CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-610

CHEMISTRY REVIEW(S)

E L E C T R O N I C M A I L M E S S A G E

Date: 10-Mar-2000 10:18am EST
From: John Gibbs
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TO: Bronwyn Collier (COLLIERB)
TO: Alice Kacuba (KACUBAA)

CC: Liang Zhou (ZHOUL)
CC: Maria Ysern (YSERNM)

ubject: Tertiary Chemistry Review of NDA 20-610

DA #20-610 Clinical Division: HFD-180

rug: [redacted] (Balzalazide disodium) Dosage Form: Capsules

ype of Letter: Approvable Drug Classification: 1S

iemistry Tertiary Review:

A: Categorical exclusion granted 5/22/98

IR: Previously Not Acceptable. Scheduled for reinspection of Anabolic 3/13/00.

O: Not Applicable. Drug Product is capsule for oral administration.

ADENAME: Tradename [redacted] " NOT ACCEPTABLE per OPDRA review dated 2/7/00.

BELING: FDA's revised labeling is being sent to applicant with action letter.

C: This NDA is APPROVABLE in chemistry pending a satisfactory GMP inspection port per Chemistry Review #5 dated 2/29/00.

hn J. Gibbs, Ph.D.

APPEARS THIS WAY
ON ORIGINAL

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA: 20-610 **CHEM REVIEW # 6** **REVIEW DATE: 06/1/00**

SUBMISSION TYPE	DATES		
	DOCUMENT	CDER	ASSIGNED
Original	Jun 23, 1997	Jun 24, 1997	Jun 26, 1997
Amendment (BC)	Sep 3, 1997	Sep 4, 1997	Sep 17, 1997
Amendment (BC)	Mar 4, 1998	Mar 06,1998	Mar 24, 1998
Amendment (BC)	Mar 11, 1998	Mar 13, 1998	Mar 13, 1998
Amendment (BC)	Apr 30, 1998	May 05,1998	May 7, 1998
Amendment (BZ)	Aug 8, 1999	Aug 9, 1999	Aug 11, 1999
Amendment (AZ)	Sep 23, 1999	Sep 24, 1999	Oct 04, 1999
Amendment (BC)	Oct 20, 1999	Oct 25, 1999	Oct 25, 1999
Amendment (BC)	Feb 11, 2000	Feb 15, 2000	Feb 18, 2000
Telefax message	Feb 28, 2000		Feb 29, 2000
Amendment (AZ)	Apr 24, 2000	May 2, 2000	May 22, 2000

NAME & ADDRESS OF APPLICANT:
Salix Pharmaceutical, Inc.
3600 W. Bayshore Roada
Suite 205
Palo Alto, CA 94303

DRUG PRODUCT NAME:

Proprietary: —

Nonproprietary/USAN: Balzalazide disodium

Code Name/#: BX661A

Chem.Type/Ther.Class 1S

PHARMACOLOGICAL CATEGORY/INDICATION:
Antiinflammatory. Treatment of mildly to moderate active ulcerative colitis.

DOSAGE FORM: Capsules

STRENGTH: 750 mg

ROUTE OF ADMINISTRATION: Oral

HOW DISPENSED: Rx

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
See Chemistry Review # 1.

SUPPORTING DOCUMENTS:

DMF #	Item referenced	Holder	Status	Review Date	Letter Date
			Adequate	Dec 9, 1994	
			Adequate	May 11, 1999	

Adequate	Aug 9, 1999	
Deficient	May 22, 1998 Aug 9, 1999 Jan ,2000	May 22. 1998 Aug 9. 1999 Jan , 2000
Deficient	May 22, 1998 Feb , 2000	May 22. 1998 Feb . 2000
Adequate	Oct 10, 1997	

Note:
DMF- are still not adequate and the deficiencies are being resolved with the holders. The pending deficiencies are not an approvability issue for this NDA.

RELATED DOCUMENTS):

CONSULTS: See Chemistry review # 1

REMARKS/COMMENTS:

With regard to CMC this is a response to a minor revision requested by the FDA in the proposed labeling:
The structural formula drawing is inappropriate (i.e. bonds are not connected to the rest of the molecule). Please redraw.
This request was adequately addressed.
In response to the FDA revised position that the trade name — is now unacceptable, Salix Pharmaceuticals, Inc is proposing:
Primary Tradename: Colazal
Alternative Tradename: —
The HOW SUPPLIED section substitutes the trade name for Colazal, corrects the color of the capsule and states BZ as the logo imprinted in black.
It is also stated that Colaza!™ is a trademark of Salix Pharmaceuticals.

APPEARS THIS WAY
ON ORIGINAL

CONCLUSIONS & RECOMMENDATIONS:

This NDA can be Approved from the standpoint of CMC pending an acceptable response regarding the consult of the proposed new tradename, Colazal.

/S/

Maria Elena Ysern, MSc
Review Chemist, HFD-180

/S/

Liang Zhou, Ph.D.
Chemistry Team Leader, HFD-180

cc:
NDA # 20-610
HFD-180/LTalarico
HFD-180/Div File/NDA #20-610
HFD-180/LZhou
HFD-180/MYsern
HFD-181/MMcNeil
R/D Init by: LZhou
MY/ F/T 06/01/00/ c:/Word/nda/ 20610002.6my

APPEARS THIS WAY
ON ORIGINAL

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

1 page

FEB 2 9 2000

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA: 20-610 **CHEM REVIEW # 5** **REVIEW DATE: 02/29/00**

SUBMISSION TYPE	DATES		
	DOCUMENT	CDER	ASSIGNED
Original	Jun 23, 1997	Jun 24, 1997	Jun 26, 1997
Amendment (BC)	Sep 3, 1997	Sep 4, 1997	Sep 17, 1997
Amendment (BC)	Mar 4, 1998	Mar 06,1998	Mar 24, 1998
Amendment (BC)	Mar 11, 1998	Mar 13, 1998	Mar 13, 1998
Amendment (BC)	Apr 30, 1998	May 05,1998	May 7, 1998
Amendment (BZ)	Aug 8, 1999	Aug 9, 1999	Aug 11, 1999
Amendment (AZ)	Sep 23, 1999	Sep 24, 1999	Oct 04, 1999
Amendment (BC)	Oct 20, 1999	Oct 25, 1999	Oct 25, 1999
Amendment (BC)	Feb 11, 2000	Feb 15, 2000	Feb 18, 2000
Telefax message	Feb 28, 2000		Feb 29, 2000

NAME & ADDRESS OF APPLICANT:
Salix Pharmaceutical, Inc.
3600 W. Bayshore Roada
Suite 205
Palo Alto, CA 94303

DRUG PRODUCT NAME:

Proprietary:	———
Nonproprietary/USAN:	Balzalazide disodium
Code Name/#:	BX661A
Chem.Type/Ther.Class	1S

ANDA Suitability Petition/DESI/Patent Status:
Patent 4,412,992 covers the composition of matter/method of manufacture/use for balzalazide and related salts. Patent owner is Biorex, Ltd, United States. Expiration date July 8, 2001.

PHARMACOLOGICAL CATEGORY/INDICATION:
Treatment of mildly to moderate active ulcerative colitis.

DOSAGE FORM: Capsules

STRENGTH: 750 mg

ROUTE OF ADMINISTRATION: Oral

HOW DISPENSED: Rx

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
See Chemistry Review # 1.

SUPPORTING DOCUMENTS:

DMF #	Item referenced	Holder	Status	Review Date	Letter Date
			Adequate	Dec 9, 1994	
			Adequate	May 11, 1999	
			Adequate	Aug 9, 1999	
			Deficient	May 22, 1998 Aug 9, 1999 Jan ,2000	May 22, 1998 Aug 9, 1999 Jan , 2000
			Deficient	May 22, 1998 Feb , 2000	May 22, 1998 Feb , 2000
			Adequate	Oct 10, 1997	

Note:
DMFs [redacted] are still not adequate and the deficiencies are being resolved with the holders. The pending deficiencies are not an approvability issue for this NDA.

RELATED DOCUMENTS):

[redacted]

CONSULTS: See Chemistry review # 1

REMARKS/COMMENTS:

This is a response to information requested to the company by the FDA on Feb 28, 2000.

CONCLUSIONS & RECOMMENDATIONS:

This NDA is can be Approved from the standpoint of CMC pending an overall ACCEPTABLE recommendation from the Office of Compliance and a minor revision of the labeling.

/S/ 2/29/00
Maria Elena Ysern, MSc
Review Chemist, HFD-180

/S/ 2/29/00
Liang Zhou, Ph.D.
Chemistry Team Leader, HFD-180

cc:
NDA # 20-610
HFD-180 LTalarico
HFD-180 Div File/NDA #20-610
HFD-180 LZhou
HFD-180 MYsern
HFD-181 MMcNeil

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

2 pages

Table III.4* Other Primary Endpoints - Analysis of patients completing 8 week treatment

Efficacy Endpoint	Treatment			p-value	
	Colazide 2.25 g/day	Colazide 6.75 g/day	Asacol 4.2 g/day	Colazide 6.75 g/day vs. 2.25 g/day	Colazide 6.75 g/day vs. Asacol
Stool Frequency					
Improved at Week 2	12/44 (27.3%)	16/44 (36.4%)	17/42 (40.5%)		
Improved at Week 4	14/41 (29.4%)	20/40 (50.0%)	23/40 (57.5%)		
Improved at Week 8	10/34 (29.4%)	20/34(58.8%)	21/36 (58.3%)	0.006 CMH	0.946 CMH
Change from Baseline -Stool frequency relative to patients normal frequency at week 8 Mean (SE)	-0.18 (0.12)	-0.82 (0.18)	-0.69 (0.12)	0.009 ANOVA	0.727 ANOVA
Change from Baseline -Daily Stool frequency at week 8 Mean (SE)	-0.20 (0.34)	-1.85 (0.40)	-1.61 (0.38)	0.006 ANOVA	0.812 ANOVA
Improved Patient Functional Assessment					
Improved at Week 2	19/45 (54.3%)	14/44 (31.8%)	18/42 (42.9%)		
Improved at Week 4	20/41 (48.8%)	20/40 (50.0%)	22/40 (55.0%)		
Improved at Week 8	19/35 (54.3%)	24/34(70.6%)	22/36 (61.1%)	0.101 CMH	0.344 CMH
Change from Baseline -Patient Functional Assessment Score Week 8, Mean (SE)	-0.33 (0.15)	-0.75 (0.12)	-0.60 (0.13)	0.065 ANOVA	0.981 ANOVA
Improved Abdominal Pain					
Improved at Week 2	11/45 (24.4%)	12/44 (27.3%)	13/42 (31.0%)		
Improved at Week 4	11/41 (26.8%)	15/40 (37.5%)	18/40 (45.0%)		
Improved at Week 8	11/35 (31.4%)	14/34 (41.2%)	16/36 (44.4%)	0.346 CMH	0.722 CMH
Change from Baseline -Abdominal Pain Score Week 8. Mean (SE)	-0.08 (0.13)	-0.38 (0.09)	-0.42 (0.10)	0.067 ANOVA	0.780 ANOVA
Improved Sigmoidoscopy					
Improved at Week 2	20/48 (41.7%)	27/48 (56.3%)	14/44 (31.8%)		
Improved at Week 4	23/45 (51.1%)	29/43 (67.4%)	22/42 (52.4%)		
Improved at Week 8	21/40 (52.5%)	30/38 (78.9%)	23/38 (60.5%)	0.015 CMH	0.096 CMH
Improved Physician s Global Assessment					
Improved at Week 2	18/48 (37.5%)	21/48 (43.8%)	15/45 (33.3%)		
Improved at Week 4	24/44 (54.5%)	28/43 (65.1%)	24/43 (55.8%)		
Improved at Week 8	20/39 (51.3%)	28/38 (73.7%)	24/39 (61.5%)	0.030 CMH	0.246 CMH

Table III.5 Continued

Improved Patient Functional Assessment					
ITT1					
Improved at Week 2	21/45 (46.7%)	16/46 (34.8%)	18/43 (41.9%)		
Improved at Week 4	21/42 (50.0%)	22/43 (51.2%)	22/42 (52.4%)		
Improved at Week 8	22/40 (55.0%)	25/36(69.4%)	22/40 (55.0%)	0.172 CMH	0.199 CMH
Change from Baseline -Patient Functional Assessment Score Week 8. Mean (SE)	-0.35 (0.13)	-0.68 (0.11)	-0.56 (0.12)	0.082 ANOVA	0.996 ANOVA
ITT2 at week 8	25/50 (50.0%)	31/49 (62.00%)	24/49 (49.0%)	0.229 CMH	0.195 CMH
Improved Abdominal Pain					
ITT1					
Improved at Week 2	11/45 (24.4%)	14/46 (30.4%)	13/43 (30.2%)		
Improved at Week 4	12/42 (28.6%)	17/43 (39.5%)	19/42 (45.2%)		
Improved at Week 8	13/40 (32.5%)	14/36 (38.9%)	16/40 (40.0%)	0.545 CMH	0.932 CMH
Change from Baseline -Abdominal Pain Score Week 8. Mean (SE)	-0.09 (0.12)	-0.36 (0.09)	-0.38 (0.09)	0.053 ANOVA	0.831 ANOVA
ITT2 at week 8	14/50 (28.0%)	18/50 (36.0%)	18/50 (36.7%)	0.394 CMH	0.940 CMH
Improved Sigmoidoscopy					
ITT1					
Improved at Week 2	20/48 (41.7%)	29/52 (55.8%)	15/46 (32.6%)		
Improved at Week 4	23/45 (51.1%)	31/46 (67.4%)	23/43 (53.5%)		
Improved at Week 8	24/44 (54.5%)	31/41 (75.6%)	27/43 (62.8%)	0.055 CMH	0.229 CMH
ITT2	26/50 (52.0%)	39/53 (73.5%)	27/51 (52.9%)	0.024 CMH	0.030 CMH
Improved Physician's Global Assessment					
ITT1					
Improved at Week 2	18/48 (37.5%)	22/52 (42.3%)	16/47 (34.0%)		
Improved at Week 4	25/45 (55.6%)	29/46 (63.0%)	25/44 (56.8%)		
Improved at Week 8	23/44 (52.3%)	28/41 (68.3%)	28/44 (63.6%)	0.123 CMH	0.623 CMH
ITT2	26/49 (53.1%)	35/52 (67.3%)	28/49 (57.1%)	0.145 CMH	0.294 CMH
Improved Overall Symptom Assessment					
ITT1					
Improved at Week 2	9/47 (19.1%)	16/46 (34.8%)	12/45 (26.7%)		
Improved at Week 4	20/43 (46.5%)	24/41 (58.5%)	22/44 (50.0%)		
Improved at Week 8	20/42 (47.6%)	22/36 (61.1%)	25/42 (59.5%)	0.222 CMH	0.883 CMH
ITT2	22/49 (44.9%)	29/49 (59.2%)	26/48 (54.2%)	0.159 CMH	0.620 CMH

* From NDA

in Colazide 6.75 g/day who experienced larger reduction than patients in the 2.25 g/day group, the mean difference was not significant due to large variation. There were no difference in remission rate and quality of life assessment between the two Colazide groups.

