

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022205Orig1s000

CHEMISTRY REVIEW(S)

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Application:	NDA 22205/000	Action Goal:	
Date:	17-JUL-2007	District Goal:	26-FEB-2010
Regulatory:	27-APR-2010		
Applicant:	SALIX PHARMS 1700 PERIMETER PARK DR MORRISVILLE, NC 27560	Brand Name:	BALSALAZIDE DISODIUM TABLETS
		Estab. Name:	
		Generic Name:	BALSALAZIDE DISODIUM TABLETS
Priority:	3S	Product Number; Dosage Form; Ingredient; Strengths	
Org. Code:	180		001; TABLET; BALSALAZIDE DISODIUM; 1100MG

Application Comment: SPONSOR STATES THAT "ALL SITES READY FOR INSPECTION". (on 16-AUG-2007 by L. CHASEY (HFC-60) 301-796-4528)
THIS IS A RESUBMISSION - THE PDUFA GOAL DATE IS: 27-APR-2010. (on 01-MAR-2010 by J. DAVID () 301-796-4247)

FDA Contacts:	J. DAVID	Project Manager	301-796-4247
	M. KOWBLANSKY	Review Chemist	301-796-1390
	M. KOWBLANSKY	Team Leader	301-796-1390

Overall Recommendation:	WITHHOLD	on 12-APR-2010	by M. STOCK	(HFD-320)	301-796-4753
	ACCEPTABLE	on 17-MAR-2008	by S. FERGUSON	(HFD-322)	301-796-3247

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
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Establishment: CFN: (b) (4)
 (b) (4)

FEI: (b) (4)

DMF No:

AADA:

Responsibilities: FINISHED DOSAGE PACKAGER

Estab. Comment:

Profile: TABLETS, PROMPT RELEASE

OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	16-AUG-2007				LATHEY
OC RECOMMENDATION	16-AUG-2007			ACCEPTABLE BASED ON PROFILE	FERGUSONS
SUBMITTED TO OC	01-MAR-2010				DAVIDJE
OC RECOMMENDATION	29-MAR-2010			ACCEPTABLE BASED ON PROFILE	STOCKM

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)



DMF No: AADA:

Responsibilities: FINISHED DOSAGE STABILITY TESTER

Estab. Comment:

Profile: CONTROL TESTING LABORATORY

OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	16-AUG-2007				LATHEY
OC RECOMMENDATION	16-AUG-2007			ACCEPTABLE BASED ON PROFILE	FERGUSONS
SUBMITTED TO OC	01-MAR-2010				DAVIDJE
OC RECOMMENDATION	02-MAR-2010			ACCEPTABLE BASED ON PROFILE	KIEL

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

Estab. Comment: SPONSOR LIST THE FIRM NAME AS (b) (4)

(b) (4)
(on 16-AUG-2007 by L. CHASEY
(HFC-60) 301-796-4528)

Profile: NON-STERILE BULK BY CHEMICAL SYNTHESIS **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	16-AUG-2007				LATHEY
SUBMITTED TO DO	16-AUG-2007	GMP Inspection			ADAMSS
DO RECOMMENDATION	25-SEP-2007			ACCEPTABLE BASED ON FILE REVIEW	ADAMSS
COMMENDATION	26-SEP-2007			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS
SUBMITTED TO OC	01-MAR-2010				DAVIDJE
OC RECOMMENDATION	01-MAR-2010			ACCEPTABLE BASED ON PROFILE	STOCKM

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: 2011194 FEI: 2011194
NEXGEN PHARMA INC
17802 GILLETTE AVE
IRVINE, CA 92614

