54-1052 and 1067/57, respectively)

   c. Genotoxicity Studies of N-acetyl-4-ABA: Ames test, L5178Y $TK^{+/-}$ mouse lymphoma assay and chromosomal aberration test in human lymphocytes (Reports # 1067/056-1052, 1067/55-1052, and 1067/058-1052, respectively)

   d. Chemo-prevention of intestinal tumor formation in B6-Min/+ mice by balsalazide

We also refer to your February 26, 1996 submission (Serial# 52) submitted in response to our June 22, 1994 and January 3, 1995 letters notifying you that the mouse carcinogenicity study (BIORECON # No. 2), conducted by Biorex, was inadequate and that your reasons for not repeating the study were not acceptable. In this submission you also requested that the carcinogenicity assessment committee (CAC) be consulted regarding our decision.

We have completed the review of the preclinical portions of your submissions, and have the following comments and requests:

1. The mouse carcinogenicity study was not acceptable because the testing was done by one laboratory and reported by another, which did not accept the responsibility for the recording or the integrity of the raw data. The dose selection was inappropriately

based on the results of a previous study in rats. The highest tested dose (1000 mg/kg/day via diet) was not the maximum feasible dose. During the study, the test drug formulation was not analyzed for stability, homogeneity, or achieved concentration. In addition, there was no evidence of any quality assurance inspections.

2. Information to show that the study met GLP requirements was not provided as follows:

   a. Names of the Study Director, other scientists or professionals and the names of all supervisory personnel involved in the study were not provided as per 21 CFR, Subpart B, 58.33 and Subpart J, 58.185.

   b. No quality assurance unit (QUA) was identified or any evidence of QUA inspection provided as per 21 CFR 58.35 and 21 CFR 58.185.

   c. No evidence for the analysis of test drug formulation for purity, stability, homogeneity or achieved concentration was provided as per 21 CFR 58.105 and 21 CFR 58.113.

   d. No approved and signed protocol was provided as per 21 CFR 58.120.

   e. No final report including the signed and dated reports of each of the individual scientists or other professionals involved in the study and the signed QUA statements was provided as per 21 CFR 58.185.

3. The Agency at this time recommends that any drug administered for prolonged or repetitive periods be assessed for carcinogenicity potential in two rodent species. You should, therefore, conduct a 13-week oral (gavage) dose-ranging study in mice to define the maximum tolerated dose (MTD) and submit the report along with the protocol for a repeat carcinogenicity study (gavage) in mice for our evaluation. The Carcinogenicity Assessment Committee (CAC) will be consulted after you provide such information.

4. Regarding the 104 week rat (Sprague-Dawley) carcinogenicity study, (Report # 1067/6-1050) you state that the rate of incidence of benign adrenal pheochromocytoma of high dose treated males (30%) was "within laboratory historical control incidence range (10-46%)." Please provide complete historical control data for the incidence of adrenal pheochromocytoma in this strain of rat from the testing laboratory _____ for the period from 1991-1995.

We also reiterate our previous request that you revise your Investigator's brochure to include a statement of the fact that balsalazide is mutagenic in the mammalian cell (CHL/HGPRT) forward gene mutation assay. You should also include the information that balsalazide, 4-ABA, and N-acetyl-4-ABA are not mutagenic in L5178Y mouse lymphoma cell assay.

If you have any questions, please contact:

Melodi McNeil
Consumer Safety Officer
(301) 443-0483

Sincerely yours,

8/14/96

Stephen B. Fredd, M.D.
Director
Division of Gastrointestinal
and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Orig
HFD-180/Division Files
HFD-180/JChoudary
HFD-180/CSO/MMcNeil
HFD-150/CAC/JDeGeorge
HFD-345/Viswanathan
HFD-345/SKelly
HFD-345/Snipes
R/D init: KJohnson 7/29/96, 7/30/96, 8/2/96, 8/14/96
JChoudary 8/5/96, 8/5/96, 8/11/96
SFredd 8/7/96, 8/12/96
Final: August 14, 1996
MMcNeil/July 22, 1996
mm/July 22, 1996/c:\wpfiles\cso\

ADVICE

MESSAGE CONFIRMATION

08/20/96 13:39
ID=DGCDP/HFD-180

DATE	S.R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
08/20	01'35"	914158561555	CALLING	04	OK	0000

08/20/96 13:37 DGCDP/HFD-180 → 914158561555 NO.066 D01

FOOD AND DRUG ADMINISTRATION
DIVISION OF GASTROINTESTINAL
AND COAGULATION DRUG PRODUCTS
DOCUMENT CONTROL ROOM 6B-24
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857

DATE 8/20/96

Center for Drug Evaluation and Research
FDA

TO:

Name Margie Nemcik-Cruz

Fax No. (415) 856-1555

Phone No. (415) 856-1558

Location Salix Pharmaceuticals

FROM:

Name Melodi McNeil

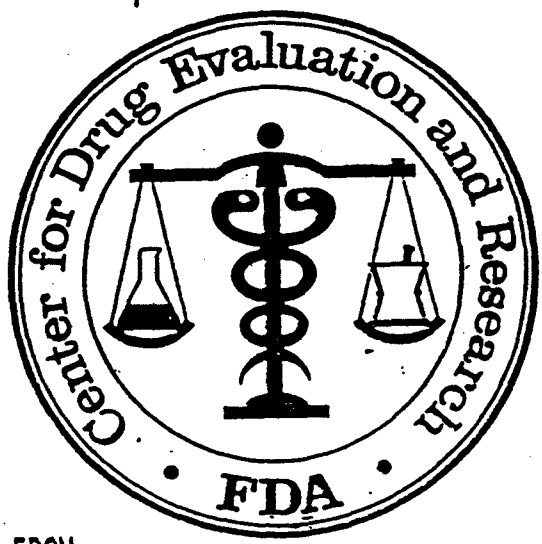
Fax No. (301) 443-9285

Phone No. (301) 443-0483

Total No. of Pages

FOOD AND DRUG ADMINISTRATION
DIVISION OF GASTROINTESTINAL
AND COAGULATION DRUG PRODUCTS
DOCUMENT CONTROL ROOM 6B-24
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857

DATE 8/20/96



TO:

Name Margie Nemcik-Cruz

Fax No. (415) 856-1555

Phone No. (415)-856-1558

Location Salix Pharmaceuticals

FROM:

Name Melodi McNeil

Fax No. (301) 443-9285

Phone No. (301) 443-0483

Total No. of Pages
Including Cover 4

Comments:

Here's the letter we discussed; I'm sorry you received an incomplete version.