Subgroup Analysis:
Sponsor's subgroup analysis for subgroups, such as, gender, age and race are summarized below.

There were only 5 patients older than 59 years of age, fewer than 7 black patients and fewer than 3 patients of race other than Caucasian or black. The confidence interval of improvement rate of each endpoint became too wide to be useful. Hence only gender analysis are reported in this review.

For the gender subgroup analysis results, two types of analyses were applied. In the analysis of patients who completed the trial, patients with missing data for the endpoint at week 8 were excluded from this analysis. In the intent-to-treat analysis, patients with missing data at week 8 were classified as "no improvement". The sample mean and 95% confidence interval of improvement rate of stool blood and improvement rate of other primary efficacy endpoint were estimated and summarized in Table III.7. In general, treatment differences were not significant in either male or female patients, and the improvement rate differences between the treatments were not significant between the male and female patients.

Table III.7* Gender Difference, Study CP099301 (Reviewer's Table)

Efficacy Endpoints	2.25g		Colazide 6.75g		Asacol 2.4g	
	Male	Female	Male	Female	Male	Female
Stool Blood						
ITT % (C.I.)	26.9 (11.6-47.8)	41.7 (22.1-63.4)	42.3 (23.4-63.1)	59.3 (38.3-77.6)	41.7 (22.1-63.4)	44.4 (25.5-64.7)
Complete Data % (C.I)	26.9 (11.6-47.8)	43.5 (23.2-55.5)	47.8 (26.8-89.4)	61.5 (40.6-79.8)	45.5 (24.4-67.8)	44.4 (25.5-64.7)
Stool Frequency						
ITT % (C.I.)	23.1 (9.0-43.6)	25.0 (9.8-46.7)	57.7 (36.9-76.6)	33.3 (16.6-54.0)	37.5 (18.8-59.4)	44.4 (25.5-64.7)
Complete Data % (C.I)	23.1 (9.0-43.6)	26.1 (10.2-48.4)	65.2 (42.7-83.6)	34.6 (17.2-55.7)	40.9 (20.7-63.6)	44.4 (25.5-64.7)
Patient Functional Assessment						
ITT % (C.I.)	57.7 (36.9-76.6)	41.7 (22.1-63.4)	53.8 (33.4-73.4)	63.0 (42.4-80.6)	37.5(18.8-59.4)	55.6 (35.3-74.5)
Complete Data % (C.I)	57.7 (36.9-76.6)	41.7 (22.1-63.4)	58.3 (36.6-77.9)	65.4 (44.3-82.8)	40.9 (20.7-63.6)	55.6 (35.3-74.5)
Abdominal Pain						
ITT % (C.I.)	23.1 (9.0-43.6)	33.3 (15.6-55.3)	30.8 (14.3-51.8)	37.0 (19.4-57.6)	20.8 (7.1-42.2)	48.1 (28.7-68.1)
Complete Data % (C.I)	23.1 (9.0-43.6)	33.3 (15.6-55.3)	33.3 (15.6-55.3)	38.5 (20.2-59.4)	22.7 (7.8-45.4)	48.1 (28.7-68.1)
Symptom Assessment						
ITT % (C.I.)	53.8 (33.4-73.4)	33.3 (15.6-55.3)	42.3 (23.4-63.1)	66.7 (46.0-83.5)	54.2 (32.8-74.4)	48.1 (28.7-68.1)
Complete Data % (C.I)	53.8 (33.4-73.4)	34.8 (16.4-57.3)	45.8 (25.6-67.2)	69.2 (48.2-85.7)	59.1 (36.4-79.3)	48.1 (28.7-68.1)

Table III.7 (continued)

Sigmoidoscopy						
ITT % (C.I.)	50.0 (29.9-70.1)	54.2 (32.8-74.4)	65.4 (44.3-82.8)	81.5 (61.9-93.7)	54.2 (32.8-74.4)	51.9 (31.9-71.3)
Complete Data % (C.I)	50.0 (29.9-70.1)	54.2 (32.8-74.4)	65.4 (44.3-82.8)	81.5 (61.9-93.7)	54.2 (32.8-74.4)	51.9 (31.9-71.3)
Physician Global Assessment						
ITT % (C.I.)	53.8 (33.4-73.4)	50.0 (29.1-70.9)	57.7 (36.9-76.6)	74.1 (53.7-88.9)	54.2 (32.8-74.4)	55.6 (35.3-74.5)
Complete Data % (C.I)	53.8 (33.4-73.4)	52.2 (30.6-73.2)	57.7 (36.9-76.6)	76.9 (56.4-891.0	59.1 (36.4-79.3)	55.6 (35.3-74.5)

* From NDA

Safety

Volunteered Complaints:

The most frequent volunteered complaints of all patients (intent-to-treat patients) were tiredness, loose stool, headache, nausea, flatus, rash, dyspepsia, and light-headed/dizzy (Table III.8). These complaints were generally the most commonly reported events in previously conducted ulcerative colitis studies. In general, the proportions of reported events were comparable among the three groups throughout the study.

Table III.8 Percent of Volunteered Patient Complaints (based on Table 23 NDA vol. 1.085 p.182), Study CP099301

Intent-to-treat Patient Complaints	Colazide 2.25 g/day N=50	Colazide 6.76 g/day N=53	Asacol N=51
Tiredness	26.5%	25.0%	32.7%
Loose Stool	24.5%	23.1%	14.3%
Other	24.5%	38.5%	34.7%
Headache	20.4%	36.5%	30.6%
Nausea	14.3%	15.4%	16/3%
Flatus	14.3%	15.4%	24.5%
Rush	8.2%	1.9%	8.2%
Light-headed/Dizzy	6.1%	7.7%	4.1%
Dyspepsia	4.1%	7.7%	8.2%

Adverse Events:

Out of 154 patients who took the randomized study medication, 48 (31%) patients withdrew from the study prior to completing all study visits. Twelve (5 in Colazide 2.25 g/day, 2 in Colazide 6.75 g/day and 5 in Asacol) patients withdrew due to adverse events. Five of these adverse events were identified as unrelated to the disease symptoms. Seven withdrew due to events related to worsening of symptoms. The following table shows the distribution of adverse events among the three groups.

Safety -
Colazide treated patients experienced more non-serious adverse events that were generally commonly reported in previously conducted ulcerative colitis studies. In general, the proportions of reported adverse events were comparable among the three groups throughout the study. Thus, in this reviewer's assessment, Colazide was shown to be tolerable among the patients in the study.

IV. STUDY 57-3001

Study 57-3001 was a phase III randomized, active-controlled, parallel group study designed as a maintenance study to demonstrate that Colazide has a higher tolerance level than Asacol. The acute phase of the study was designed as a double blind, double dummy phase. Patients enrolled into the trial were randomized to receive either Colazide 2.25 g t.i.d. or Asacol 0.8 g t.i.d. for 4 weeks, or if necessarily, 8 to 12 weeks. Patients were provided with Colifoam as relief medication for use on a p.r.n basis throughout the trial. All patients in asymptotic remission (to be defined later) and who had not used relief medication in the 4 days before the clinic visit at 4 or 8 weeks underwent a sigmoidoscopy/colonoscopy. Patients who had achieved both sigmoidoscopic remission (grade 0-1) and symptomatic remission and had used no relief medicating in the last 4 days before the clinic visit at either 4, 8 or 12 weeks were eligible to be re-randomized into the maintenance (Chronic) phase of the study. All remaining patients underwent a sigmoidoscopy at 12 weeks. Study 57-3001 was designed to test the difference in tolerance rates and not remission rates. This review documents only the results of the acute phase of the study.

The primary endpoint was the proportion of patients in complete remission at 12 week of the study. The secondary endpoints were

1) The proportion of patients in symptomatic remission after 2 weeks of treatment;
2) The proportion of patients in remission (symptomatic and sigmoidscopically proven) after 4, 8 and 12 weeks;
3) The median time to relief of day-time and night-time diarrhea after treatment using daily diary card assessment;
4) The cumulative number of symptom-free days on which no relief medication is used per patient during treatment.

Overall study plan -
The overall study plan is given in the following figure

Figure IV.1* Overall Study Plan, Study 57-3001

Clinic Visit	1A	1B	2	3	3A	3B
	Randomization					
Day	-3 to -1	0				
Week		0	2	4	8	12
Range (days)			±3	±3	±3	±3
Clinical History		x				
Sigmoidoscopy		x[a]- x[a]		x[**a]	[x[**a]]	(x[a])
Rectal Biopsy		x--x		x**	[x**]	(x)
Stool culture		x--x				
Symptoms		x	x	x	[x]	(x)
Laboratory Screen		x		x**	[x**]	(x)
Adverse events			x	x	[x]	(x)
Compliance			x	x	[x]	(x)

* From NDA
x--x sigmoidoscopy or colonoscopy, biopsy and stool culture
a sigmoidoscopy or colonoscopy
* patients in symptomatic remission only
** patients in symptomatic and sigmoidoscopic/colonoscopic remission only
[ ] Patients with symptomatic remission or unhealed at visit 3
( ) Patients with symptomatic remission or unhealed at visit 3A

Patient population and sample size -
The study was originally planned to enroll 296 patients in 37 hospitals throughout the UK and the Republic of Ireland. Each center was expected to enroll an initial target recruitment of 8 patients over a maximum of 1 year. The sample size was determined to detect (80% power, 5% significance level) a 15% difference in withdrawals for intolerance between the two treatment groups with an additional 20% patients allowance for non-drug related drop-outs. Due to difficulties experienced in recruitment, the sponsor enrolled only 101 patients within the scheduled recruiting period. Consequently, the study only had a power of 43% to detect the pre-specified difference of 15% in patient discontinuation. Since the study was powered for comparison in the chronic phase, the sample size issue was not directly addressed for the comparison in this phase.

Of the 101 patients enrolled and randomized into the trial, one patient was identified as erroneously included with no ulcerative colitis. In addition, one patient was randomized but failed to take study medication. Overall, only 19 centers (instead of the originally planned 37 centers) enrolled patients into the acute phase of the study (Table IV.1)

Table IV.1* Recruitment by Study Center, Study 57-3001

Center Number	Center	Investigator	No. of Patients
36	Sheffield	Hpldsworth/Lobo	14 (1)*
25	London	Leicester/Howard	11
2	Stafford	Gibson	10 (1)**
4	Shrewbury	Kerr	10
30	London	Hodgson	8
31	Middlesborough	Bramble	7
29	Bury	Goodman	7
1	Stoke	Green	7
6	Hemel Hempstead	Barrison	5
11	Basildon	Willoughby	5
37	Southhampton	Arthur	4
3	Telford	Brown	2
32	Huntington	Dickinson	2
20	Blackford	Isaacs	2
13	Ashford	Wheeler	2
27	Stevenage	Willoughby	2
8	Ipswich	Bell	1
18	Ilford	Grainger	1
21	Salford	Shaffer	1
Total			101

* From NDA
*: included one patient without ulcerative colitis
**: included one patient who failed to start the study medication after randomization

To assure balance, a block of six patients was used in randomizing patients to Colazide or Asacol. There were 52 patients randomized to receive Colazide and 49 to receive Asacol. Of the one hundred and one patients recruited and randomized, 100 patients received blinded study treatment.

Disposition of Patients - The disposition of patients is given in the table below.

Table IV.2* Disposition of Patients, Study 57-3001

	Colazide	Asacol	Total
Randomized	52	49	101
Treated	51	49	100
Discontinued	15	23	38
Completed treatment in remission at week 4	18	6	24
Completed treatment in remission at week 8	9	5	14
Completed treatment in remission at week 12	4	7	11
Total completed in remission	31	18	49
Total not in remission after 12 weeks	6	8	14
Total eligible for analysis	50	49	99

*From NDA

Demographics and patients characteristics
Patient demographics, baseline characteristics, and medical history are given in Tables 3-8 of vol. 1.087, pp 244-248 of NDA. There was no statistically significant differences between the treatment groups in the mean age, sex distribution, smoking history, disease duration, disease status, extent of disease and duration of current relapses at baseline.

Clinical Efficacy primary endpoint - Complete Remission Rate:
After up to 12 weeks of treatment duration, patients treated with Colazide achieved significantly higher rate of complete remission than the Asacol treatment group (62% vs. 37%, p=0.0159 Fisher's Exact test), (see Table IV.3, page 18 of this review).

Secondary Efficacy Endpoint:
Complete Remission Rate at Clinic Visits -
The differences at week 4 and 8 were also statistically significant (See Table IV.3, page 18 of this review)

Table IV.3* Complete Remission Rate at Each Clinic Visit, Study 57-3001

Visit	Colazide (N=50)	Asacol (N=49)	p-value Exact test
4 weeks	19 (38%)	6 (12%)	0.0050
8 weeks	27 (54%)	11 (22%)	0.0018
12 weeks	31 (62%)	18 (37%)	0.0159

* From NDA

Symptomatic Remission Rate at Clinic Visits -
Symptomatic remission rate was significantly higher in the Colazide treated patients at week 8 and 12 (See Table IV.4).

Table IV.4* Symptomatic Remission Rate at Each Clinic Visit, Study 57-3001

Visit	Colazide (N=50)	Asacol (N=49)	p-value Exact test
2 week	32 (64%)	21 (43%)	**0.0446**
4 weeks	35 (70%)	25 (51%)	0.0656
8 weeks	39 (78%)	22 (45%)	**0.0009**
12 weeks	44 (88%)	28 (57%)	**0.0007**

*Ffrom NDA

Sigmoidoscopic Healing Rate at Clinic Visits -
Among the patients in complete remission, the percentage of patients achieving sigmoidoscopic healing was higher in the Colazide treated patient group than in the Asacol treated patient group. The difference was statistically significant at the week 4 visit only (See Table IV.5 below).