DMF No: AADA: N 020610

Responsibilities: FINISHED DOSAGE MANUFACTURER

Estab. Comment: SPONSOR LIST THE FIRM NAME NEXGEN PHARMA, INC., 17802 GILLETTE AVE., IRVINE, CA 92614. (on 16-AUG-2007 by L. CHASEY (HFC-60) 301-796-4528)
THE FIRM FORMERLY KNOWN AS ANABOLIC LABORATORIES IS NOW NAMED NEXGEN PHARMA. SAME FEI, SAME ADDRESS. (on 21-NOV-2007 by C. MCNAB (HFR-PA250) 949-608-4472)

Profile: TABLETS, PROMPT RELEASE **OAI Status:** OAI ALERT

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	16-AUG-2007				LATHEY
SUBMITTED TO DO	16-AUG-2007	10-Day Letter			FERGUSONS
ASSIGNED INSPECTION TO IB	16-OCT-2007	Product Specific			CEVERLY
INSPECTION SCHEDULED	24-JAN-2008		07-MAR-2008		CEVERLY
INSPECTION PERFORMED	07-MAR-2008		07-MAR-2008		KHAM.PHOMMACHANH

This pre-announced full GMP and Pre Approval inspection of a solid oral dosage form drug and dietary supplement manufacturer was conducted in response to CDER EES assignment requesting coverage of ANDA 40-885, (Butalbital, Acetaminophen, and Caffeine) sponsored by Nexgen Pharma Inc and NDA 22-205 (Balsalazide Disodium Tablets) sponsored by Salix Pharmaceuticals Inc as well as part of LOS-DO FY08 performance goal work-plan under FACTS Assignment ID 4323560. The inspection followed Compliance Programs 7346.832 (Pre-Approval Inspections) and 7356.002 (Drug Manufacturing Inspections). Profile classes manufactured at this firm are TCM, CHG, TTR, and POW. CARS reported in FACTS for voluntary corrections that was corrected and verified.

The previous PAI and GMP inspection was conducted on 5/10/2006 and was classified as No Action Indicated (NAI).

This current inspection revealed some observations in GMP and Pre-Approval. GMP observations noted were not having second person review on lab notebook, not monitoring temperature control for retain samples, and not destroying discontinued labels. Pre-approval observations noted were not following USP method procedures and no deviation report generated for caps used without certificate of analysis. An FDA-483, Inspectional Observations, was issued to Mr. Robert van Osdel, Vice President of RA/QA and Product Development. Some of the observations noted were corrected and verified during the inspection. Mr. van Osdel stated that the firm will respond to the FDA-483 in writing within fifteen days. The firm is currently drug registered.

INSPECTION PERFORMED	07-MAR-2008	07-MAR-2008		CEVERLY
DO RECOMMENDATION	14-MAR-2008		ACCEPTABLE	CEVERLY

A PRODUCT SPECIFIC PRE-APPROVAL AND GMP INSPECTION WAS CONDUCTED 3/3/08 - 3/7/08. OBSERVATIONS INCLUDED:

(b) (4)

-RESERVE SAMPLES OF DRUGS WERE NOT STORED UNDER LABELED CONDITIONS (PEG, COLAZAL CAPSULES, ASCOMP WITH CODEINE).

- OUTDATED LABELS WERE NOT DESTROYED.

- PACKAGING WAS STARTED ON BALSALAZIDE LOT 318231 (NDA 22-205) WITH A LOT OF CAPS WITHOUT A COA. THE LOT WAS REPACKAGED WITH A DIFFERENT LOT OF CAPS HOWEVER NO DEVIATION REPORT WAS GENERATED & NO INVESTIGATION WAS PERFORMED.