Melodi McNeil

JAN 3 1995

Salix Pharmaceuticals
Attention: Margie Nemcik-Cruz
3600 W. Bayshore Road, Suite 205
Palo Alto, CA 94303

Dear Ms. Cruz:

Please refer to your Investigational New Drug Application (IND) submitted pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act for Colazide (balsalazide) Capsules.

We also refer to your amendment dated September 20, 1994, serial number 039, submitted in response to our letter dated June 22, 1994 informing you of the inadequacy of the mouse (Report # — No. 2) and rat (Report # — No. 1) carcinogenicity studies conducted by Biorex, and requesting that you inform all investigators that balsalazide was mutagenic in the mammalian cell (CHL/HGPRT) forward gene mutation assay. In this amendment you acknowledge that carcinogenicity studies in mouse and rats were not conducted according to GLP regulations, were not inspected by QUA and the dose selection in bioassay in mouse and rat conducted by Biorex was not based on dose-ranging studies. However, you indicate that a repeat mouse carcinogenicity study is not needed since no tumorigenic potential of the drug was seen in the Biorex mouse carcinogenicity study.

We have completed the review of your submission, and have the following comments and requests:

1. Your reasons for not repeating the mouse carcinogenicity study are not acceptable because the mouse carcinogenicity study conducted by Biorex is inadequate. We reiterate our suggestion that you conduct a 13-week oral (gavage) dose-ranging study in mice and submit the report along with the protocol for repeat carcinogenicity study in mice for our review and evaluation.

2. We note that you have decided to conduct a mouse lymphoma cell L15178/TK forward gene mutation assay to further clarify the observed positive results in the CHL/HGPRT forward gene mutation assay. In the meantime, we ask that you amend the present Investigator's brochure (pages 1016 and 1020 of Volume 1 of the initial submission) which inaccurately depicts the results of CHL/HGPRT forward gene mutation assay as negative. Your amended brochure should reflect the positive results of the test accurately.

If you have any questions, please contact:

Kati Johnson
Consumer Safety Officer
(301) 443-0487

Sincerely yours,

1/3/95

SF 1/3/95

Stephen B. Fredd, M.D.
Director
Division of Gastrointestinal
and Coagulation Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Orig IND
HFD-180
HFD-180/JChoudary
HFD-180/CSO
R/D init: JChoudary 12/13/94
SFredd 12/28/94
kj/November 28, 1994
kj/November 28, 1994/c:\wpfiles\cso

AD

APPEARS THIS WAY
ON ORIGINAL

JUN 22 1994

Salix Pharmaceuticals
Attention: Margie Nemcik-Cruz
3600 W. Bayshore Road
Palo Alto, CA 94303

Dear Ms. Nemcik-Cruz:

Please refer to your Investigational New Drug Application (IND) submitted pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act for Colazide (balsalazide sodium) Capsules.

We also refer to your amendments dated January 15 and 29, 1992, August 18, November 3, December 1, 1993, and January 6, 1994.

We have completed the pharmacology review of the preclinical portions of your submissions, and have the following recommendations and requests:

1. The carcinogenicity studies in mouse (Report # ——, No. 2) and rats (Report # —— No. 1) are inadequate for the following reasons:

   a. These studies were presumably conducted by Biorex Pharmaceuticals Ltd. in the early 1980's and —— "reconstructed or reassembled" the information for submission in November 1993.

   b. —— accepts no responsibility for the recording or integrity of the raw data.

   c. There was no evidence that the conduct of the studies complied with FDA GLP guidelines and quality assurance was also lacking.

   d. There were no previous dose-ranging studies for the selection of the doses for the mouse and rat carcinogenicity studies and sufficiently high doses were not employed in the carcinogenicity studies.

2. We recommend that you conduct oral gavage dose-ranging studies of balsalazide in mice and rats for selecting appropriate doses for the oral (gavage) carcinogenicity studies in the same strains of animals. We recommend that you submit the full reports of such dose-ranging studies along with the protocols for the proposed repeat carcinogenicity studies of balsalazide in mice and rats for our consideration.

3. You should inform all the investigators that balsalazide was mutagenic in the mammalian cell (CHO/HGPRT) forward gene mutation assay. In addition, you should conduct forward gene mutation assay at the TK locus in L15178 mouse lymphoma cells.

If you have any questions, please contact:

Kati Johnson
Consumer Safety Officer
(301) 443-0487

Sincerely yours,

Stephen B. Fredd, M.D.
Director
Division of Gastrointestinal
and Coagulation Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Orig IND
HFD-180
HFD-180/JChoudary
HFD-180/CSO
R/D init: JChoudary 6/21/94
SFredd 6/21/94
kj/June 17, 1994
kj/June 17, 1994/c:\wp51\

AD

McNeil

MEMORANDUM OF MEETING MINUTES

Meeting Date: October 9, 1996
Time: 9-11 AM
Location: Conference Room "B" (PKLN)

Application: ———
Colazide (balsalazide) Capsules

Type of Meeting: Pre-NDA

Meeting Chair: Dr. Stephen B. Fredd

Meeting Recorder: Melodi McNeil, CSO

FDA Attendees, titles, and Office/Division:

Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

Dr. Stephen Fredd, Division Director
Dr. Jose Canchola, Medical Officer
Dr. Hugo Gallo-Torres, Medical Officer
Dr. Kathy Robie-Suh, Medical Officer
Dr. John Senior, Medical Officer
Dr. Robert Prizont, Medical Officer
Dr. Eric Duffy, Chemistry Team Leader
Dr. Tanveer Ahmad, Reviewing Pharmacologist
Dr. Jasti Choudary, Pharmacology Team Leader
Ms. Melodi McNeil, Consumer Safety Officer
Mr. Brian Strongin, Consumer Safety Officer

Division of Biopharmaceutics (HFD-870)

Dr. Lydia Kaus, Biopharmaceutics Team Leader

Division of Biometrics (HFD-720)

Dr. Milton Fan, Statistician

External Constituent Attendees and titles:

Salix Pharmaceuticals, Inc.