Table IV.5* Sigmoidoscopic Grade in Patients Achieving Symptomatic Remission, Study 57-3001

Sigmoidoscopic Grade	Colazide	Asacol	p-value (Exact)
4 weeks			
0 or 1	19 (88%)	7 (44%)	0.0172
2, 3 or 4	4 (17%)	9 (56%)	
Missing	12	9	
8 weeks			
0 or 1	28 (90%)	11 (65%)	0.0510
2, 3 or 4	3 (10%)	6 (35%)	
Missing	8	5	
12 weeks			
0 or 1	34 (87%)	19 (73%)	0.1972
2, 3 or 4	5 (13%)	7 (35%)	
Missing	5	2	

* From NDA

Median Time to Complete Remission -
The median time to complete remission is significantly shorter in the Colazide treated patient group than in the Asacol treated patient group (10 days vs. 25 days, p=0.0039) (See Figure 2 of vol. 1.087. page 261 of NDA).

Subgroup Analysis:
Sponsor's results of subgroup analysis for subgroups such as gender, race and age are summarized below.

There were only fewer than 7 patients per treatment of age older than 59 years. Confidence

symptom improvement rates in Study CP099301 can not be replicated by this study.

Safety -
There were fewer patients with AEs in the Colazide group than in the Asacol group. The Colazide to Asacol AE ratios ranged from 0.20 to 0.73 in each of the 5 body systems.

V. STUDY CP069101

Study CP069101 was a phase III randomized, placebo-controlled, double-blind, dose-response study designed to compare Colazide® 4.5 g and 6.75 g daily with placebo in patients with mildly to moderately active ulcerative colitis. The comparisons are for safety and rates of symptom improvement. The treatment period was 4 weeks.

The primary efficacy endpoints were improvement in individual symptom scores, physician's global assessment, flexible sigmoidoscopy, and overall symptom assessment. The seconadary endpoint was cumulative proportion of patients achieving remission.

The overall study plan is given in the following figure

Figure V.1* Overall Study Plan, Study CP069101

	Clinic Visit			
	Screening	Baseline	2 Week	4 Week
	-7 to 0 day	96 hrs Initial	48 hrs | 48 hrs Midpoint Daily Assessment	96 hrs Final
Clinical History	x			
Sigmoidoscopy	x		x	x
Biopsy	x		(x)	(x)
Stool culture	x			
Symptoms	x	x	x	x
Laboratory	x		x	x
Adverse events	x	x	x	x

(x) biopsies were only taken at follow-up visits if the investigator determined that the patients was in remission.

* From NDA.

Patient population and sample size - The study was originally planned to enroll 280 patients so as to have 80% power to detect a two-fold improvement rate in Colazide group of the assumed 20 percent improvement rate in the placebo group. However, due to the difficulties in recruitment, of 211patients with mildly to moderately active ulcerative colitis who were screened in 21 centers, only 180 were enrolled into this study (72 to Colazide 6.75 g/day, 73 to 4.5g/day and 35 to placebo in a 2:2:1 randomization ratio).

Disposition of Patients - The disposition of patients is given the table below.

Table V.1* Disposition of patients, Study CP069101

	Colazide 6.75 g/day	Placebo	Colazide 4.5 g/day
Enrolled	72	35	73
Protocol Entrance violation	2	0	1
Noncompliance	1	2	0
Spnsor claimed ineligible for efficacy	3	2	1
ITT analysis	72	35	73
Withdrew prior to week 2	8	1	6
Completed week 2	64	34	67
Withdrew at week 2	8	2	9
Withdrew prior to week 4	4	2	3
Completed week 4	52	30	55

* From NDA

Demographics and Baseline Characteristics

Patient demographics and baseline characteristics are given in Table 6 in vol.1.083 page 224 of NDA. There were no statistically significant differences among the three treatment groups in mean age. sex distribution, and in smoking history, disease duration, disease status, extent of disease and duration of current relapses at baseline. However, the number of episodes of ulcerative colitis in the past two years is significantly less in the placebo group (4.6 episodes, p=0.021 by 2-way ANOVA controlling for site). There is no statistically significant difference in disease activity scores at entry among the three treatment groups (Table VII, vol. 1.083, page 188 of NDA).

Clinical Efficacy

Primary efficacy endpoint:

As shown in Table V.2, results of the analyses of improvement rate of stool blood fail to show either efficacy of Colazide over placebo (36.5% vs. 31.1%, p=0.456, with 24 hr data or 40.3% vs. 34.0%, p=0.898, with 96 hr data, Colazide 6.75 vs. Placebo by CMH test) or dose response (36.5% vs. 40.0%, p=0.718 or 40.3% vs. 33.3%, p=0.582 with 96 hr data).

Table V.2* Improvement in Stool Blood, Study CP069101

Physician Global Assessment Change at	Colazide 6.75g/day	Placebo	Colazide 4.5g/day	p-value 6.75 vs. Placebo	p-value 4.5 vs. Placebo
24 hr data at week 4					
Improved	23 (36.5%)	12 (40.0%)	19 (31.1%)	0.718 CMH	0.456 CMH
Not improved	40 (63.5%)	18 (60.0%)	42 (68.9%)		
Missing	6	3	8		
Total assessed	63	30	61		

statistical testing (Tables 3 and 4, vol 7.1, page 179-282 of NDA) suggested

(1) Significant treatment-by-age group interaction in pain score improvement when comparing low dose Colazide with placebo (p=0.040 in ITT1 and p=0.069 in ITT2).

(2) Significant treatment-by-race group interaction in stool frequency when comparing high dose Colazide with placebo (p=0.005 in both ITT1 and ITT2).

Safety

Volunteered Complaints:

The most frequent volunteered complaints were nausea, tiredness, headache, rash, flatus, dyspepsia, heartburn and others. These complaints were generally the most commonly reported events in previously conducted ulcerative colitis studies. In general, the proportions of reported events were comparable among the three groups.

Adverse Events:

Out of the 43 (23.9%) patients prematurely withdrew before completing all the study visits, ten (5 of Colazide 6.75 g/day and 5 of Colazide 4.25 g/day) were due to adverse events. Of those 10, seven were adverse events related to worsening of ulcerative colitis symptoms. The remaining three included nausea, chest pain and oral ulcers with rash. The following table shows the distribution of adverse events among the three groups.

Table V.4* Number of patients with adverse events, Study CP069101

Adverse Events	Treatment Group		
	6.75g/day (N=75)	Placebo (N=35)	4.25 g/day (N=73)
Serious Adverse Events	3 (4.2%)	0	0
Withdrawals due to AEs	5 (6.9%)	0	6 (8.2%)
AEs	24 (33.3%)	21 (60.0%)	38 (52.1%)
Causally related AEs	10 (13.9%)	4 (11.9%)	18 (24.7%)

* From NDA

Reviewer's Conclusions on Study CP069101

This is the only placebo controlled randomized study submitted as a supporting study. Colazide treatment failed to show significant benefit over placebo in almost all primary efficacy endpoints proposed by the sponsor. This study failed also in showing a significant dose response trend of Colazide in treatment of up to 4 weeks. Colazide appeared to be well tolerated by study patients.

VI. META ANALYSIS OF EFFICACY IN SUBGROUPS

In meta analysis, data of the two pivotal studies (CP099301, 057-3001), and three supporting studies (CP069101, 028-011, 028-017) were pooled by the sponsor. The purpose of the meta analysis was to examine if there were patterns suggesting treatment by gender, race and age interaction.

Due to the difference in length of the studies, analyses were carried out at the final visits of the studies. Hence analysis was applied at week 4, 8 and 12. Results of the analyses carried out by the sponsor (Tables 1.1 to 4.1, NDA vol. 7.2 and 7.3, pp.081-452) failed to demonstrate any statistically significant difference in Colazide treatment response between the gender, race or age groups.

VII. CONCLUSION

Efficacy -
The results of the efficacy analyses of the two pivotal phase III clinical studies can be summarized as follow:

1) In Study 57-3001, complete remission and symptomatic remission were used as primary endpoints in a study designed primarily as a maintenance trial. Remission rates were significantly higher in Colazide patients than in Asacol patients (62% vs. 37%, p=0.0159 in complete remission, 44% vs. 28%, p=0.0007 in symptomatic remission) at the last clinic visit (week 12).

2) In Study CP099301, results of analyses failed to show that the Colazide treated group 6.75g/day had a higher symptom improvement rate than the Asacol treatment group at week 8 in stool bleeding (64.7% vs. 52.8%, p=0.275 among completers, and 55.1% vs. 44.9%, p=0.315 for the intent-to-treat analysis) or any of the six other primary endpoints. However, a dose response relationship was shown in the comparison of the two Colazide treatment groups. In the analyses of completers, this study showed a higher improvement rate in the Colazide 6.75g/day group as compared to the Colazide 2.25g/day group for stool blood (64.7% vs. 32.4%, p=0.006) and for stool frequency (58.8% vs. 29.4%, p=0.006); these results remained significant after adjusting for multiple endpoints. The relationship held for the intent-to-treat analysis, in which the last-observation-carried-forward principle was applied to all patients with early termination to determine the improvement rate (55.1% vs. 34.7%, p=0.004 for stool blood and 49.0% vs. 24.5%, p=0.012 for stool frequency); these results remained significant after adjusting for multiple endpoints by the correlation based method (Tukey, Heyes and Ciminera(1985)).

3) It should be noted that the different primary endpoints in the two studies addressed different indications, acute treatment in CP099301, and remission in 57-3001. Thus the two studies provided results that were not supportive of each other.

4) Colazide tablets used in the two pivotal trials were manufactured by different manufacturers. In the absence of bioequivalence report, it is a chemistry issue whether the same conclusion can be drawn for the two products.

5) In the last phase III clinical trial and the only placebo controlled trial, Study CP069101, results of the analyses failed to demonstrate the efficacy of Colazide in improvement of symptoms over placebo or low dose of Colazide. Thus, again, this study failed to provide support for Study CP099301.

Safety -
In general, the proportions of reported events were comparable among Colazide and the control groups. In all studies, Colazide was shown to be tolerable among the patients in the study.

/S/

Yi Tsong, PhD, Mathematical Statistician, HFD-720

/S/

Abdul J. Sankoh, PhD, Team Leader, HFD-720

/S/ 5/13/98

Michael Welch, PhD, Acting Division Director, HFD-720

Original : NDA 20610
HFD-720/MWelch/AJSankoh/YTsong
HFD-720/file copy
HFD-180/LTalarico/RPrizont/MMcNeil/Division file
YT/yt pp. 30, May 6, 1998. NDA20610/efficacy.rev

APPEARS THIS WAY
ON ORIGINAL

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA: 20-610 **CHEM REVIEW # 4** **REVIEW DATE: 02/18/00**

SUBMISSION TYPE	DATES		
	DOCUMENT	CDER	ASSIGNED
Original	Jun 23, 1997	Jun 24, 1997	Jun 26, 1997
Amendment (BC)	Sep 3, 1997	Sep 4, 1997	Sep 17, 1997
Amendment (BC)	Mar 4, 1998	Mar 06,1998	Mar 24, 1998
Amendment (BC)	Mar 11, 1998	Mar 13, 1998	Mar 13, 1998
Amendment (BC)	Apr 30, 1998	May 05,1998	May 7, 1998
Amendment (BZ)	Aug 8, 1999	Aug 9, 1999	Aug 11, 1999
Amendment (AZ)	Sep 23, 1999	Sep 24, 1999	Oct 04, 1999
Amendment (BC)	Oct 20, 1999	Oct 25, 1999	Oct 25, 1999
Amendment (BC)	Feb 11, 2000	Feb 15, 2000	Feb 18, 2000

NAME & ADDRESS OF APPLICANT:
Salix Pharmaceutical, Inc.
3600 W. Bayshore Roada
Suite 205
Palo Alto. CA 94303

DRUG PRODUCT NAME:

Proprietary:	—
Nonproprietary/USAN:	Balzalazide disodium
Code Name/#:	BX661A
Chem.Type/Ther.Class	1S

ANDA Suitability Petition/DESI/Patent Status:
Patent 4,412,992 covers the composition of matter/method of manufacture/use for balzalazide and related salts. Patent owner is Biorex, Ltd, United States. Expiration date July 8, 2001.

PHARMACOLOGICAL CATEGORY/INDICATION:
Treatment of mildly to moderate active ulcerative colitis.

DOSAGE FORM: Capsules

STRENGTH: 750 mg

ROUTE OF ADMINISTRATION: Oral

HOW DISPENSED: Rx

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
See Chemistry Review # 1.

SUPPORTING DOCUMENTS:

DMF #	Item referenced	Holder	Status	Review Date	Letter Date
			Adequate	Dec 9, 1994	
			Adequate	May 11, 1999	
			Adequate	Aug 9, 1999	
			Deficient	May 22, 1998 Aug 9, 1999 Jan ,2000	May 22, 1998 Aug 9, 1999 Jan , 2000
			Deficient	May 22, 1998 Feb , 2000	May 22, 1998 Feb , 2000
		Owens-Brockway	Adequate	Oct 10, 1997	

Note:
DMFs are still not adequate and the deficiencies are being resolved with the holders.
The pending deficiencies are not an approvability issue for this NDA.

RELATED DOCUMENTS):

CONSULTS: See Chemistry review # 1

REMARKS/COMMENTS:
This amendment is in reference to the proposed package insert provided by the applicant.

CONCLUSIONS & RECOMMENDATIONS:
An overall Acceptable recommendation from the office of compliance is still pending.
The applicant should respond to the information requested in the deficiency letters.
This NDA is APPROVABLE from the standpoint of CMC.

/S/ 02/25/00
Maria Elena Ysern, MSc
Review Chemist, HFD-180

/S/
Liang Zhou, Ph.D.
Chemistry Team Leader, HFD-180

cc:
NDA # 20-610
HFD-180/LTalarico
HFD-180/Div.File/NDA #20-610
HFD-180/LZhou
HFD-180/MYsern
HFD-181/MMcNeil
R/D Init by: LZhou
MY/ F/T 02/18/00/ c:/Word/nda/ 20610002.4my

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

2 pages

FEB 14 2000

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA: 20-610 · **CHEM REVIEW # 3** **REVIEW DATE: 01/07/00**

SUBMISSION TYPE	DATES		
	DOCUMENT	CDER	ASSIGNED
Amendment (BZ)	Aug 8, 1999	Aug 9, 1999	Aug 11, 1999
Amendment (AZ)	Sep 23, 1999	Sep 24, 1999	Oct 04, 1999
Amendment (BC)	Oct 20, 1999	Oct 25, 1999	Oct 25, 1999

NAME & ADDRESS OF APPLICANT:
Salix Pharmaceutical, Inc.
3600 W. Bayshore Roada
Suite 205
Palo Alto, CA 94303

DRUG PRODUCT NAME:

Proprietary:	[redacted]
Nonproprietary/USAN:	Balzalazide disodium
Code Name/#:	BX661A
Chem.Type/Ther.Class	1S

ANDA Suitability Petition/DESI/Patent Status:
Patent 4,412,992 covers the composition of matter/method of manufacture/use for balzalazide and related salts. Patent owner is Biorex, Ltd, United States. Expiration date July 8, 2001.