DISSOLUTION RESULTS FOR BALSALAZIDE TABLETS LOT 318231 AT 90 MINUTES REPORTED IN THE NDA ARE NOT ACCURATE. A NOTE IN THE RAW DATA INDICATES THAT THE DATA CALCULATION WAS INVALIDATED AND RESULTS WERE RECALCULATED. THE RECALCULATED RESULTS WERE AVAILABLE AT THE TIME OF THE NDA SUBMISSION. THE

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FIRM COULD NOT EXPLAIN WHY THE RESULTS WERE RECALCULATED OR WHY THE "NEW" RESULTS WERE NOT SUBMITTED IN THE APPLICATION. BOTH SETS OF RESULTS WERE WITHIN SPECIFICATION (SEE BELOW)

TAB# ORIG NEW
(b) (4)

THESE DEFICIENCIES WERE NOT SIGNIFICANT ENOUGH TO WARRANT WITHHOLDING APPROVAL; THEREFORE LOS-DO RECOMMENDS APPROVAL.

CARYN MCNAB
PRE-APPROVAL MANAGER

OC RECOMMENDATION	17-MAR-2008		ACCEPTABLE	FERGUSONS
			DISTRICT RECOMMENDATION	
SUBMITTED TO OC	01-MAR-2010			DAVIDJE
SUBMITTED TO DO	01-MAR-2010	10-Day Letter		STOCKM
DO RECOMMENDATION	05-APR-2010		WITHHOLD	CEVERLY
			(b) (4)	PEND REG ACTION - WARNING LTR

CARYN MCNAB, PAI MANAGER

OC RECOMMENDATION	12-APR-2010		WITHHOLD	STOCKM
PENDING WL			DISTRICT RECOMMENDATION	

**FDA CDER EES
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APPEARS THIS WAY ON
ORIGINAL

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: [REDACTED] (b) (4) FEI: [REDACTED] (b) (4)

DMF No: [REDACTED] AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Estab. Comment: SPONSOR LIST THE FIRM NAME AS [REDACTED] (b) (4)
[REDACTED] (b) (4)
[REDACTED] (on 16-AUG-2007 by L. CHASEY (HFC-60) 301-796-4528)

Profile: NON-STERILE BULK BY CHEMICAL SYNTHESIS OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	16-AUG-2007				LATHEY
SUBMITTED TO DO	16-AUG-2007	GMP Inspection			ADAMSS
ASSIGNED INSPECTION TO IB	24-SEP-2007	GMP Inspection			ADAMSS
INSPECTION SCHEDULED	24-SEP-2007		[REDACTED] (b) (4)		ADAMSS
INSPECTION PERFORMED	[REDACTED] (b) (4)		[REDACTED]		ADAMSS
DO RECOMMENDATION	07-MAR-2008			ACCEPTABLE ADEQUATE FIRM RESPONSE INSPECTION	ADAMSS
OC RECOMMENDATION	07-MAR-2008			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS
SUBMITTED TO OC	01-MAR-2010				DAVIDJE
OC RECOMMENDATION	01-MAR-2010			ACCEPTABLE BASED ON PROFILE	STOCKM

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: **CFN:** [REDACTED] **FEI:** [REDACTED] (b) (4)

DMF No: (b) (4) **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

Estab. Comment: SPONSOR LIST THE FIRM NAME AS [REDACTED] (b) (4)
[REDACTED] (b) (4)
[REDACTED] (on 16-AUG-2007 by L. CHASEY
(HFC-60) 301-796-4528)

Profile: NON-STERILE BULK BY CHEMICAL SYNTHESIS **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	16-AUG-2007				LATHEY
SUBMITTED TO DO	16-AUG-2007	GMP Inspection			ADAMSS
DO RECOMMENDATION	25-SEP-2007			ACCEPTABLE BASED ON FILE REVIEW	ADAMSS
COMMENDATION	26-SEP-2007			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS
SUBMITTED TO OC	01-MAR-2010				DAVIDJE
OC RECOMMENDATION	01-MAR-2010			ACCEPTABLE BASED ON PROFILE	STOCKM

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NIKOO N MANOCHEHRI KALANTARI
02/14/2012

NDA 22-205

Giazo (balsalazide disodium) tablets

1.1 g per tablet

Salix Pharmaceuticals

Marie Kowblansky, Ph.D.