Ms. Margie Nemcik-Cruz, Director, Regulatory Affairs
Dr. Lorin Johnson, VP, Research and Development
Dr. Donald Jung, Pharmacokineticist
Mr. Donald Young, Statistician

———

Dr. Elliott Berger, Executive Director, Regulatory Affairs, Astra Merck
Dr. Bo Joelsson, Executive Director, Clinical Research, Astra Merck
Mr. Bjorn Hansson, Associate Director, Regulatory Affairs, Astra

Background: — was submitted on December 13, 1991 to investigate Colazide (balsalazide) 750 mg Capsules for the treatment and maintenance of patients with mild to moderate ulcerative colitis (UC). According to the firm, Colazide is a pro-drug, which, like sulfasalazine, delivers 5-aminosalicylic acid (5-ASA) to the colon, but is better tolerated. Salix anticipates a late 1996 NDA submission for the treatment of mild to moderate active UC.

Meeting Objectives:

1. To provide a brief overview of the content and format of the proposed NDA.

2. To present a summary of the phase III clinical trials conducted to date.

3. To obtain Agency comment on the whether the proposed NDA is acceptable for submission.

Discussion Points:

Introduction:

Dr. Fredd began by emphasizing the importance of a clearly organized, well indexed application with consistent medical and scientific information.

1. CANDA

   The firm briefly reviewed the CANDA to be submitted during the first quarter of 1997.

2. Proposed CMC Section:

   a. Drug Substance

      Commenting that, since drug substance manufacture is performed by two contract facilities, , Dr. Duffy directed the firm to address potential manufacturing, synthesis, and impurity profile differences in the NDA.

      Dr. Fredd questioned if the firm has evaluated whether the drug substances are bioequivalent and added that blood levels could be used to make this determination. In response, Ms. Nemcik-Cruz stated that while Salix has not specifically tested for bioequivalence, drug substance from both manufacturers has been used in a number of PK studies which measured blood levels. She also noted that drug substance from both manufacturers had been used in the clinical trials. Dr. Kaus observed that the formulation proposed for marketing should be the same as that which was studied in the trials. Ms. Nemcik-Cruz replied that

the formulation had remained relatively constant during the drug development period.

In response to a question from Dr. Duffy, the firm replied that the NDA will contain complete information about drug substance proof of identity in the form of [redacted].

b. Drug Product

The drug product is also produced by a contract facility [redacted] which, according to the firm, has been inspected for GMPs.

c. Stability

Dr. Duffy questioned whether the stability studies will include any data for the drug product under bulk storage conditions. Ms. Nemcik-Cruz replied that the firm anticipated little holding time before shipment, but bulk stability data was available. In response to a question from Dr. Duffy, Ms. Nemcik-Cruz responded that stability information was collected at room temperature (25 and 30°C) and 60% relative humidity as well as at accelerated room temperature (40 and 50°C) and 75% relative humidity, according to ICH guidelines. According to Ms. Nemcik-Cruz, the firm has one year of stability data from six lots of drug product stored in the proposed container closure system. She added that the firm has two years of additional stability data in a slightly modified container closure system. She noted that after the initial batches were put on stability the firm slightly modified the container closure system so that it included a child resistant closure (CRC), but retained the same inner induction seal.

3. Proposed Clinical Section

The firm asked if case report forms (CRFs) could be submitted in electronic format. Dr. Fredd replied that electronically submitted CRFs must be identical in content to a hard copy. He invited the firm to submit a proposal as to exactly what information the electronic versions would contain so that a decision could be made as to the suitability of electronic case report forms in addition to or in lieu of paper copies.

Dr. Johnson briefly described the proposed efficacy and safety databases. In response, Dr. Fredd noted that all studies conducted to date have been in adult patients and questioned the firm as to any plans to investigate this drug in pediatric patients. Dr. Johnson said that Salix and Astra Merck are co-developers of this product, and both firms will consider conducting pediatric trials.

Concerning the safety database, Dr. Johnson noted that, in the US studies, commonly reported AEs were collected as "volunteered complaints" (VCs) and that severity,

causality, and outcome are not available for them. He questioned whether the NDA should contain a merged listing/analysis of AEs and VCs, in addition to separate listings of each type. Dr. Fredd replied that this approach would be acceptable.

Dr. Johnson summarized information about the following completed phase III clinical studies.

a. **Study 573001** (UK study) was a 12 week, double blind, double dummy, parallel group U.K. study in which 101 active UC patients were randomized to a daily dose of Colazide 6.75 gm (in three divided doses) or Asacol 2.4 gm (in three divided doses). Rectal hydrocortisone was provided as relief medication for use as needed throughout the trial.

The primary objective of this study was to compare the level of drug intolerance observed between the two treatment groups. Secondary endpoints included symptomatic and complete remission rates, the time to complete relief of symptoms, and sigmoidoscopy scores. Symptomatic remission was defined as having mild or no symptoms and complete remission was defined as mild or no symptoms, sigmoidoscopic grade of zero or one, and no use of relief medication in the four days prior to the assessment. All endpoints were prospectively defined. Patients were evaluated at two, four, eight, and twelve weeks.