PHARMACOLOGICAL CATEGORY/INDICATION:
Treatment of mildly to moderate active ulcerative colitis.

DOSAGE FORM: Capsules

STRENGTH: 750 mg

ROUTE OF ADMINISTRATION: Oral

HOW DISPENSED: Rx

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
See Chemistry Review # 1.

SUPPORTING DOCUMENTS:

DMF #	Item referenced	Holder	Status	Review Date	Letter Date
[redacted]			Adequate	Dec 9, 1994	
			Adequate	May 11, 1999	
			Adequate	Aug 9, 1999	

Deficient	May 22, 1998 Aug 9, 1999 Jan ,2000	May 22, 1998 Aug 9, 1999 Jan , 2000
Deficient	May 22, 1998 Feb , 2000	May 22, 1998 Feb , 2000
Adequate	Oct 10, 1997	

Note:
are still not adequate and the deficiencies are being resolved with the holders. The pending deficiencies are not an approvability issue for this NDA.

RELATED DOCUMENTS):

Chemistry Reviews # 1 and # 2

CONSULTS:

- The Division of Biopharmaceutics has been consulted with regard to the dissolution data and is also reviewing the dissolution data to support the possible equivalence of the drug product used in the pivotal studies compared to the approved US formulation of the active control.

- A request for Trademark review was submitted to the Label and Nomenclature Committee and was found acceptable. The firm was notified May 20, 1998.

- The stability data were sent to Statistics for consult.
- The EER was submitted. Response is still pending.

REMARKS/COMMENTS:

BZ Amendment dated Aug 6, 1999 is a response to the FDA letter dated March 16, 1999 concerning the active control used in the two Phase II Pivotal studies, Studies CP099301 and 57-3001.

AZ Amendment dated Sep 23, 1999 is a response to the Approvable Letter and FDA Letter dated March 16, 1999. The company indicates it is a complete response.

BC Amendment dated October 20, 1999 presents data supporting a change in the hard gelatin capsule for the drug product and a minor modification to the manufacturing equipment to accommodate process scale-up.

The original NDA submission identified as the contract packager. will replace as the contract packager. There have been no changes to the packaging components as specified in the original NDA (Vol. 1.004, p 066).
A new packaging site needs to be inspected. EER was submitted Jan 10, 2000.

CONCLUSIONS & RECOMMENDATIONS:

An overall Acceptable recommendation from the Office of Compliance is still pending.
The applicant should respond to the information requested in the deficiency letter. The applicant should easily address these deficiencies.

This NDA is APPROVABLE from the standpoint of CMC.

/S/ 02/14/00

Maria Elena Ysern, MSc
Review Chemist, HFD-180

/S/ 2/14/00

Liang Zhou, Ph.D.
Chemistry Team Leader, HFD-180

cc:
NDA # 20-610
HFD-180/LTalarico
HFD-180/Div File/NDA #20-610
HFD-180/LZhou
HFD-180/MYsern
HFD-181/MMcNeil
R/D Init by: LZhou
MY: F/T 02/14/00 c:/Word/nda/ 20610002.3my

APPEARS THIS WAY
ON ORIGINAL

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

14 pages

MEMORANDUM

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

DATE: Mar 12, 1999

FROM: Maria Elena Ysern, MSc,
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

THROUGH: Eric P. Duffy, Ph.D., /S/ 3/16/99
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: NDA 20-610- CMC Request for Comments on Multi-point Dissolution Study Design Associated with Manufacturing Changes and clarification of Drug Product Dissolution Specifications.

TO: NDA 20-610

Salix Pharmaceutical has provided an outline of the proposed multipoint dissolution profile that would support manufacturing revisions. Salix Pharmaceutical is proposing to demonstrate equivalency of the pre-and post change material by comparison of one pre-change and one post-change batch. Salix intends to place the three validation batches that incorporate these changes on stability.

Salix is also proposing to correct a discrepancy associated with a transcription error in the dissolution specification limits.

Summary of the proposed component and process changes:

Process and equipment changes:
In order to efficiently scale-up the commercial process, an alternative blender and encapsulator will be used

Unit operatio				
	Class	Subclass	Class	Subclass
Blending				
Unit dosing				

With respect to the change in blenders, based upon the SUPAC Equipment Addendum, it would be a Level I change, and one batch of long term stability in the Annual Report would be sufficient.

With regard to the change in encapsulator to another one with different operation procedure, the company could be asked to provide a Prior Approval Supplement for this change if any differences are observed during the multipoint dissolution testing.

The multipoint Dissolution Study outline was consulted informally to the Biopharm division and they have considered the protocol to be adequate.

Salix is also notifying the Agency that the proposed dissolution specification limit would be revised since they found a discrepancy between the dissolution specification and the specification limits used for stability analysis. The EurPh dissolution method (used initially), is [redacted]. Based on the dissolution data available at the time, a specification of [redacted] was established. When the USP testing was adopted, the absolute dissolution specification was assigned inadvertently as the Q value. The company would revise the dissolution specification to [redacted]. This correction is acceptable.

CONCLUSION:
The firm should be notified that the proposed dissolution testing to support capsule composition, and manufacturing changes is acceptable.

**APPEARS THIS WAY
ON ORIGINAL**

CC: NDA 20-610
NDA 20-610 Division Files
HFD-180/McNeil
HFD-180/MYsern MYsern 3/16/99
HFD-180/EDuffy
MY/dob F/T 3-15-99\WORD: n:\wordfiles\chem\N\20610MEM.1MY

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #:20610 **CHEM.REVIEW #:** 2 MAY 22 1998

REVIEW DATE: 5/8/98

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AMENDMENT:	March 4, 1998	March 06,1998	March 24, 1998
AMENDMENT:	March 11, 1998	March 13, 1998	March 13, 1998
AMENDMENT:	March 30, 1998	March 05,1998	May 7, 1998

NAME & ADDRESS OF APPLICANT:
Salix Pharmaceuticals, Inc.
3600 W. Bayshore Road
Suite 205
Palo Alto, CA 94303

DRUG PRODUCT NAME

Proprietary:	Colazide
Nonproprietary/USAN:	Balzalazide disodium
Code Name/#:	BX661A
Chem.Type/Ther.Class:	1

ANDA Suitability Petition/DESI/Patent Status:
Patent 4,412,992 covers the composition of matter/method of manufacture/use for balzalazide and related salts. Patent owner is Biorex, Ltd, United States. Expiration date July 8, 2001.

PHARMACOL.CATEGORY/INDICATION:
Treatment of mildly to moderately active ulcerative colitis.

DOSAGE FORM:	Capsules
STRENGTHS:	750 mg
ROUTE OF ADMINISTRATION:	Oral
DISPENSED:	__X__ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

See Review #1

SUPPORTING DOCUMENTS:

NDA Review #1. Completed, deficiencies sent to the company.

CONSULTS: N/A

REMARKS/COMMENTS:

All analytical work reported in these amendments was conducted either by [redacted]. The Sample testing Matrix (Table 1 is attached).

The March 13, 1998 amendment was the copy of the FDA483 issued to Anabolic Laboratories, Inc and the prepared response. It also includes the revised HPLC and revised dissolution method.

April 17, 1998 HFD-180 received a Memorandum from the Division of Manufacturing and Product Quality (HFD-320) with regards to their completes review of the EIR. The EIR covers an inspection conducted at the Anabolic manufacturing facility from February 9 to 17, 1997. Finished product manufacture and testing is performed at this site.

DMPQ concurs with the District recommendation to withhold approval of this NDA based on the following significant GMP observations:

- Failure to perform testing on incoming raw materials. This includes identity testing. Please note that the EIR is mute on whether or not identity testing was performed on raw materials used in the manufacture of the clinical batch.
- Failure to demonstrate that the quality control test methods for balzalazide (dissolution, identification by [redacted] used to test and release active ingredients and finished product are reproducible and validated. These tests have been transferred from [redacted] a control lab in the UK. However, method validation has not been accomplished.

Anabolic has provided a response to the FDA-483, but DMPQ believes that corrections to the deficiencies should be verified during the next EI.

The Division HFD-180 agrees with this decision.

CONCLUSIONS & RECOMMENDATIONS:

The company has provided the results of the tests conducted at ——

The data from the chemical and physical studies supports the —— and the —— drug substance being equivalent products. No evidence of polymorphism was found, and the crystallinity of the drug substance from both sources was proven to be the same.

The company should address the deficiencies indicated in the letter.

This submission is aprovable pending satisfactory inspection of the Anabolic site. The Anabolic facility is currently UNACCEPTABLE, Therefore from a CMC perspective the NDA is NOT APPROVABLE.

cc:
Orig. NDA
HFD-180/Division File
DISTRICT OFFICE
HFD-180/MYsern
HFD-180/MMcNeil
R/D Init by:E.Duffy
filename: FT/EPD 5/22/98/WORD/CHEM/N/20610805.2MY

/S/ 5-22-98

Maria Elena Ysern,MSc
Review Chemist, HFD-180

APPEARS THIS WAY
ON ORIGINAL

/S/ 5/22/98

Eric P. Duffy,PhD
Chemistry Team Leader, HFD-180

These amendments provide a response from Salix to the chemistry, manufacturing and control inquiries contained in the FDA letter of December 15, 1997. (Questions in bold letters).

I. **Regarding Drug Substance:**

1. **Please provide a comparison of the solubility profiles from both suppliers. Include the same solvents and temperatures for both. (Response in April 30, 1998 amendment)**

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

33 pages

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA: 20-610 **CHEM.REVIEW:** #1 **REVIEW DATE:** May 5, 1998

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	Jun 23 1997	Jun 24 1997	Jun 26 1997
Amendment	Sep 3, 1997	Sep 4, 1997	Sep 17, 1997

NAME & ADDRESS OF APPLICANT:
Salix Pharmaceutical
Suite 205
3600 W Bayshore Rd.
Palo Alto, California 94303

MAY 22 1998

DRUG PRODUCT NAME

Proprietary:	Colazide®
Nonproprietary/USAN:	Balsalazide disodium
Code Name/#:	BX661A
Chem.Type/Ther.Class:	1

ANDA Suitability Petition/DESI/Patent Status:
Patent 4,412,992 covers the composition of matter/method of manufacture/use for Balsalazide and related salts. Patent owner is Biorex, Ltd., United States. Expiration date July 8, 2001.

PHARMACOL.CATEGORY/INDICATION:
Treatment of mildly to moderately active ulcerative colitis

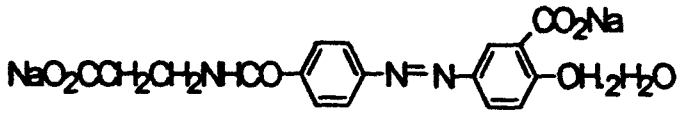
DOSAGE FORM: Capsules
STRENGTHS: 750 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: XX Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

USAN name: Balzalazide Disodium
INN name: Balzalazide Sodium
Chemical names:
(E)-5-[[4-[[(2-carboxyethyl)amino]carbonyl]phenyl]azo]-2-hydroxybenzoic acid, disodium salt, dihydrate.

(E)-5-[[p-[(2-carboxyethyl)carbamoyl]phenyl}azo}saliccylic acid, disodium salt, dihydrate.

British adopted name (BAN): Balzalazide
Proprietary name: Colazide®
Generic name: Balzalazide disodium is the intended generic name.
Chemical Abstracts Service (CAS) registry number: 1500399-21-6
Laboratory code: BX 661A.



Molecular Formula: $C_{17}H_{13}N_3O_6Na_2.2H_2O$
Molecular weight: 401.32 (437.32 for the dihydrate)
Molecular weight of the corresponding di-acid: 357.32
Chirality: There are no asymmetric carbons in the molecule.
The optical rotation for a 1% solution in H_2O is -0.5°.

SUPPORTING DOCUMENTS:

RELATED DOCUMENTS (if applicable):

CONSULTS:

- A consults of the data was sent to the Division of Biopharm, a preliminary letter requesting more information has been sent.
- A request for Trademark review was submitted to the Label and Nomenclature Committee and their conclusions were the following: Upon the review of the proposed trade name, Colazide Capsules, it was noted the following **look alike/sound alike** conflicts:

  Corazide, Capozide and Dyazide. This was seen as a high potential for confusion, and in addition there was concern with respect to the suffix "**-azide**" which is widely associated with thiazide diuretics. For this reason we recommended against the use of the name Colazide. The company was informed of this conclusion in a letter Oct 3, 1997.

- The stability data was sent to statistics for consult. A response was received March 30, 1998 (see attached copy).
  The expiration date recommended (not more than 6 months beyond the last observation date) is as follows:

40cc	CRC, manufacturer	24 months
600cc	CRC, manufacturer	24 months
40cc	CRC, manufacturer	18 months
600cc	CRC, manufacturer	18 months

REMARKS/COMMENTS:

- Salix Pharmaceuticals, Inc. claims exclusivity for Colazide® (Balzalazide disodium) Capsules under 21 CFR 314.108(b)(2). Colazide® is a new drug product which is the subject of this application, NDA 20-2610.

- Colazide is not marketed anywhere in the world. A marketing authorization application was submitted in the UK and approval is pending. The company indicates that there are no significant differences between the label proposed in the UK/EU and that proposed in the US in terms of indication, dosing, or safety information.

- The company indicates that Patent No. 4,412,992 covers the composition, method of manufacture, and method of use of Balzalazide disodium.

- Pursuant to the small business exception, FDA has granted a deferral of payment of the application fee from one year from the date of submission of the marketing application. (See Vol 1.1 page 011 for more details.)