Office of New Drug Quality Assessment

Division of New Drug Quality Assessment II, Branch IV

**DIVISION OF GASTROINTESTINAL AND COAGULATION
DRUG PRODUCTS**

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Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA 22-205
2. REVIEW #: 4
3. REVIEW DATE: December 15, 2011
4. REVIEWER: Marie Kowblansky, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original Submission	16-JUL-2007
amendment (BZ)	21-NOV-2007
Amendment (BL)	15-FEB-2008
Amendment (BL)	10-MAR-2008
Resubmission	30-JUN-2008
amendment (BL)	19-SEP-2008
Resubmission	26-OCT-2009

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Resubmission	03-AUG-2011
Amendment	07-DEC-2011

7. NAME & ADDRESS OF APPLICANT:

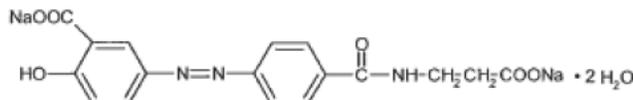
Name: Salix Pharmaceuticals, Inc.
Address: 1700 Perimeter Park Drive
Morrisville, NC 27560
Representative: Benjamin Burgin
Telephone: (919) 447-3404
Fax: (919)-447-3410

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: **Giazo**
- b) Non-Proprietary Name (USAN): **balsalazide disodium**
- c) Code Name/# (ONDCS only): **NA**
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: **3**
 - Submission Priority: **Standard**

Chemistry Review Data Sheet

9. **LEGAL BASIS FOR SUBMISSION:** 505(b)(1)
10. **PHARMACOL. CATEGORY:** Treatment of ulcerative colitis.
11. **DOSAGE FORM:** tablet
12. **STRENGTH/POTENCY:** 1.1 g per tablet
13. **ROUTE OF ADMINISTRATION:** oral
14. **Rx/OTC DISPENSED:** Rx OTC
15. **SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):**
 SPOTS product – Form Completed
 Not a SPOTS product
16. **CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:**



CHEMICAL NAME: (E)-5-[[4-[[[(2-carboxyethyl) amino]carbonyl] phenyl]azo]-2-hydroxybenzoic acid, disodium salt, dihydrate

MOLECULAR FORMULA: C₁₇H₁₃N₃O₆Na₂•2H₂O

MOLECULAR WEIGHT: 437.32

17. **RELATED/SUPPORTING DOCUMENTS:**A. **DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS	
(b) (4)		(b) (4)	rug substance	(b) (4)	1	Adequate	11/17/2011	Adequate
	2							
	3				4			adequate information in NDA (see review #1)

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	20-610	Colazal (balsalazide disodium) capsules
IND	38,492	

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not Applicable*		
EES	ACCEPTABLE	December 15, 2011	M. Stock
Pharm/Tox	Not Applicable*		
Biopharm	Not Applicable*		
LNC	Not Applicable*		
Methods Validation	Not required*		
DMETS	Not Applicable*		
EA	Not required**		
Microbiology	Not Applicable*		

* Not applicable to information provided in this resubmission.

** Categorical exclusion granted in accordance to 21CFR§25.31

The Chemistry Review for NDA 22-205

The Executive Summary

I. Recommendations

A. Recommendations and Conclusions on Approvability

This application has provided sufficient CMC information to assure the identity, strength, purity, and quality of the commercial drug product. Labels and labeling contain all required CMC information. The Office of Compliance has issued an overall Acceptable recommendation for all facilities involved in the manufacture of this product. From the ONDQA perspective, this application may be approved.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable –

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

See reviews # 1 and # 2 for a complete CMC description of the drug substance and drug product. A revised drug substance specification, bringing the drug substance into conformance with the USP monograph, has been provided in the current resubmission

B. Description of How the Drug Product is Intended to be Used

Three tablets administered twice daily (for a total dose of 6.6 g/day), over an eight week period.