According to the firm, the median time to complete relief of symptoms was ten days for the Colazide patients and 28 days for the Asacol patients ($p=0.005$). At the end of the trial, 88% of the Colazide patients, as compared to 57% of the Asacol patients, were in symptomatic remission ($p=0.001$), and 62% of the Colazide patients versus 37% of the Asacol patients ($p=0.016$) were in complete remission. The firm's pre-meeting submission contained a number of responses from the subjects' daily diary cards for parameters such as blood on toilet paper, blood on stools, stool frequency, abdominal pain, etc. In response to a question, Dr. Johnson stated that results were being presented for what was "essentially" the intent-to-treat (ITT) population.

In response to a question, the firm replied that there had been no statistical correction for the multiple endpoints and assessments. Dr. Fredd questioned that if corrections were made by, for example, the Hochberg procedure, would statistical significance be maintained. Dr. Fredd read the firm's definition of "remission" (no visible blood in the stools for at least four consecutive days before clinic visit, a return to the patient's usual stool frequency for at least four consecutive days before clinic visit, absence of symptoms or the presence of only mild symptoms of colitis, no use of relief medication in the four days prior to clinic visit, and a sigmoidoscopic grade of zero or one) from the protocol and suggested that the primary analysis in the NDA should be of that parameter, as

specified in the protocol, instead of individual symptoms. In addition, Dr. Fredd said the number of patients who achieved complete remission should be easily discernable in the case report tabulations (CRTs). Dr. Fredd noted that the NDA should explicitly address the statistical correction issue and also advised the firm to clearly outline and explain any additional endpoints. In addition, he said the NDA should address, for each clinical study 1) a demography of the patient population, 2) the number of patients which were newly diagnosed with UC at the time of randomization, 3) previous use by subjects of 5-ASA products, and 4) subject withdrawals.

In response to questions, Dr. Johnson said that an interim analysis was not performed and that all reported p values are two sided. He also stated that approximately 70% of the subjects were newly diagnosed with UC and that these patients were balanced between the treatment groups.

According to the firm, patients in study 057301 experienced adverse events commonly associated with 5-ASA: headache, nausea, and abdominal pain. Dr. Johnson said that there was a similar distribution of adverse events between the treatment groups. In response to a question from Dr. Robie-Suh, Dr. Johnson said patient compliance was assessed at approximately 95%.

In response to a question, Dr. Johnson replied that the Asacol formulation used in this study is the same as that which is currently available in the United States. He also stated his opinion that the difference in efficacy between the two groups is related to the difference in bioavailability between the two products and commented that Asacol tablets have been to known to pass through the stool undisintegrated. Dr. Johnson speculated that Colazide is most useful in the treatment of left-sided disease, which was the major diagnosis in the patients studied. Dr. Kaus questioned whether there was any interaction between Colazide and hydrocortisone at the cellular level. Dr. Johnson responded that data which specifically addresses this is not available but stated his opinion that there may be some synergy between the two agents.

b. **Study CP099301** (US study) was an eight week, double-blind, double-dummy, parallel group, dose-response U.S. study which randomized 154 subjects to a daily dose of Colazide 6.75 gm, 2.25 gm, or Asacol 2.4 gm.

Primary endpoints were improvement in individual symptom scores, physician global assessment (PGA), sigmoidoscopic grade, and improvement in overall symptom assessment (defined as improvement in PGA plus improvement in one other symptom without worsening in any symptom). Secondary endpoints included the cumulative proportion of patients achieving remission and time to remission. Remission was defined as stool frequency score of "normal" and rectal bleeding score of "none" for 48 hours prior to the visit, a PGA score of

"quiescent disease" and a sigmoidoscopic score of 1 (normal mucosa) or 2 (mild: edema loss of vascular pattern, fine granularity without ulceration). Patients were evaluated at baseline, two, four, and eight weeks.

1). Efficacy Analysis: Change in Mean Score

The change in mean symptom score between baseline and the end of the study was compared between groups. According to the firm, this change was non-significant for Colazide 6.75 gm versus Asacol 2.4 gm for any of the symptoms which were evaluated, including stool frequency, total blood loss, patient functional assessment (PFA), and abdominal pain (range: $p = 0.476$ to 0.888). Colazide 6.75 gm was statistically superior to Colazide 2.25 gm per day for stool frequency ($p=0.031$), stool score ($p=0.007$), total blood loss ($p=0.050$), PFA ($p=0.035$), and abdominal pain ($p=0.026$).

Dr. Fredd noted, however, that the firm's analysis does not include a statistical correction for multiple endpoints and evaluations. Dr. Fan added that, once a correction is made, it is unlikely statistical significance will be maintained.

2). Efficacy Analysis: Percentage of Improved Patients

According to the firm, Colazide 6.75 gm was not significantly superior to Asacol 2.4 gm per day for any variable (range: $p = 0.133$ to 1). Colazide 6.75 gm per day was significantly superior to Colazide 2.25 gm per day, for sigmoidoscopy ($p=0.018$), stool score ($p=0.027$), and stool blood score ($p=0.015$).

Dr. Fredd reiterated his concern that, once the analysis was corrected, results would no longer achieve significance. He also observed that p values are not trending in a consistent basis and questioned why, for example, the p value for PGA ($p=0.06$) was so much different than for PFA ($p=0.216$). In response, the firm said that results for these parameters numerically trended in the same direction, and that this study may have been undersized.

There was no difference between the treatment groups with regard to the number of adverse reactions. Dr. Johnson said the majority of the adverse events were worsening symptoms of ulcerative colitis. In response to a question, the firm clarified that the Colazide used in this study was made with balsalazide from a single source.

Dr. Fredd questioned whether patients in this study were comparable to those in the UK study. Dr. Johnson responded that this study included a lower percentage of newly diagnosed UC patients than the UK study (20% versus 70%). Dr. Senior observed that newly diagnosed patients often respond more strongly to treatment. Dr. Fredd noted the small number of randomized patients in each study and questioned whether, given the differences in patient populations, data from the UK study could be reliably extrapolated to this one, or vice-versa, and stated that this issue must be fully addressed in the NDA. Dr. Senior questioned why the results from this study were so different from the UK study. In response, Dr. Johnson stated that the UK study primarily evaluated patient status, i.e. remission, at different time points whereas this study looked at patient improvement. Dr. Johnson said this difference in analysis plans would also be explained in the NDA.

c. **Study CP069101** (PBO study), a four week, double-blind U.S. study, randomized 180 newly diagnosed or recently relapsed patients to daily doses of Colazide 6.75 gm, 4.5 gm or placebo (PBO).