- An inspection of the pharmaceutical testing laboratory in —— United Kingdom took place on August 27 and 28, 1997 and revealed significant deviations from Current Good Manufacturing Practices (cGMPs) in the laboratory dealing with pharmaceutical stability samples. A FDA-483 was issued. These cGMP deviations cause pharmaceutical products tested by this facility to be unacceptable for use in the US because the products are now considered to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act.

  The company responded in September 23, 1997, but the response was found to lack sufficient detail, explanations, or documentation to adequately address the deviations noted during the Aug 26, 1997 inspection. After review of an additional letter dated 26 Nov 1997 showing completion of corrective actions to the objectionable observations reported on the FDA-483 it was concluded that the responses adequately address the deficiencies. The compliance office will recommend approval of any applications listing —— —— UK as an acceptable contract laboratory. They have however requested a reinspection of the stability testing laboratory within the next few months to verify implementation of corrections promised in the response.

- An inspection to Anabolic laboratories was conducted from February 9 to 17, 1997. The Division of Manufacturing and Product Quality (HFD-320) completed the review of the EIR and concurs with the District's recommendation to withhold approval of this NDA. See attached letter.

- Following the Federal register Notice of July 29, 1997, National Environmental Policy Act. Salix Pharmaceutical would like to withdraw the environmental assessment report submitted in the original NDA application (NDA 20-610) for —— They would like to amend the application with a statement claiming categorical exclusion in accordance to 21 CFR Part 25.31(b). This product complies with Tier O, as described in the Guidance. We consider that the claim is adequate.

CONCLUSIONS & RECOMMENDATIONS:

- The company can withdraw the environmental assessment report as solicited.

- The related DMF's are being reviewed and any deficiencies will be conveyed to the holder.

An important issue pending at this time is to have the complete verification that the drug substance produced by both ——— are equivalent.

This NDA is found deficient at this time and is non-approvable.

/S/ 5-22-98
Maria Elena Ysern, MSc
Review Chemist, HFD-180

/S/ 5/22/98
Eric P. Duffy, Ph.D.
Chemistry Team Leader, HFD-180

cc:
Orig. NDA 20-610
HFD-180/Division File
DISTRICT OFFICE
HFD-180/CSO/MMcNeil
HFD-180/LTalarico
HFD-180/MYsern
R/D Init: E.Duffy/5-4-98
MY/dob F/T 5-6-98/WP: c:\wpfiles\chem\N\20610707.1am

APPEARS THIS WAY
ON ORIGINAL

A. DRUG SUBSTANCE

1. DESCRIPTION & CHARACTERIZATION:

A. DESCRIPTION (Vol. 1.003, page 001)

Appearance and Physical Form:
Orange to yellow odorless powder.

Solubility Profile:
The following results were obtained from bulk drug substance manufactured by ———

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

50 pages

DEPARTMENT OF HEALTH & HUMAN SERVICES

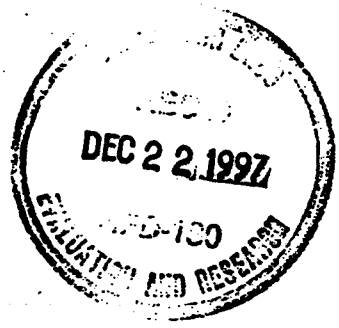
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

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



Dear [redacted]

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] United Kingdom, 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] United Kingdon, as an acceptable contract laboratory of pharmaceutical products. However, we have requested a reinspection of your [redacted], United Kingdom, 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

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

Dear —

This is regarding an inspection of your pharmaceutical testing laboratory in United Kingdom 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 — GRSC, Quality Assurance Manger. 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

Ysern

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,

/S/

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)

Memorandum

Date APR 17 1998

From Consumer Safety Officer, Investigations & Preapproval Compliance Branch/DMPQ (HFD-324)

Subject Concurrence with District Withhold Recommendation, NDA 20-610
Balsalazide (Colazide) Capsules 750 mg

To Kati Johnson, Division of Gastrointestinal and Coagulation, HFD-180

Applicant: Salix
3600 West Bayshore Rd.
Suite 205
Palo Alto, CA 94303

Mfging facility: Anabolic Laboratories, Inc.
17802 Gillette Ave.
Irvine, CA 92614
CF #2011194

Division of Manufacturing and Product Quality (HFD-320) has completed review of the EIR of the subject NDA. The EIR covers an inspection conducted at the Anabolic manufacturing facility from February 9 - 17, 1997. The applicant is listed in the NDA to perform finished product manufacture and testing at this site.

DMPQ concurs with the District's recommendation to withhold approval of this NDA. Our concurrence with LOS-DO's withhold recommendation is based on the following significant GMP observations:

- Failure to perform testing on incoming raw materials. This includes identity testing. Please note that the EIR is mute on whether or not identity testing was performed on raw materials used in the manufacture of the clinical batch.

- Failure to demonstrate that the quality control test methods for balsalazide (dissolution, identification by used to test and release active ingredients and finished product are reproducible and validated. These tests have been transferred from a control lab in the United Kingdom. However, method validation has not been accomplished.

FDA Chemist Lee informed me in a April 16, 1998 tel-con that this deficiency also meant that no comparative sample had been analyzed at both locations. (i.e. A sample of a lot analyzed at [redacted] has not been analyzed at Anabolic Labs using the same methodology to determine if favorably comparative results are obtained.)

Although, Anabolic has provided a response to the FDA-483 that promises correction of the deficiencies, DMPQ continues to support the LOS-DO withhold recommendation. We believe the corrections to the deficiencies relative to this application should be verified during the next EI.

Furthermore, the FDA-483 noted numerous GMP deficiencies not directly related to this pending application. LOS-DO has provided Anabolic Laboratories, Inc., a warning letter addressing these deficiencies. DMPQ also recommends that these deficiencies should be verified as corrected by LOS-DO prior to this application being approved. A copy of the EIR and exhibits are attached for your review. If you have questions, please contact me at (301)-827-0065.

/S/

Randall L. Woods

Attachments - EIR and Exhibits
- Responses from applicant & LOS-DO evaluation

APPEARS THIS WAY
ON ORIGINAL

cc:
HFA-224
HFD-320 R/F
HFD-324 RWoods
HFD-180 MYsern
HFR-PA380 SLee
HFR-PA250 TBogan
HFR-PA255 JConnors
Draft:RLWoods
Concur:BHartman 4/12/98
Final:RLWoods
a:\nda20.180

a:\nda20.610

APPEARS THIS WAY
ON ORIGINAL

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 20610/000
Stamp: 23-JUN-1997
Regulatory Due: 24-MAR-2000
Applicant: SALIX
3600 WEST BAYSHORE RD STE 205
PALO ALTO, CA 94303
Priority: 1S
Org Code: 180

Action Goal:
District Goal: 21-FEB-1998
Brand Name: [redacted] (BALSALAZIDE DISODIUM) 750MG CAP
Estab. Name:
Generic Name: BALSALAZIDE DISODIUM

Dosage Form: (CAPSULE)
Strength: 750 MG

Application Comment: THE USER FEE GOAL DATE IS 6/23/98. (on 08-JUL-1997 by M. MCNEIL (HFD-180) 301-827-7310)

FDA Contacts: M. YSERN (HFD-180) 301-827-7310 , Review Chemist

Overall Recommendation: WITHHOLD on 22-APR-1998 by R. WOODS (HFD-324) 301-827-0062
ACCEPTABLE on 21-MAR-2000 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: 2011194
ANABOLIC LABORATORIES INC
17802 GILLETTE AVE
IRVINE, CA 92714

DMF No: AADA:
Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER

Profile: CHG OAI Status: NONE

Estab. Comment: NOTE: DESPITE THE FACT THAT THE FIRM CERTIFIED IN WRITING THAT THIS FACILITY WOULD NOT BE READY UNTIL 10/13/97, THEY JUST CALLED TO INFORM ME THAT IT WILL NOT BE READY UNTIL 11/3/97. (on 01-OCT-1997 by M. MCNEIL (HFD-180) 301-827-7310)
RE-INSPECTION IS PLANNED FOR 13 MAR 2000 IN ORDER TO VERIFY CORRECTIONS TO THE LAST PRE-APPROVAL FOR THIS NDA. THE INSPECTION WILL ONLY COVER PROFILE CHG. (on 02-MAR-2000 by C. EVERLY (HFR-PA235) 949-798-7722)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	08-JUL-1997				MCNEILM
SUBMITTED TO DO	08-JUL-1997	PS			DAMBROGIOJ
REQUEST CANCELLED	25-JUL-1997				MCNEILM
				APPLICATION WITHDRAWN	
SUBMITTED TO OC	19-AUG-1997				MCNEILM
SUBMITTED TO DO	19-AUG-1997	PS			DAMBROGIOJ
ASSIGNED INSPECTION	08-DEC-1997	PS			KCHILDRE
INSPECTION SCHEDULED	08-DEC-1997		13-FEB-1998		KCHILDRE
INSPECTION PERFORMED	02-MAR-1998		17-FEB-1998		KCHILDRE
SIGNIFICANT PRODUCT SPECIFIC PRE-APPROVAL AND CGMP ISSUES.					
DO RECOMMENDATION	02-MAR-1998			WITHHOLD	KCHILDRE
				DEVIATION FROM DMF/NDA/ANDA	
				EQUIPMENT CLEANING VALIDATION	
				EQUIPMENT QUALIFICATION	
				REPROCESSING/REWORKS	

LOS-DO RECENTLY CONDUCTED A PRODUCT SPECIFIC PRE-APPROVAL INSPECTION OF NDA 20-610, BALSALAZIDE DISODIUM, 750MG ON 2/9-17/98, WHICH REVEALED SIGNIFICANT PRE-APPROVAL SPECIFIC AND GMP DEFICIENCIES. SIGNIFICANT PRE-APPROVAL SPECIFIC DEFICIENCIES INCLUDED: LACK OF POLYMORPHISM AND PARTICLE SIZE DISTRIBUTION SPECIFICATIONS FOR RAW MATERIALS INCLUDING BALSALAZIDE

DISODIUM, LACK OF FINAL BLEND PARTICLE SIZE DISTRIBUTION AND TAPPED DENSITY SPECIFICATIONS FOR BALSALAZIDE, INCOMPLETE FINAL BLEND STUDIES TO ENSURE CONTENT UNIFORMITY ACROSS ALL DRUMS PRIOR TO ENCAPSULATION, FAILURE TO VALIDATE THE TRANSFER OF ANALYTICAL METHODS USED TO TEST AND RELEASE ACTIVE PHARMACEUTICAL INGREDIENTS AND FINISHED DRUG PRODUCTS, FAILURE TO FOLLOW PROCEDURES FOR SAMPLE AND STANDARD PREPARATION AS SPECIFIED IN THE A/NDAS, FAILURE TO VALIDATE CONTENT UNIFORMITY SAMPLING TECHNIQUES, FAILURE TO PERFORM ——— QUALIFICATION STUDIES, FAILURE TO FOLLOW CHANGE CONTROL PROCEDURES WHEN MAKING CHANGES TO BATCH RECORDS, AND FAILURE TO PROPERLY CALIBRATE PRODUCTION AND ANALYTICAL TEST EQUIPMENT WITHIN THE ACTUAL DAY TO DAY RANGE OF OPERATIONS.

SIGNIFICANT GMP DEFICIENCIES INCLUDED: FAILURE TO INITIATE FAILURE REWORK INVESTIGATIONS, FAILURE TO APPROVE REWORK STEPS PRIOR TO IMPLEMENTATION, FAILURE TO ASSESS WHETHER OR NOT THERE WAS SUFFICIENT RATIONALE OR SOUND SCIENCE WHEN RELEASING REWORKED LOTS, FAILURE TO DOCUMENT THE RATIONALE FOR SELECTION OF HARDEST TO CLEAN DRUG PRODUCTS STUDIED IN CLEANING VALIDATION STUDIES, FAILURE TO DOCUMENT MINOR AND MAJOR CLEANING PRACTICES, FAILURE TO DOCUMENT AN ASSESSMENT AS TO WHY TEMPERATURE AND HUMIDITY ARE NOT MONITORED DURING DRUG PRODUCT ENCAPSULATION.

BASED UPON THESE OBSERVATIONS, LOS-DO RECOMMENDS WITHHOLDING APPROVAL OF NDA 20-610, BALSALAZIDE DISODIUM, 750MG.

ELAINE C. MESSA
DISTRICT DIRECTOR
LOS ANGELES DISTRICT

EIR RECEIVED BY OC	09-MAR-1998		WOODSR
OC RECOMMENDATION	22-APR-1998	WITHHOLD EIR REVIEW-CONCUR W/DISTRICT	WOODSR
SUBMITTED TO OC	20-DEC-1999		YSERNM
SUBMITTED TO DO	21-DEC-1999 10D		FERGUSONS
DO RECOMMENDATION	28-DEC-1999	WITHHOLD PEND REG ACTION - SEIZURE	CEVERLY

THE MOST RECENT COMPREHENSIVE GMP INSPECTION OF THE FIRM CONDUCTED 8/11-9/9/99 REVEALED SIGNIFICANT DEFICIENCIES, SUCH AS:

1. LACK OF BLEND VALIDATION ON 11 PRODUCTS.
2. RELEASE OF THREE LOTS OF BULK BLEND THAT FAILED UNIFORMITY SPECIFICATIONS.
3. RELEASE OF FINISHED PRODUCT THAT FAILED IN-PROCESS BLEND UNIFORMITY WITHOUT ADEQUATE FINISHED PRODUCT SAMPLING & TESTING.
4. FAILURE TO TEST FOR ALL ACTIVE INGREDIENTS IN ROUTINE IN-PROCESS BLEND TESTING.
5. INADEQUATE OR LACKING FAILURE INVESTIGATIONS.
6. NO WRITTEN PROCEDURE FOR SAMPLING IN-PROCESS BLENDS DURING VALIDATION.
7. SCALE UP WITHOUT PROSPECTIVE RE-VALIDATION.
8. FAILURE TO FOLLOW CHANGE CONTROL PROCEDURES.
9. NO RAW MATERIAL PARTICLE SIZE SPECIFICATIONS.
10. NO IN-PROCESS PARTICLE SIZE SPECIFICATIONS FOR CHILSONATED PRODUCTS.
11. NO IN-PROCESS PARTICLE SIZE SPECIFICATIONS FOR PRODUCTS WITH A WET GRANULATION STEP.
12. FAILURE TO FOLLOW PROCESS VALIDATION PROTOCOLS.
13. MANUFACTURE OF VALIDATION BATCHES PRIOR TO THE APPROVAL OF A VALIDATION

PROTOCOL.
14. INADEQUATE SAMPLING PLANS TO ASSURE REPRESENTATIVE TESTING OF FINISHED DOSAGE UNITS.
15. NO SET OPERATING PARAMETERS FOR COATING MACHINES USED IN THE MANUFACTURE OF 10 DRUG PRODUCTS.
16. INADEQUATE LABEL CONTROL.