C. Basis for Approvability

In review # 2 (June 2008) it was concluded that the application had provided sufficient information to assure the identity, strength, purity, and quality of the commercial drug product over a 36-month expiration dating period with room temperature storage. Also, at that time (March 2008) the Office of Compliance issued an overall recommendation of ACCEPTABLE for all facilities involved in manufacture of the product. Consequently, "Approval" of this NDA was recommended from the ONDQA perspective, but because of clinical deficiencies the NDA was not approved.

Review #3 (October 2009) dealt primarily with clinical issues, no new CMC information was submitted, only labeling information (package insert, carton, and container). It was concluded that all labels and labeling contained the required CMC information, and consequently, were considered acceptable. On April 10, 2010, however, the Office of Compliance issued a new overall recommendation of WITHHOLD for the proposed manufacturing facilities. Therefore, ONDQA recommended that this NDA not be approved until the acceptability of all manufacturing sites was established.

Review #4 (August 2011): With the current resubmission, two of the three drug substance manufacturing sites identified in previous submissions have been withdrawn, leaving (b) (4)

Chemistry Assessment Section

(b) (4) as the sole supplier. DMF (b) (4) was reviewed in connection with this submission and found acceptable. The Office of Compliance has issued an overall recommendation of ACCEPTABLE for all facilities involved in the manufacture of this product (see appended EES report). The new information submitted to this NDA continues to provide assurance that the commercial product will have the required identity, strength, purity, and quality. The labeling has not been revised since the last submission and continues to be acceptable. Consequently, from the ONDQA perspective this NDA may be Approved.

III. Administrative**A. Reviewer's Signature**

Signed electronically

B. Endorsement Block

CMC Lead: Marie Kowblansky, Ph.D.

Branch Chief: Moo-Jhong Rhee, Ph.D.

C. CC Block

4 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARIE KOWBLANSKY
01/09/2012

MOO JHONG RHEE
01/09/2012
Chief, Branch IV

NDA 22-205

Giazo (balsalazide disodium) tablets

1.1 g per tablet

Salix

**DIVISION OF GASTROINTESTINAL AND COAGULATION
DRUG PRODUCTS**

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DOSAGE FORMS AND STRENGTHS	Error! Bookmark not defined.
Chemistry Assessment.....	8
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	8
S DRUG SUBSTANCE [balsalazide].....	8
<i>See Review #1</i>	8
P DRUG PRODUCT [Giazo (balsalazide disodium) tablets].....	8
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II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1.....	8
A. Labeling & Package Insert.....	8
III. List Of Deficiencies To Be Communicated -- none	9

Chemistry Review Data Sheet

1. **NDA 22-205**
2. **REVIEW #:** 3
3. **REVIEW DATE:** April 15, 2010
4. **REVIEWER:** Marie Kowblansky, Ph.D.

5. **PREVIOUS DOCUMENTS:**

<u>Previous Documents</u>	<u>Document Date</u>
Original Submission	16-JUL-2007
amendment (BZ)	21-NOV-2007
Amendment (BL)	15-FEB-2008
Amendment (BL)	10-MAR-2008
Resubmission	30-JUN-2008
amendment (BL)	19-SEP-2008

6. **SUBMISSION(S) BEING REVIEWED:**

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Resubmission	26-OCT-2009
amendment (LC)	10-JAN-2010

7. **NAME & ADDRESS OF APPLICANT:**

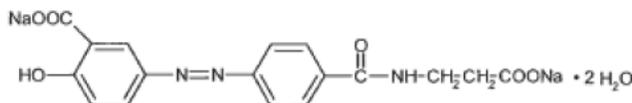
Name: Salix Pharmaceuticals, Inc.
 Address: 1700 Perimeter Park Drive
 Morrisville, NC 27560
 Representative: Benjamin Burgin
 Telephone: (919) 447-3404
 Fax: (919)-447-3410