The primary endpoints and remission criteria were identical to those for study CP099301. Secondary endpoints were the cumulative proportion of patients achieving remission and time to remission. All treatment groups were evenly matched with respect to ulcerative colitis disease duration, length of relapse or current symptoms, extent of disease and smoking status. In response to a question, Dr. Johnson replied that the short study duration was intended to facilitate subject recruitment.

1). Efficacy Analysis: Change in Mean Score at Final Visit (four weeks)

According to the firm, neither the 6.75 gm nor 4.5 gm doses of was statistically superior to PBO for stool frequency, total blood loss, PFA, or abdominal pain.

2). Efficacy Analysis: Percentage of Improved Patients at Final Visit (four weeks)

According to the firm, neither dose of Colazide was statistically superior to PBO for any of the evaluated variables, including sigmoidoscopy, abdominal pain, remission, or stool blood score.

Dr. Fredd expressed concern about Colazide's lack statistical of significance when compared to PBO. According to the firm, possible reasons for Colazide's lack of efficacy include the short study duration and the possibility that the patient population may have been enriched with 5-ASA unresponsive patients. As evidence, they cited the low number of newly diagnosed patients (11%) and the

high numbers of patients with either previous use of 5-ASA therapies or incidence of relapse within the past two years. In response, Dr. Fredd noted that 5-ASA resistance would not explain the high PBO response rate to many of the efficacy parameters. In response to a question, Dr. Johnson said the PBO was lactose. Dr. Fredd, noting lactose can cause diarrhea in intolerant patients, commented that the study was inherently biased against PBO and expressed his concern that Colazide did not compare favorably.

Dr. Johnson commented that patients in the Colazide 6.75 gm group experienced significantly fewer adverse event than those in the PBO group (33.3% versus 60%, p=0.009).

Citing section 505(d) of the Federal Food, Drug, and Cosmetic Act, Dr. Fredd said approval of this application must be based on at least two adequate and well-controlled studies. Given the existing efficacy database, Dr. Fredd strongly advised the firm to conduct an additional PBO-controlled clinical trial of longer than four weeks duration and with a larger number of patients than study CP069101. He noted that the UK study was designed as a tolerance study and randomized approximately 70% new patients, the statistical analysis issues with the first US study, and the fact that Colazide did not beat PBO in the second US study as potential problems. He questioned whether greater efficacy could be achieved with a higher dose. In response, the firm stated that the dose proposed for approval, 6.75 gm, requires patients to take nine capsules daily. Dr. Johnson expressed the firm's belief that patient compliance issues would become a problem if the dose is increased. In response to a question, he noted that the capsule size precludes the addition of additional drug substance. Dr. Senior suggested that the firm consider a suspension formulation, and Dr. Johnson responded that this formulation is currently under development in Japan. In response to a question from Dr. Prizont, the firm replied that the current dose was chosen because 6.75 gm of Colazide delivers approximately the same amount of 5-ASA to the colon as 2.4 gm of Asacol. However, Dr. Fredd observed that 2.4 gm represents the beginning of the Asacol dose response curve. He stated that if the NDA was submitted for review with the current clinical database, it would possibly be sufficient for filing, but that he would not comment on whether it would be approved.

4. Proposed Biopharmaceutics Section

Dr. Jung briefly discussed a number of PK studies, conducted in Japan and the United Kingdom. In response to a question from Dr. Kaus, Dr. Jung replied that the PK studies had a considerable degree of intersubject variability. Dr. Kaus noted the small numbers of subjects and said only qualitative conclusions could be reliably drawn from the presented data.

5. Proposed Pharmacology Section

According to Ms. Nemcik-Cruz, Salix Pharmaceuticals, Inc. obtained the rights to balsalazide from Biorex. Although Biorex conducted several preclinical toxicology tests the tests had not been done according to current GLPs and many were repeated. (Note: The 18 month mouse carcinogenicity study (1067/31) conducted by Biorex was not repeated, and in a letter dated August 15, 1996, our Division informed Salix that results from this study would not be accepted).

The firm presented information about their proposal to conduct a 26-week oral gavage toxicity study of balsalazide disodium in a transgenic mouse model in lieu of conducting a two year standard mouse carcinogenicity study.

a. Basis for Proposal to Use Transgenic Mice:

According to ——, the use of the transgenic mouse model is currently under consideration by the National Toxicology Program (NTP), ICH, and PMA. Dr. Choudary noted that while the agencies listed above are considering this model, it is not yet the standard of practice. —— said that the preexisting non-GLP studies (rat and mouse) as well as the GLP rat study for Colazide each had negative findings. Dr. Choudary responded that, in addition to the previously discussed GLP problems, the Biorex-conducted studies also used questionable scientific methods.

b. Proposed Range Finding Study:

[redacted]

c. Proposed Carcinogenicity Study:

[redacted]

Conclusions:

1. Approval will be based on adequate and well-controlled studies. Given the existing clinical database, the firm was strongly advised to conduct an additional PBO-controlled study, of longer than four weeks' duration, with a sufficiently large number of patients, prior to submitting an NDA.

2. Dr. Duffy advised the firm to thoroughly address the issue of two drug substance manufacturers and describe any resulting clinical implications.

3. The clinical section should include a statistical correction of all study results for multiple endpoints and evaluations. In addition, efficacy results should be presented individually for each trial and analyzed according to the prospectively defined statistical analysis plan in each study protocol.

4. If submitted with the existing database, the NDA may be filed, but Dr. Fredd did not comment on the possibility of approval.