ALTHOUGH THE FIRM HAS NOTIFIED THE DISTRICT THEY ARE READY FOR THEIR PAI, A SEIZURE RECOMMENDATION IS PENDING REVIEW IN THE CENTER. LOS-DO CONTINUES TO RECOMMEND WITHHOLDING APPROVAL OF NDA 20-610 AT THIS TIME.

ACTING DISTRICT DIRECTOR
LOS ANGELES DISTRICT

INSPECTION SCHEDULED	02-MAR-2000	17-MAR-2000		CEVERLY
INSPECTION PERFORMED	20-MAR-2000	20-MAR-2000		CEVERLY
DO RECOMMENDATION	20-MAR-2000		ACCEPTABLE INSPECTION	CEVERLY

A PRODUCT SPECIFIC INSPECTION WAS CONDUCTED 3/15,16 & 20/00. THE INSPECTION WAS LIMITED TO THE REVIEW OF NDA 20-610 (THERE WAS NO GMP COVERAGE). AN FDA-483 WAS ISSUED FOR LACK OF AN SOP FOR , WHICH IS AN IN-PROCESS TEST FOR THIS PRODUCT. THE FIRM JUST PUT THEIR SOP INTO EFFECT ON 1/20/00. THE DISTRICT IS RECOMMENDING APPROVAL FOR THIS SITE TO MANUFACTURE THE PRODUCT.

CARYN EVERLY
PRE APPROVAL MONITOR

OC RECOMMENDATION	21-MAR-2000	ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ

Establishment

DMF No: DA:
Responsibilities:
Profile: CHG OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	10-JAN-2000				YSERNM
SUBMITTED TO DO	10-JAN-2000	GMP			FERGUSONS
ASSIGNED INSPECTION	11-JAN-2000	PS			RBROWN4
INSPECTION PERFORMED	03-MAR-2000		01-MAR-2000		RBROWN4
DO RECOMMENDATION	03-MAR-2000			ACCEPTABLE INSPECTION	RBROWN4
OC RECOMMENDATION	06-MAR-2000			ACCEPTABLE DISTRICT RECOMMENDATION	FERGUSONS

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

DMF No: AADA:
Responsibilities:
Profile: CTL OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	08-JUL-1997				MCNEILM
SUBMITTED TO DO	08-JUL-1997	GMP			EGASM
ASSIGNED INSPECTION	09-JUL-1997	GMP			EGASM
ASSIGNED INSPECTION	18-JUL-1997	GMP			RKIMMEL
INSPECTION PERFORMED	28-AUG-1997		26-AUG-1997		EGASM
ONE ITEM					
DO RECOMMENDATION	07-OCT-1997			ACCEPTABLE	EGASM
				INSPECTION	
OC RECOMMENDATION	07-OCT-1997			ACCEPTABLE	EGASM
				DISTRICT RECOMMENDATION	
SUBMITTED TO OC	20-DEC-1999				YSERNM
SUBMITTED TO DO	21-DEC-1999	10D			EGASM
DO RECOMMENDATION	22-DEC-1999			ACCEPTABLE	EGASM
				BASED ON FILE REVIEW	
BASED ON EI OF 8/97, FUR					
OC RECOMMENDATION	27-DEC-1999			ACCEPTABLE	EGASM
				DISTRICT RECOMMENDATION	

Establishment:

DMF No: AADA:
Responsibilities:
Profile: CSN OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	08-JUL-1997				MCNEILM
SUBMITTED TO DO	08-JUL-1997	GMP			EGASM
ASSIGNED INSPECTION	09-JUL-1997	GMP			EGASM
ASSIGNED INSPECTION	18-JUL-1997	GMP			RKIMMEL
INSPECTION SCHEDULED	22-AUG-1997		21-AUG-1997		DPAULSGR
INSPECTION PERFORMED	22-AUG-1997		21-AUG-1997		DPAULSGR
DO RECOMMENDATION	07-OCT-1997			ACCEPTABLE	EGASM
				INSPECTION	
OC RECOMMENDATION	07-OCT-1997			ACCEPTABLE	EGASM
				DISTRICT RECOMMENDATION	
SUBMITTED TO OC	20-DEC-1999				YSERNM
SUBMITTED TO DO	21-DEC-1999	10D			EGASM
DO RECOMMENDATION	22-DEC-1999			ACCEPTABLE	EGASM
				BASED ON FILE REVIEW	
BASED ON EI OF 8/97, FUR					
OC RECOMMENDATION	27-DEC-1999			ACCEPTABLE	EGASM
				DISTRICT RECOMMENDATION	

Establishment:

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

DMF No: AADA:
Responsibilities:
Profile: CSN OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	08-JUL-1997				MCNEILM
OC RECOMMENDATION	08-JUL-1997			ACCEPTABLE BASED ON PROFILE	EGASM
SUBMITTED TO OC	20-DEC-1999				YSERNM
SUBMITTED TO OC	20-DEC-1999				YSERNM
SUBMITTED TO DO	21-DEC-1999	10D			EGASM
DO RECOMMENDATION	22-DEC-1999			ACCEPTABLE BASED ON FILE REVIEW	EGASM
OC RECOMMENDATION	27-DEC-1999			ACCEPTABLE DISTRICT RECOMMENDATION	EGASM

Establishment

DMF No: AADA:
Responsibilities:
Profile: CSN OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
REQUEST CANCELLED	08-JUL-1997			IRRELEVANT FACILITY/PROFILE	MCNEILM
SUBMITTED TO OC	20-DEC-1999				YSERNM
OC RECOMMENDATION	21-DEC-1999			ACCEPTABLE BASED ON PROFILE	EGASM

Establishment:

DMF No: AADA:
Responsibilities:

Profile: CTL OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	08-JUL-1997				MCNEILM
SUBMITTED TO DO	08-JUL-1997	10D			EGASM
ASSIGNED INSPECTION	09-JUL-1997	GMP			EGASM
ASSIGNED INSPECTION	18-JUL-1997	GMP			RKIMMEL
INSPECTION PERFORMED	22-SEP-1997		28-AUG-1997		EGASM
DO RECOMMENDATION	28-OCT-1997			WITHHOLD INADEQUATE LAB CONTROLS	EGASM

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

RECORDS/REPORTS

EI DISLCOSED DEFICIENCIES REAGRDING FAILURE TO INVESTIGATE OOS RESULTS, NOT MEETING PROGRAM COMMITMENTS, AND INADQUATE PREVENTIVE MAINTENANCE PROGRAM. FIRM'S RESPONSE LETTER WAS INADEQUATE. UNTITLED LETTER ISSUED 10/23/97.

OC RECOMMENDATION	28-OCT-1997	WITHHOLD	EGASM
		DISTRICT RECOMMENDATION EIR REVIEW-CONCUR W/DISTRICT	
DO RECOMMENDATION	23-DEC-1997	ACCEPTABLE	EGASM
		ADEQUATE FIRM RESPONSE	
OC RECOMMENDATION	23-DEC-1997	ACCEPTABLE	EGASM
		DISTRICT RECOMMENDATION	
SUBMITTED TO OC	20-DEC-1999		YSERNM
SUBMITTED TO DO	21-DEC-1999 10D		EGASM
DO RECOMMENDATION	22-DEC-1999	ACCEPTABLE	EGASM
		BASED ON FILE REVIEW	
	BASED ON EI OF 8/97. EUR		
OC RECOMMENDATION	27-DEC-1999	ACCEPTABLE	EGASM
		DISTRICT RECOMMENDATION	

APPEARS THIS WAY
ON ORIGINAL

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 20610/000
Stamp: 23-JUN-1997
Regulatory Due: 24-MAR-2000
Applicant: SALIX
3600 WEST BAYSHORE RD STE 205
PALO ALTO, CA 94303
Priority: 1S
Org Code: 180

Action Goal:
District Goal: 21-FEB-1998
Brand Name [redacted] (BALSALAZIDE DISODIUM) 750MG CAP
Estab. Name:
Generic Name: BALSALAZIDE DISODIUM

Dosage Form: (CAPSULE)
Strength: 750 MG

Application Comment: THE USER FEE GOAL DATE IS 6/23/98. (on 08-JUL-1997 by M. MCNEIL (HFD-180) 301-827-7310)

FDA Contacts: M. YSERN (HFD-180) 301-827-7310 , Review Chemist

Overall Recommendation: WITHHOLD on 22-APR-1998 by R. WOODS (HFD-324) 301-827-0062

Establishment: ~~2011194~~ [redacted]
ANABOLIC INC
17802 GILLETTE AVE
IRVINE, CA 92714

DMF No: AADA:

Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER

Profile: CHG OAI Status: OAI ALERT

Estab. Comment: NOTE: DESPITE THE FACT THAT THE FIRM CERTIFIED IN WRITING THAT THIS FACILITY WOULD NOT BE READY UNTIL 10/13/97, THEY JUST CALLED TO INFORM ME THAT IT WILL NOT BE READY UNTIL 11/3/97. (on 01-OCT-1997 by M. MCNEIL (HFD-180) 301-827-7310)
RE-INSPECTION IS PLANNED FOR 13 MAR 2000 IN ORDER TO VERIFY CORRECTIONS TO THE LAST PRE-APPROVAL FOR THIS NDA. THE INSPECTION WILL ONLY COVER PROFILE CHG. (on 02-MAR-2000 by C. EVERLY (HFR-PA235) 949-798-7722)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	08-JUL-1997				MCNEILM
SUBMITTED TO DO	08-JUL-1997	PS			DAMBROGIOJ
REQUEST CANCELLED	25-JUL-1997				MCNEILM
				APPLICATION WITHDRAWN	
SUBMITTED TO OC	19-AUG-1997				MCNEILM
SUBMITTED TO DO	19-AUG-1997	PS			DAMBROGIOJ
ASSIGNED INSPECTION	08-DEC-1997	PS			KCHILDRE
INSPECTION SCHEDULED	08-DEC-1997		13-FEB-1998		KCHILDRE
INSPECTION PERFORMED	02-MAR-1998		17-FEB-1998		KCHILDRE
	SIGNIFICANT PRODUCT SPECIFIC PRE-APPROVAL AND CGMP ISSUES.				
DO RECOMMENDATION	02-MAR-1998			WITHHOLD	KCHILDRE
				DEVIATION FROM DMF/NDA/ANDA	
				EQUIPMENT CLEANING	
				VALIDATION	
				EQUIPMENT QUALIFICATION	
				REPROCESSING/REWORKS	

LOS-DO RECENTLY CONDUCTED A PRODUCT SPECIFIC PRE-APPROVAL INSPECTION OF NDA 20-610, BALSALAZIDE DISODIUM, 750MG ON 2/9-17/98, WHICH REVEALED SIGNIFICANT PRE-APPROVAL SPECIFIC AND GMP DEFICIENCIES. SIGNIFICANT PRE-APPROVAL SPECIFIC DEFICIENCIES INCLUDED: LACK OF POLYMORPHISM AND PARTICLE SIZE DISTRIBUTION SPECIFICATIONS FOR RAW MATERIALS INCLUDING BALSALAZIDE DISODIUM, LACK OF FINAL BLEND PARTICLE SIZE DISTRIBUTION AND SPECIFICATIONS FOR BALSALAZIDE, INCOMPLETE FINAL BLEND STUDIES TO ENSURE

CONTENT UNIFORMITY ACROSS ALL DRUMS PRIOR TO ENCAPSULATION, FAILURE TO VALIDATE THE TRANSFER OF ANALYTICAL METHODS USED TO TEST AND RELEASE ACTIVE PHARMACEUTICAL INGREDIENTS AND FINISHED DRUG PRODUCTS, FAILURE TO FOLLOW PROCEDURES FOR SAMPLE AND STANDARD PREPARATION AS SPECIFIED IN THE A/NDAS, FAILURE TO VALIDATE CONTENT UNIFORMITY SAMPLING TECHNIQUES, FAILURE TO PERFORM EQUIPMENT QUALIFICATION STUDIES, FAILURE TO FOLLOW CHANGE CONTROL PROCEDURES WHEN MAKING CHANGES TO BATCH RECORDS, AND FAILURE TO PROPERLY CALIBRATE PRODUCTION AND ANALYTICAL TEST EQUIPMENT WITHIN THE ACTUAL DAY TO DAY RANGE OF OPERATIONS.

SIGNIFICANT GMP DEFICIENCIES INCLUDED: FAILURE TO INITIATE FAILURE REWORK INVESTIGATIONS, FAILURE TO APPROVE REWORK STEPS PRIOR TO IMPLEMENTATION, FAILURE TO ASSESS WHETHER OR NOT THERE WAS SUFFICIENT RATIONALE OR SOUND SCIENCE WHEN RELEASING REWORKED LOTS, FAILURE TO DOCUMENT THE RATIONALE FOR SELECTION OF HARDEST TO CLEAN DRUG PRODUCTS STUDIED IN CLEANING VALIDATION STUDIES, FAILURE TO DOCUMENT MINOR AND MAJOR CLEANING PRACTICES, FAILURE TO DOCUMENT AN ASSESSMENT AS TO WHY TEMPERATURE AND HUMIDITY ARE NOT MONITORED DURING DRUG PRODUCT ENCAPSULATION.

BASED UPON THESE OBSERVATIONS, LOS-DO RECOMMENDS WITHHOLDING APPROVAL OF NDA 20-610, BALSALAZIDE DISODIUM, 750MG.