5. The proposed transgenic mouse carcinogenicity study, revised as described above, is an acceptable substitute for the Biorex 18 month mouse carcinogenicity study.

6. In general, the NDA should be well organized and all information, including medical and scientific themes, should be easily locatable.

Minutes Preparer: /S/

Chair Concurrence: /S/

Attachments/Handouts: Overheads

cc: Original
HFD-180/Div. Files
HFD-180/Minutes Files
HFD-180/CSO and attendees
HFD-870/MChen

drafted: MMcNeil/October 22, 1996
r/d initials: BStrongin 10/24/96
SFredd 10/25/96
final: October 28, 1996

MEETING MINUTES

Number of Pages Redacted 50

❖❖❖

Confidential,
Commercial Information

Extra

Presentation on the Use of a 26-Week Carcinogenicity Study in Transgenic Mice as a Substitute for a 2-Year Standard Mouse Carcinogenicity Study in Support of the NDA for Colazide

To: Division of Gastrointestinal and Coagulation Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

For: Salix Pharmaceuticals, Inc.
3600 W. Bayshore Rd.
Suite 205
Palo Alto, CA 94303

October 9, 1996

Basis for Proposal to Use Transgenic Mice

Current use of transgenic mice by NTP

Current consideration by ICH

Current interest in transgenic animals by PMA

Preexisting non-GLP studies (rat and mouse)
as well as GLP rat study conducted with Colazide

Advantages of p53 +\- Transgenic Mouse Carcinogenicity Study

p53 most frequently mutated gene in human cancer

p53 mutated in a wide range of tumor types

p53 central to viral transformation

Uniform sensitivity to tumor induction

Decreased spontaneous tumor incidence

Reduced number of animals

Shorter duration of study

Range Finding Study

Species/Strain:	C57Bl/6 (wild type)
Group No.:	5 (control + 4 treated)
No. An./Group:	10/sex
Route:	Gavage
Frequency of Treatment:	7 da/week
Duration of Study:	2 weeks
Technical Parameters:	Clinical Obs. (Daily) Body Weight (Weekly) Food Consumption (Weekly) Clinical Path. (Termination) Necropsy (Comprehensive) Tissue Collection (Comprehensive) Histopathology (All Tissues - High Dose & Control + Target Tissues in Mid & Low Dose)

26 Week Study Design

Species/Strain:	C57Bl/6 p53+/-
Group No.:	4 (control + 3 treated)
No. An./Group:	20/sex
Route:	Gavage
Frequency of Treatment:	7 da/week
Duration of Study:	26 weeks
Technical Parameters:	Clinical Obs. (Weekly) Body Weight (Weekly/Monthly) Food Consumption (Weekly/ Monthly) Necropsy (Comprehensive) Tissue Collection (Comprehensive) Histopathology (All Tissues - High Dose & Control + Target Tissues in Mid & Low Dose)

MEMORANDUM OF MEETING
DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

Colazide (balsalazide) Tablets
March 9, 1994
Computer Assisted NDA (CANDA) Presentation

BETWEEN

Salix Pharmaceuticals:

Lorin Johnson, PhD-Vice President
Margie Nemcik-Cruz-Regulatory Affairs
Al Carvajal-Director, Management Information

AND

Food and Drug Administration, HFD-180 Professional Staff

BACKGROUND

This IND, submitted December 13, 1991, proposed to investigate this compound for the treatment and maintenance of patients with mild to moderate ulcerative colitis. According to the firm, Colazide is a pro-drug which, like sulfasalazine, delivers 5-aminosalicylic acid to the colon, but without the side effects.

In anticipation of a late 1994 NDA submission, the firm requested a meeting to discuss their plans to submit a computer assisted NDA (CANDA) in addition to the standard hard copy.

MEETING

Dr. Johnson provided a brief overview of Salix Pharmaceuticals. The private company was founded in 1989, is based in Palo Alto, CA, and currently employs — working exclusively on Colazide. A contract research organization, — , is collecting data, monitoring sites, scanning data in the database and performing the statistical analysis for the ongoing Phase III studies. For any changes made to the data in the CANDA database, Dr. Fredd requested that both the unchanged and changed data be available to the reviewers to determine whether those changes affect the outcome of the analysis.

In response to a question from Dr. Fredd, Dr. Johnson stated that the extent of computerization is dependent on the preferences of the Division. However, the firm is prepared to provide an integrated database for all disciplines.

Dr. Fredd stressed that the format and presentation of data in the CANDA must be identical to the paper copy. In response to a question as to how this can be assured, Dr. Johnson said that the data will be loaded in a controlled manner, then locked into a "read only" format. They are still working on the method for validation.

Dr. Johnson and Mr. Carvajal provided a demonstration of the CANDA capabilities. While most of the discussion focused on the clinical portion of the CANDA, Dr. Johnson said that all of the technical sections can be involved. The following topics were discussed:

Clinical

1. While 21 CFR 314.50(f)(2) requires that Case Report Forms (CRFs) be provided only for patients who died during the study or withdrew because of an adverse event, Dr. Fredd said that some of the medical reviewers prefer to have access to all of them. To prevent the archival copy of the application from becoming unwieldy, the firm asked about submitting those CRFs not required on optical disc, rather than paper. Dr. Fredd said he would have to check with the Office Level to determine Agency policy on this proposal. (On March 25, 1994, the firm was informed that this proposal was acceptable).

2. Dr. Robie-Suh requested that the NDA included baseline characteristics and Dr. Fredd asked that a center-by-center efficacy analysis be included to see if the study results are driven by a particular center.

Preclinical

1. Dr. Choudary noted that most of the preclinical data generated to date has come from foreign (UK) studies. According to Dr. Choudary, some of the final reports for these studies are incomplete, and asked if the original data for these studies is available. Dr. Johnson agreed that many of the studies are deficient and, for this reason, are being redone.

2. Dr. Choudary also stressed the need for contemporary historical control information (same animal strain and laboratory).

Chemistry

Chemistry reviewers expressed an interest in having the chemistry section computerized, particularly the specifications of the product used in the clinical trials. In response to a question from Dr. Fredd, the firm said that all Phase III trials have been conducted using the proposed market formulation.

General

1. Many reviewers requested that a "Restore" function be available, to undo any notations, manipulations, etc.

2. An example of the CANDA's searching capability was described. If, during the preclinical review, animals were found to have ataxia, the rest of the application could be searched for the term "ataxia".

3. When Dr. Robie-Suh requested the capability of locating documents other than through the Table of Contents, the firm requested guidance on the preset queries for each discipline. Dr. Fredd suggested that, in a future correspondence, the firm present the database for each discipline and we could then provide them with the questions that could be incorporated into a preset query. He added that a draft package insert would also be helpful in developing our questions.

4. The firm requested Division input as to the preferred programs for the various applications. They propose using WordPerfect for word processing, Lotus Windows for spreadsheet, Visual Basic for programming and a SAS format database. Dr. Robie-Suh added that we have Paradox, which is useful for sorting information. Dr. Fredd requested that existing equipment and software should be used whenever possible.

/S/ 3/31/94
Kati Johnson
Consumer Safety Officer

cc: orig IND
HFD-180
HFD-180/meeting file
HFD-181/KJohnson
R/D init:MFolkendt 3/30/94
SFredd 3/31/94

There are no plans to convene the Agency's Gastrointestinal Advisory Committee to discuss NDA 20-610 (Colazide Capsules).

/S/ 2/25/98

Melodi McNeil
Regulatory Health Project Manager

APPEARS THIS WAY
ON ORIGINAL

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

JUL 25 1997

Application Number: NDA 20-610

Name of Drug: Colazide (balsalazide disodium) Capsules

Sponsor: Salix Pharmaceuticals, Inc.

Material Reviewed

Submission Date(s): June 23, 1997

Receipt Date(s): June 23, 1997

Background and Summary Description: NDA 20-610, consisting of archival volumes numbered 1.1 through 1.112, was submitted to market Colazide (balsalazide disodium) Capsules, at a dose of 2.25 gm three times daily, for the treatment of mildly to moderately active ulcerative colitis.

Review

I. Overall Format and Content: All elements listed in the "Guideline on Formatting, Assembling, and Submitting New Drug and Antibiotic Applications" (February 1987) are addressed, except that the phrase "____ of____ volumes" is not completed on the lower right hand corner of the archival volume jackets, as suggested on page 11 of the Guideline.

II. Summaries: All elements listed in the "Guideline for the Format and Content of the Summary for New Drug and Antibiotic Applications" (February 1987) are addressed, except for the following:

A. The lot numbers of the investigational formulations used in the clinical trials could not be located in the summary volume, as suggested on page 8 of the Guideline. However, they are present in the chemistry, manufacturing, and controls section.

B. The table of all controlled studies, located in Volume 1.2, page 63, does not contain the names the investigators, as suggested on page 18 of the Guideline.

C. According to Volume 1.2, page 63, the final report for study 0028/017 is in Volume 1.75, page 187 and Volume 1.091, page 187, however, this report could not be located.

III. Clinical and Statistical: All elements in the "Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications" (July 1988) are addressed.

Conclusions

The firm will be asked to clarify the location of the report for study 0028/017. The other items will be conveyed to the firm if deemed necessary by the relevant reviewers.

/S/ 7/25/97
Regulatory Health Project Manager

cc:
Original 20-610
HFD-180/Div. Files
HFD-180/MMcNeil
HFD-180/LTalarico LT 7-25-97
HFD-180/Prizont
HFD-180/Duffy
HFD-180/Ysern
HFD-180/Choudary
HFD-870/Kaus
HFD-870/Cronenberger
HFD-870/Chen
HFD-720/Huque

draft: mm/July 22, 1997/c:\wpfiles\cso\reviews\20610707.adm
r/d Initials: KJohnson 7/25/97
final: July 25, 1997

CSO REVIEW

APPEARS THIS WAY
ON ORIGINAL

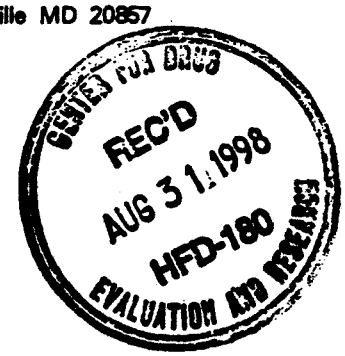
from DSI CSO McNeil

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

AUG 26 1998



Roger J. Leicester, OBE, FRCS, FICS
St. Georges Hospital
Blackshaw Road
London SW17 0QT
United Kingdom

Dear Dr. Leicester:

On May 7-8, 1998, Doctors Gerald N. McGirl and Robert Young, representing the Food and Drug Administration (FDA), conducted an inspection of your conduct, as Principal Investigator, of a clinical study of the investigational drug Colazide (balsalazide), performed for ~~~ This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From an evaluation of the inspection report and of the documents collected during the inspection, we conclude that there were no substantial departures from good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects. We understand that your study was not conducted under an IND. At the conclusion of the inspection Doctors McGirl and Young discussed FDA's current practices regarding medical records with you.

We appreciate the cooperation shown Doctors McGirl and Young during the inspection.