ELAINE C. MESSA
DISTRICT DIRECTOR
LOS ANGELES DISTRICT

EIR RECEIVED BY OC	09-MAR-1998		WOODSR
OC RECOMMENDATION	22-APR-1998	WITHHOLD EIR REVIEW-CONCUR W/DISTRICT	WOODSR
SUBMITTED TO OC	20-DEC-1999		YSERNM
SUBMITTED TO DO	21-DEC-1999 10D		FERGUSONS
DO RECOMMENDATION	28-DEC-1999	WITHHOLD PEND REG ACTION - SEIZURE	CEVERLY

THE MOST RECENT COMPREHENSIVE GMP INSPECTION OF THE FIRM CONDUCTED 8/11-9/9/99 REVEALED SIGNIFICANT DEFICIENCIES, SUCH AS:

1. LACK OF BLEND VALIDATION ON 11 PRODUCTS.
2. RELEASE OF THREE LOTS OF BULK BLEND THAT FAILED UNIFORMITY SPECIFICATIONS.
3. RELEASE OF FINISHED PRODUCT THAT FAILED IN-PROCESS BLEND UNIFORMITY WITHOUT ADEQUATE FINISHED PRODUCT SAMPLING & TESTING.
4. FAILURE TO TEST FOR ALL ACTIVE INGREDIENTS IN ROUTINE IN-PROCESS BLEND TESTING.
5. INADEQUATE OR LACKING FAILURE INVESTIGATIONS.
6. NO WRITTEN PROCEDURE FOR SAMPLING IN-PROCESS BLENDS DURING VALIDATION.
7. SCALE UP WITHOUT PROSPECTIVE RE-VALIDATION.
8. FAILURE TO FOLLOW CHANGE CONTROL PROCEDURES.
9. NO RAW MATERIAL PARTICLE SIZE SPECIFICATIONS.
10. NO IN-PROCESS PARTICLE SIZE SPECIFICATIONS FOR CHILSONATED PRODUCTS.
11. NO IN-PROCESS PARTICLE SIZE SPECIFICATIONS FOR PRODUCTS WITH A WET GRANULATION STEP.
12. FAILURE TO FOLLOW PROCESS VALIDATION PROTOCOLS.
13. MANUFACTURE OF VALIDATION BATCHES PRIOR TO THE APPROVAL OF A VALIDATION PROTOCOL.
14. INADEQUATE SAMPLING PLANS TO ASSURE REPRESENTATIVE TESTING OF FINISHED

ESTABLISHMENT EVALUATION REQUEST
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DOSAGE UNITS.
15. NO SET OPERATING PARAMETERS FOR COATING MACHINES USED IN THE MANUFACTURE OF 10 DRUG PRODUCTS.
16. INADEQUATE LABEL CONTROL.

ALTHOUGH THE FIRM HAS NOTIFIED THE DISTRICT THEY ARE READY FOR THEIR PAI, A SEIZURE RECOMMENDATION IS PENDING REVIEW IN THE CENTER. LOS-DO CONTINUES TO RECOMMEND WITHHOLDING APPROVAL OF NDA 20-610 AT THIS TIME.

ACTING DISTRICT DIRECTOR
LOS ANGELES DISTRICT

scheduled to start 3-13-2000

INSPECTION SCHEDULED 02-MAR-2000 17-MAR-2000 CEVERLY

Establishment:

DMF No:
Responsibilities:
Profile: CHG OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	10-JAN-2000				YSERNM
SUBMITTED TO DO	10-JAN-2000	GMP			FERGUSONS
ASSIGNED INSPECTION	11-JAN-2000	PS			RBROWN4
INSPECTION PERFORMED	03-MAR-2000		01-MAR-2000		RBROWN4
DO RECOMMENDATION	03-MAR-2000			ACCEPTABLE	RBROWN4
OC RECOMMENDATION	06-MAR-2000			INSPECTION ACCEPTABLE DISTRICT RECOMMENDATION	FERGUSONS

Establishment:

DMF No: AADA:
Responsibilities:
Profile: CTL OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	08-JUL-1997				MCNEILM
SUBMITTED TO DO	08-JUL-1997	GMP			EGASM
ASSIGNED INSPECTION	09-JUL-1997	GMP			EGASM
ASSIGNED INSPECTION	18-JUL-1997	GMP			RKIMMEL
INSPECTION PERFORMED	28-AUG-1997		26-AUG-1997		EGASM
DO RECOMMENDATION	07-OCT-1997	ONE ITEM		ACCEPTABLE	EGASM

			INSPECTION	
OC RECOMMENDATION	07-OCT-1997		ACCEPTABLE	EGASM
			DISTRICT RECOMMENDATION	
SUBMITTED TO OC	20-DEC-1999			YSERNM
SUBMITTED TO DO	21-DEC-1999	10D		EGASM
DO RECOMMENDATION	22-DEC-1999		ACCEPTABLE	EGASM
			BASED ON FILE REVIEW	
BASED ON EI OF 8/97, FUR				
OC RECOMMENDATION	27-DEC-1999		ACCEPTABLE	EGASM
			DISTRICT RECOMMENDATION	

Establishment:

DMF No: , AADA:
Responsibilities:
Profile: CSN OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	08-JUL-1997				MCNEILM
SUBMITTED TO DO	08-JUL-1997	GMP			EGASM
ASSIGNED INSPECTION	09-JUL-1997	GMP			EGASM
ASSIGNED INSPECTION	18-JUL-1997	GMP			RKIMMEL
INSPECTION SCHEDULED	22-AUG-1997		21-AUG-1997		DPAULSGR
INSPECTION PERFORMED	22-AUG-1997		21-AUG-1997		DPAULSGR
DO RECOMMENDATION	07-OCT-1997			ACCEPTABLE	EGASM
				INSPECTION	
OC RECOMMENDATION	07-OCT-1997			ACCEPTABLE	EGASM
				DISTRICT RECOMMENDATION	
SUBMITTED TO OC	20-DEC-1999				YSERNM
SUBMITTED TO DO	21-DEC-1999	10D			EGASM
DO RECOMMENDATION	22-DEC-1999			ACCEPTABLE	EGASM
				BASED ON FILE REVIEW	
BASED ON EI OF 8/97, FUR					
OC RECOMMENDATION	27-DEC-1999			ACCEPTABLE	EGASM
				DISTRICT RECOMMENDATION	

Establishment:

DMF No: AADA:
Responsibilities:
Profile: CSN OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	08-JUL-1997				MCNEILM
OC RECOMMENDATION	08-JUL-1997			ACCEPTABLE	EGASM
				BASED ON PROFILE	
SUBMITTED TO OC	20-DEC-1999				YSERNM
SUBMITTED TO OC	20-DEC-1999				YSERNM
SUBMITTED TO DO	21-DEC-1999	10D			EGASM
DO RECOMMENDATION	22-DEC-1999			ACCEPTABLE	EGASM

BASED ON FILE REVIEW

BASED ON EI OF 2/97, FUR
OC RECOMMENDATION 27-DEC-1999 ACCEPTABLE EGASM
DISTRICT RECOMMENDATION

Establishment:

DMF No: AADA:
Responsibilities:
Profile: CSN OAI Status: NONE
Estab. Comment:

.TS

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
REQUEST CANCELLED	08-JUL-1997				MCNEILM
				IRRELEVANT FACILITY/PROFILE	
SUBMITTED TO OC	20-DEC-1999				YSERNM
OC RECOMMENDATION	21-DEC-1999			ACCEPTABLE	EGASM
				BASED ON PROFILE	

Establishment:

DMF No: AADA:
Responsibilities:

Profile: CTL OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	08-JUL-1997				MCNEILM
SUBMITTED TO DO	08-JUL-1997	10D			EGASM
ASSIGNED INSPECTION	09-JUL-1997	GMP			EGASM
ASSIGNED INSPECTION	18-JUL-1997	GMP			RKIMMEL
INSPECTION PERFORMED	22-SEP-1997		28-AUG-1997		EGASM
DO RECOMMENDATION	28-OCT-1997			WITHHOLD	EGASM
				INADEQUATE LAB CONTROLS	
				RECORDS/REPORTS	
EI DISLCOSED DEFICIENCIES REAGRDING FAILURE TO INVESTIGATE OOS RESULTS, NOT MEETING PROGRAM COMMITMENTS, AND INADQUATE PREVENTIVE MAINTENANCE PROGRAM. FIRM'S RESPONSE LETTER WAS INADEQUATE. UNTITLED LETTER ISSUED 10/23/97.					
OC RECOMMENDATION	28-OCT-1997			WITHHOLD	EGASM
				DISTRICT RECOMMENDATION	
				EIR REVIEW-CONCUR W/DISTRICT	
DO RECOMMENDATION	23-DEC-1997			ACCEPTABLE	EGASM
				ADEQUATE FIRM RESPONSE	
OC RECOMMENDATION	23-DEC-1997			ACCEPTABLE	EGASM
				DISTRICT RECOMMENDATION	
SUBMITTED TO OC	20-DEC-1999				YSERNM

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

SUBMITTED TO DO	21-DEC-1999 10D		EGASM
DO RECOMMENDATION	22-DEC-1999	ACCEPTABLE	EGASM
		BASED ON FILE REVIEW	
BASED ON EI OF 8/97, FUR			
OC RECOMMENDATION	27-DEC-1999	ACCEPTABLE	EGASM
		DISTRICT RECOMMENDATION	

APPEARS THIS WAY
ON ORIGINAL

Electronic Mail Message

Date: 03/06/2000 8:36:00 AM
From: EES Questions (EESQUESTIONS)
To: Alice Kacuba (KACUBAA)
Cc: Maria Ysern (YSERNM)
Subject: Re:

I have just been notified that the inspection for Anabolic has been scheduled to begin March 13, 2000. The district cannot give approval until they can verify the firm's corrections to a previous PAI.

Hopefully we can make the PDUFA date.

Janine

APPEARS THIS WAY
ON ORIGINAL

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 20610/000
Stamp: 23-JUN-1997
Regulatory Due: 24-MAR-2000
Applicant: SALIX
3600 WEST BAYSHORE RD STE 205
PALO ALTO, CA 94303
Priority: 1S
Org Code: 180

Action Goal:
District Goal: 21-FEB-1998
Brand Name: [redacted] (BALSALAZIDE DISODIUM) 750MG CAP
Estab. Name:
Generic Name: BALSALAZIDE DISODIUM

Dosage Form: (CAPSULE)
Strength: 750 MG

Application Comment: THE USER FEE GOAL DATE IS 6/23/98. (on 08-JUL-1997 by M. MCNEIL (HFD-180) 301-827-7310)
FDA Contacts: M. YSERN (HFD-180) 301-827-7310 , Review Chemist

Overall Recommendation: WITHHOLD on 22-APR-1998 by R. WOODS (HFD-324) 301-827-0062

Establishment: 2011194
ANABOLIC INC
17802 GILLETTE AVE
IRVINE, CA 92714

DMF No:
AADA:
Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER

Profile: CHG
OAI Status: OAI ALERT
Estab. Comment: NOTE: DESPITE THE FACT THAT THE FIRM CERTIFIED IN WRITING THAT THIS FACILITY WOULD NOT BE READY UNTIL 10/13/97, THEY JUST CALLED TO INFORM ME THAT IT WILL NOT BE READY UNTIL 11/3/97. (on 01-OCT-1997 by M. MCNEIL (HFD-180) 301-827-7310)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	08-JUL-1997				MCNEILM
SUBMITTED TO DO	08-JUL-1997	PS			DAMBROGIOJ
REQUEST CANCELLED	25-JUL-1997				MCNEILM
				APPLICATION WITHDRAWN	
SUBMITTED TO OC	19-AUG-1997				MCNEILM
SUBMITTED TO DO	19-AUG-1997	PS			DAMBROGIOJ
ASSIGNED INSPECTION	08-DEC-1997	PS			KCHILDRE
INSPECTION SCHEDULED	08-DEC-1997		13-FEB-1998		KCHILDRE
INSPECTION PERFORMED	02-MAR-1998		17-FEB-1998		KCHILDRE
SIGNIFICANT PRODUCT SPECIFIC PRE-APPROVAL AND CGMP ISSUES.					
DO RECOMMENDATION	02-MAR-1998			WITHHOLD	KCHILDRE
				DEVIATION FROM DMF/NDA/ANDA	
				EQUIPMENT CLEANING VALIDATION	
				EQUIPMENT QUALIFICATION	
				REPROCESSING/REWORKS	

LOS-DO RECENTLY CONDUCTED A PRODUCT SPECIFIC PRE-APPROVAL INSPECTION OF NDA 20-610, BALSALAZIDE DISODIUM, 750MG ON 2/9-17/98, WHICH REVEALED SIGNIFICANT PRE-APPROVAL SPECIFIC AND GMP DEFICIENCIES. SIGNIFICANT PRE-APPROVAL SPECIFIC DEFICIENCIES INCLUDED: LACK OF POLYMORPHISM AND PARTICLE SIZE DISTRIBUTION SPECIFICATIONS FOR RAW MATERIALS INCLUDING BALSALAZIDE DISODIUM, LACK OF FINAL BLEND PARTICLE SIZE DISTRIBUTION AND TAPPED DENSITY SPECIFICATIONS FOR BALSALAZIDE, INCOMPLETE FINAL BLEND STUDIES TO ENSURE CONTENT UNIFORMITY ACROSS ALL DRUMS PRIOR TO ENCAPSULATION, FAILURE TO VALIDATE THE TRANSFER OF ANALYTICAL METHODS USED TO TEST AND RELEASE ACTIVE PHARMACEUTICAL INGREDIENTS AND FINISHED DRUG PRODUCTS, FAILURE TO FOLLOW PROCEDURES FOR SAMPLE AND STANDARD PREPARATION AS SPECIFIED IN THE A/NDAS, FAILURE TO VALIDATE CONTENT UNIFORMITY SAMPLING TECHNIQUES, FAILURE TO PERFORM [redacted] R EQUIPMENT QUALIFICATION STUDIES, FAILURE TO

FOLLOW CHANGE CONTROL PROCEDURES WHEN MAKING CHANGES TO BATCH RECORDS, AND FAILURE TO PROPERLY CALIBRATE PRODUCTION AND ANALYTICAL TEST EQUIPMENT WITHIN THE ACTUAL DAY TO DAY RANGE OF OPERATIONS.

SIGNIFICANT GMP DEFICIENCIES INCLUDED: FAILURE TO INITIATE FAILURE REWORK INVESTIGATIONS, FAILURE TO APPROVE REWORK STEPS PRIOR TO IMPLEMENTATION, FAILURE TO ASSESS WHETHER OR NOT THERE WAS SUFFICIENT RATIONALE OR SOUND SCIENCE WHEN RELEASING REWORKED LOTS, FAILURE TO DOCUMENT THE RATIONALE FOR SELECTION OF HARDEST TO CLEAN DRUG PRODUCTS STUDIED IN CLEANING VALIDATION STUDIES, FAILURE TO DOCUMENT MINOR AND MAJOR CLEANING PRACTICES, FAILURE TO DOCUMENT AN ASSESSMENT AS TO WHY TEMPERATURE AND HUMIDITY ARE NOT MONITORED DURING DRUG PRODUCT ENCAPSULATION.

BASED UPON THESE OBSERVATIONS, LOS-DO RECOMMENDS WITHHOLDING APPROVAL OF NDA 20-610, BALSALAZIDE DISODIUM, 750MG.

ELAINE C. MESSA
DISTRICT DIRECTOR
LOS ANGELES DISTRICT

EIR RECEIVED BY OC	09-MAR-1998		WOODSR
OC RECOMMENDATION	22-APR-1998	WITHHOLD EIR REVIEW-CONCUR W/DISTRICT	WOODSR
SUBMITTED TO OC	20-DEC-1999		YSERNM
SUBMITTED TO DO	21-DEC-1999 10D		FERGUSONS
DO RECOMMENDATION	28-DEC-1999	WITHHOLD PEND REG ACTION - SEIZURE	CEVERLY

THE MOST RECENT COMPREHENSIVE GMP INSPECTION OF THE FIRM CONDUCTED 8/11-9/9/99 REVEALED SIGNIFICANT DEFICIENCIES, SUCH AS:

1. LACK OF BLEND VALIDATION ON 11 PRODUCTS.
2. RELEASE OF THREE LOTS OF BULK BLEND THAT FAILED UNIFORMITY SPECIFICATIONS.
3. RELEASE OF FINISHED PRODUCT THAT FAILED IN-PROCESS BLEND UNIFORMITY WITHOUT ADEQUATE FINISHED PRODUCT SAMPLING & TESTING.
4. FAILURE TO TEST FOR ALL ACTIVE INGREDIENTS IN ROUTINE IN-PROCESS BLEND TESTING.
5. INADEQUATE OR LACKING FAILURE INVESTIGATIONS.
6. NO WRITTEN PROCEDURE FOR SAMPLING IN-PROCESS BLENDS DURING VALIDATION.
7. SCALE UP WITHOUT PROSPECTIVE RE-VALIDATION.
8. FAILURE TO FOLLOW CHANGE CONTROL PROCEDURES.
9. NO RAW MATERIAL PARTICLE SIZE SPECIFICATIONS.
10. NO IN-PROCESS PARTICLE SIZE SPECIFICATIONS FOR ~~—~~ PRODUCTS.
11. NO IN-PROCESS PARTICLE SIZE SPECIFICATIONS FOR PRODUCTS WITH A WET GRANULATION STEP.
12. FAILURE TO FOLLOW PROCESS VALIDATION PROTOCOLS.
13. MANUFACTURE OF VALIDATION BATCHES PRIOR TO THE APPROVAL OF A VALIDATION PROTOCOL.
14. INADEQUATE SAMPLING PLANS TO ASSURE REPRESENTATIVE TESTING OF FINISHED DOSAGE UNITS.
15. NO SET OPERATING PARAMETERS FOR COATING MACHINES USED IN THE MANUFACTURE OF 10 DRUG PRODUCTS.
16. INADEQUATE LABEL CONTROL.

ALTHOUGH THE FIRM HAS NOTIFIED THE DISTRICT THEY ARE READY FOR THEIR PAI, A SEIZURE RECOMMENDATION IS PENDING REVIEW IN THE CENTER. LOS-DO CONTINUES TO RECOMMEND WITHHOLDING APPROVAL OF NDA 20-610 AT THIS TIME.

ACTING DISTRICT DIRECTOR

LOS ANGELES DISTRICT

Establishment: [redacted]

DMF No: AADA:
Responsibilities: R
Profile: CHG OAI Status: NONE
Estab. Comment:

NUMBER) (on 10-JAN-2000 by M. YSERN (HFD-180) 301-827-7310)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	10-JAN-2000				YSERNM
SUBMITTED TO DO	10-JAN-2000	GMP			FERGUSONS
ASSIGNED INSPECTION	11-JAN-2000	PS			RBROWN4

Establishment: [redacted]

DMF No: AADA:
Responsibilities:
Profile: CTL OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	08-JUL-1997				MCNEILM
SUBMITTED TO DO	08-JUL-1997	GMP			EGASM
ASSIGNED INSPECTION	09-JUL-1997	GMP			EGASM
ASSIGNED INSPECTION	18-JUL-1997	GMP			RKIMMEL
INSPECTION PERFORMED	28-AUG-1997		26-AUG-1997		EGASM
ONE ITEM					
DO RECOMMENDATION	07-OCT-1997			ACCEPTABLE	EGASM
				INSPECTION	
OC RECOMMENDATION	07-OCT-1997			ACCEPTABLE	EGASM
				DISTRICT RECOMMENDATION	
SUBMITTED TO OC	20-DEC-1999				YSERNM
SUBMITTED TO DO	21-DEC-1999	10D			EGASM
DO RECOMMENDATION	22-DEC-1999			ACCEPTABLE	EGASM
				BASED ON FILE REVIEW	
BASED ON EI OF 8/97, FUR					
OC RECOMMENDATION	27-DEC-1999			ACCEPTABLE	EGASM
				DISTRICT RECOMMENDATION	

Establishment: [redacted]

DMF AADA:
Responsibilities:
Profile: CSN OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	08-JUL-1997				MCNEILM
SUBMITTED TO DO	08-JUL-1997	GMP			EGASM
ASSIGNED INSPECTION	09-JUL-1997	GMP			EGASM
ASSIGNED INSPECTION	18-JUL-1997	GMP			RKIMMEL
INSPECTION SCHEDULED	22-AUG-1997		21-AUG-1997		DPAULSGR
INSPECTION PERFORMED	22-AUG-1997		21-AUG-1997		DPAULSGR
DO RECOMMENDATION	07-OCT-1997			ACCEPTABLE	EGASM
				INSPECTION	
OC RECOMMENDATION	07-OCT-1997			ACCEPTABLE	EGASM
				DISTRICT RECOMMENDATION	
SUBMITTED TO OC	20-DEC-1999				YSERNM
SUBMITTED TO DO	21-DEC-1999	10D			EGASM
DO RECOMMENDATION	22-DEC-1999			ACCEPTABLE	EGASM
				BASED ON FILE REVIEW	
BASED ON EI OF 8/97, FUR					
OC RECOMMENDATION	27-DEC-1999			ACCEPTABLE	EGASM
				DISTRICT RECOMMENDATION	

Establishment: [redacted]

[redacted]

DMF No: [redacted] AADA:

Responsibilities: [redacted]

Profile: CSN OAI Status: NONE

Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	08-JUL-1997				MCNEILM
OC RECOMMENDATION	08-JUL-1997			ACCEPTABLE	EGASM
				BASED ON PROFILE	
SUBMITTED TO OC	20-DEC-1999				YSERNM
SUBMITTED TO OC	20-DEC-1999				YSERNM
SUBMITTED TO DO	21-DEC-1999	10D			EGASM
DO RECOMMENDATION	22-DEC-1999			ACCEPTABLE	EGASM
				BASED ON FILE REVIEW	
BASED ON EI OF 2/97, FUR					
OC RECOMMENDATION	27-DEC-1999			ACCEPTABLE	EGASM
				DISTRICT RECOMMENDATION	

Establishment: [redacted]

[redacted]

DMF No: [redacted] AADA:

Responsibilities: [redacted]

Profile: CSN OAI Status: NONE

Estab. Comment: [redacted]

[redacted]

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
REQUEST CANCELLED	08-JUL-1997				MCNEILM
				IRRELEVANT FACILITY/PROFILE	
SUBMITTED TO OC	20-DEC-1999				YSERNM

OC RECOMMENDATION 21-DEC-1999 ACCEPTABLE EGASM
BASED ON PROFILE

Establishment:

DMF No: AADA:

Responsibilities:

Profile: CTL OAI Status: NONE

Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	08-JUL-1997				MCNEILM
SUBMITTED TO DO	08-JUL-1997	10D			EGASM
ASSIGNED INSPECTION	09-JUL-1997	GMP			EGASM
ASSIGNED INSPECTION	18-JUL-1997	GMP			RKIMMEL
INSPECTION PERFORMED	22-SEP-1997		28-AUG-1997		EGASM
DO RECOMMENDATION	28-OCT-1997			WITHHOLD	EGASM
				INADEQUATE LAB CONTROLS RECORDS/REPORTS	
EI DISLCOSED DEFICIENCIES REAGRDING FAILURE TO INVESTIGATE OOS RESULTS, NOT MEETING PROGRAM COMMITMENTS, AND INADQUATE PREVENTIVE MAINTENANCE PROGRAM. FIRM'S RESPONSE LETTER WAS INADEQUATE. UNTITLED LETTER ISSUED 10/23/97.					
OC RECOMMENDATION	28-OCT-1997			WITHHOLD	EGASM
				DISTRICT RECOMMENDATION EIR REVIEW-CONCUR W/DISTRICT	
DO RECOMMENDATION	23-DEC-1997			ACCEPTABLE	EGASM
				ADEQUATE FIRM RESPONSE	
OC RECOMMENDATION	23-DEC-1997			ACCEPTABLE	EGASM
				DISTRICT RECOMMENDATION	
SUBMITTED TO OC	20-DEC-1999				YSERNM
SUBMITTED TO DO	21-DEC-1999	10D			EGASM
DO RECOMMENDATION	22-DEC-1999			ACCEPTABLE	EGASM
				BASED ON FILE REVIEW	
BASED ON EI OF 8/97, FUR					
OC RECOMMENDATION	27-DEC-1999			ACCEPTABLE	EGASM
				DISTRICT RECOMMENDATION	

APPEARS THIS WAY
ON ORIGINAL

for May 27, 1998

Application: NDA 20610/000
Stamp: 23-JUN-1997 Regulatory Due: 23-JUN-1998
Applicant: SALIX
3600 WEST BAYSHORE RD STE 205
PALO ALTO, CA 94303

Priority: 1S
Action Goal:
Brand Name: COLAZIDE (BALSALAZIDE DISODIUM)750MG CAP
Established Name:
Generic Name: BALSALAZIDE DISODIUM
Dosage Form: CAP (CAPSULE)
Strength: 750 MG

Org Code: 180
District Goal: 21-FEB-1998

FDA Contacts: M. YSERN (HFD-180) 301-443-0483 , Review Chemist

Overall Recommendation:

WITHHOLD on 22-APR-1998 by R. WOODS (HFD-324) 301-827-0062

Establishment: 2011194
ANABOLIC INC
17802 GILLETTE AVE
IRVINE, CA 92714

DMF No:
AADA No:

Profile: CHG
Last Milestone: OC RECOMMENDATION
Milestone Date 22-APR-1998
Decision: WITHHOLD
Reason: EIR REVIEW-CONCUR W/DISTRIC

OAI Status: OAI ALERT

Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER

Establishment:

DMF No:
AADA No:

Profile: CTL
Last Milestone: OC RECOMMENDATION
Milestone Date 07-OCT-1997
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

OAI Status: NONE

Responsibilities:

Establishment:

DMF No:
AADA No:

Profile: CSN
Last Milestone: OC RECOMMENDATION
Milestone Date 07-OCT-1997
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

OAI Status: NONE

Responsibilities:

Establishment: [redacted] DMF No: [redacted]
AADA No:

[redacted]

Profile: CSN OAI Status: NONE Responsibilities: [redacted]
Last Milestone: OC RECOMMENDATION
Milestone Date 08-JUL-1997
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment: [redacted] DMF No:
AADA No:

[redacted]

Profile: CTL OAI Status: NONE Responsibilities:
Last Milestone: OC RECOMMENDATION
Milestone Date 23-DEC-1997
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

APPEARS THIS WAY
ON ORIGINAL

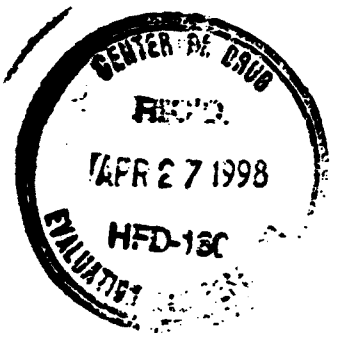
DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date APR 17 1998

From Consumer Safety Officer, Investigations & Preapproval Compliance Branch/DMPQ (HFD-324)



Subject Concurrence with District Withhold Recommendation, NDA 20-610
Balsalazide (Colazide) Capsules 750 mg

To Kati Johnson, Division of Gastrointestinal and Coagulation, HFD-180

Applicant: Salix
3600 West Bayshore Rd.
Suite 205
Palo Alto, CA 94303

Mfging facility: Anabolic Laboratories, Inc.
17802 Gillette Ave.
Irvine, CA 92614
CF #2011194

Division of Manufacturing and Product Quality (HFD-320) has completed review of the EIR of the subject NDA. The EIR covers an inspection conducted at the Anabolic manufacturing facility from February 9 - 17, 1997. The applicant is listed in the NDA to perform finished product manufacture and testing at this site.

DMPQ concurs with the District's recommendation to withhold approval of this NDA. Our concurrence with LOS-DO's withhold recommendation is based on the following significant GMP observations:

- Failure to perform testing on incoming raw materials. This includes identity testing. Please note that the EIR is mute on whether or not identity testing was performed on raw materials used in the manufacture of the clinical batch.

- Failure to demonstrate that the quality control test methods for balsalazide (dissolution, identification by HPLC and UV and potency by HPLC) used to test and release active ingredients and finished product are reproducible and validated. These tests have been transferred from

However, method validation has not been accomplished.

FDA Chemist Lee informed me in a April 16, 1998 tel-con that this deficiency also meant that no comparative sample had been analyzed at both locations. (i.e. A sample of a lot analyzed at [redacted] has not been analyzed at Anabolic Labs using the same methodology to determine if favorably comparative results are obtained.)

Although, Anabolic has provided a response to the FDA-483 that promises correction of the deficiencies, DMPQ continues to support the LOS-DO withhold recommendation. We believe the corrections to the deficiencies relative to this application should be verified during the next EI.

Furthermore, the FDA-483 noted numerous GMP deficiencies not directly related to this pending application. LOS-DO has provided Anabolic Laboratories, Inc., a warning letter addressing these deficiencies. DMPQ also recommends that these deficiencies should be verified as corrected by LOS-DO prior to this application being approved. A copy of the EIR and exhibits are attached for your review. If you have questions, please contact me at (301)-827-0065.

Randall L. Woods

Randall L. Woods

Attachments - EIR and Exhibits
- Responses from applicant and LOS-DO evaluation

APPEARS THIS WAY
ON ORIGINAL

Number of Pages Redacted 60

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Commercial Information