Sincerely yours,

S

Bette L. Barton, Ph.D., M.D.
Chief
Clinical Investigations Branch
Division of Scientific
Investigations
Office of Compliance
Center for Drug Evaluation and
Research

cc:
HFA-224
HFD-180Review Division Div. Dir./Doc. Rm.: NDA#_20-610____
HFD-180 MO:
HFD-180 PM:
HFD-340/R/F
HFD-344
HFR-PA150 DIB
HFR-PA150 BIMO Monitor
HFR-PA150 Field Investigator McGirl

CFN:
Field classification: NAI
Headquarters classification:
___X__1)NAI
_____2)VAI-no response required
_____3)VAI-response requested
_____4)OAI

If Headquarters classification is different classification, explain why:

r/d:RSKY:8/16/98
finaled:slk:8/17/98

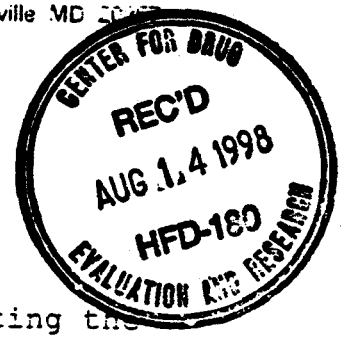
N20610 McNeil

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD

AUG 1 1 1998



Dennis S. Riff, M.D.
1211 West La Palma Ave., STE.306
Anaheim, California 92801

Dear Dr. Riff,

Between 17-26 March 1998, Mr. Allen F. Hall, representing the Food and Drug Administration (FDA), conducted an inspection of your conduct, as the investigator of record, of a clinical study (protocol #CP099301) of the investigational drug Colazide (balsalazide). You performed the study for Salix Pharmaceutical, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From an evaluation of the inspection report and the documents collected during the inspection, we conclude that you did not adhere to the pertinent federal regulations and/or good clinical practices governing your conduct of clinical investigations and the protection of human subjects in the following respects:

A. Investigators are required to conduct studies in accordance with the current protocol [21 CFR 312.53(c)(1)(vi)(a)]. Some examples of your deviations from the protocol are as follows:

1. Subject #5612 was admitted to the study and given the study medication although suffering at least 13 bloody stools per day and albumin 3.2gm/dl.

2. Subject #5710 entered the open-label part of the study without completing the blinded phase or being terminated due to treatment failure.

3. Subject #5259 was given medication for #5461.

4. Subjects #5259 and #5662 were admitted before obtaining negative stool cultures.

5. Subject #5603 was admitted to the open-label part of the study without your answering no to all the exclusionary eligibility questions (i.e., question #3 through #15 on Form 11).

6. Pregnancy tests were not done for subject #5662.

B. Investigators are required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual treated with the investigational drug. [21 CFR 312.62(b)].

The study records show many errors, missing data, and inconsistencies.

C. An investigator may not involve a human being as a subject in research that is covered by FDA regulation unless the investigator has obtained a legally effective informed consent for the subject [21 CFR 50.20].

Records of subjects #5007 and #5603 document that their informed consents were obtained months after they entered the open label study.

In addition, it is not good clinical practice to sign a CRF before it is completed. On 12 January 1996 you signed Form 8 and Form 9 for subject #546. Neither of these forms was completed until 19 January 1996.

Please make appropriate corrections/changes to your procedures to assure that the findings noted above are not repeated in any ongoing or future studies.

We appreciate the cooperation shown Mr. Hall during the inspection.

Sincerely yours,

/S/

Bette L. Barton, Ph.D., M.D.
Chief
Clinical Investigations Branch
Division of Scientific
Investigations
Office of Compliance
Center for Drug Evaluation
and Research

cc:
HFA-224
HFD-180 Doc. Rm. NDA 20610
HFD-180 Review Div. Dir. Talarico, L.
HFD-180 MO Prizont, R.
HFD-180 PM McNeil, M.
HFD-340/R/F
HFD-344
HFR-PA250 DIB Kozick
HFR-PA2565 BIMO MONITOR Koller
HFR-PA2585 FIELD INVESTIGATOR Hall

CFN: 2060695
Field Classification: VAI
Headquarters Classification:
_____1)NAI
__x_ 2)VAI-no response required
_____ 3)VAI-response requested
_____4)OAI

If the Field and Headquarters classifications are different, explain why:

Deficiencies noted:
___X_ failure to obtain consent prior to study entry
_____ inadequate drug accountability
___X_ deviations from protocol
___X_ inadequate records
_____ other (specify)

drafted:KM:5/29/98
reviewed:BLB:7/23/98
finaled:slk:7/28/98

Note to Medical Officer:

Subject #5662 was later diagnosed as having Crohn's disease.

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: MAY 22 1998

FROM: Robert S.K. Young, M.D., Ph.D.
Khairy Malek, M.D., Ph.D. K.M.
CIB/HFD-344

TO: Project Manager -HFD-180
Melodi McNeil - CSO
Robert Prizont - M.D

SUBJECT: NDA - 20-610
SPONSOR - Salix
PRODUCT - Colazide (balsalazide)

SNAME	CITY	REVIEWER
Leicester	London	RSKY
Hodgson	London	RSKY/KMalek
Wruble	Memphis	RSKY/KMalek
Riff	Anaheim	RSKY/KMalek

All four requested inspections have been completed. No objectionable conditions were found which would impair the use of the data submitted in support of pending NDA.

Key to Classifications
NAI = No deviation from regulations
VAI = Minor deviation(s) from regulations
Data acceptable

cc:CAC

APPEARS THIS WAY
ON ORIGINAL

McNeil

Request for Audit

DATE: November 12, 1997

FROM: Dr. Lilia Talarico, Division Director, Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

/S/ 11-12-97

SUBJECT: Request for Study-Oriented Audits for NDA 20-610, Colazide (balsalazide disodium) Capsules.

TO: Dr. David LePay, Division Director, DSI, HFD-340, MPN1 103

Based on the recommendation of Dr. Robert Young in his October 28, 1997 e-mail, we are requesting DSI inspections of the following clinical sites:

Protocol 57-3001:
Dr. R. Leicester (London)
Dr. H. Hodgson (London)

The reviewing medical officer for this application is **Dr. Robert Prizont**, phone: (301) 443-0479.
The responsible project manager/CSO is **Melodi McNeil**, phone (301) 443-0483.

The user fee goal date is **June 23, 1998.**
The Division's action goal date is **March 16, 1998.**

cc:
Original NDA 20-610
HFD-180/Div. files
HFD-344/Div. Liaison
HFD-344/SKline
HFD-180/MO/Dr. Robert Prizont
HFD-180/PM/CSO/M.McNeil