8. **DRUG PRODUCT NAME/CODE/TYPE:**

- a) Proprietary Name: **Giazo**
- b) Non-Proprietary Name (USAN): **balsalazide disodium**
- c) Code Name/# (ONDCS only): **NA**
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: **3**
 - Submission Priority: **Standard**

Chemistry Review Data Sheet

9. **LEGAL BASIS FOR SUBMISSION:** 505(b)(1)
10. **PHARMACOL. CATEGORY:** Treatment of ulcerative colitis.
11. **DOSAGE FORM:** tablet
12. **STRENGTH/POTENCY:** 1.1 g per tablet
13. **ROUTE OF ADMINISTRATION:** oral
14. **Rx/OTC DISPENSED:** Rx OTC
15. **SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):**
 SPOTS product – Form Completed
 Not a SPOTS product
16. **CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:**



CHEMICAL NAME: (E)-5-[[4-[[[(2-carboxyethyl) amino]carbonyl] phenyl]azo]-2-hydroxybenzoic acid, disodium salt, dihydrate

MOLECULAR FORMULA: C₁₇H₁₃N₃O₆Na₂•2H₂O

MOLECULAR WEIGHT: 437.32

17. **RELATED/SUPPORTING DOCUMENTS:**A. **DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	2	(b) (4)	Drug substance	7	Adequate	5/14/2006	**
	2		Drug substance	7	Adequate	3/29/2006	**
	2		Drug substance	7	Adequate	1/18/ 2005	**
	3		(b) (4)	4			adequate information provided in NDA

DMF was formally reviewed (in writing) and found adequate on the date indicated in the "Date Review Completed" column. All amendments to the DMF received after the formal review, have been evaluated in connection with the current resubmission of the NDA, but no written review has been prepared. The status indicated in the table is based on the additional evaluation of the DMF that has been conducted.

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

Chemistry Review Data Sheet

- 3 – Reviewed previously and no revision since last review
 - 4 – Sufficient information in application
 - 5 – Authority to reference not granted
 - 6 – DMF not available
 - 7 – Other (explain under "Comments")
- ² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	20-610	Colazal balsalazide disodium capsules
IND	38,492	

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not Applicable		
EES	WITHHOLD	12-April-2010	M. Stock
Pharm/Tox	Not Applicable		
Biopharm	Pending		
LNC	Not Applicable		
Methods Validation	Not required		
DMETS	pending		
EA	Not required*		
Microbiology	Not Applicable		

* Categorical exclusion granted in accordance to 21CFR§25.31

Chemistry Assessment Section

The Chemistry Review for NDA 22-205

The Executive Summary

I. Recommendations

A. Recommendations and Conclusions on Approvability

This NDA application has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. Labels and labeling contain all required CMC information. However, facilities proposed for the manufacture of this product are not in compliance with cGMP and the Office of Compliance (OC) has issued an overall Withhold recommendation. Therefore, from the CMC perspective, this NDA should not be approved until the manufacturing site deficiencies are resolved and the OC finds all sites acceptable.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable –

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

See reviews # 1 and # 2.

B. Description of How the Drug Product is Intended to be Used

Three tablets administered twice daily (for a total dose of 6.6 g/day), over an eight week period.

C. Basis for Approvability or Not-Approval Recommendation

In review # 2 it was concluded that the application had provided sufficient information to assure the identity, strength, purity, and quality of the commercial drug product over a 36-month expiration dating period (when stored at 15-30°C in 40 cc to 950 cc HDPE bottles with induction seal closures). Also, at that time (March 2008) the Office of Compliance issued an overall recommendation of ACCEPTABLE for all manufacturing facilities involved in the production of the product. Consequently, from the CMC perspective “Approval” of this NDA was recommended, but because of clinical deficiencies the NDA was not approved.

With the current resubmission, which deals primarily with clinical issues, no new CMC information has been submitted, only labeling information (package insert, carton, and container). All labels and labeling have the required CMC information, and consequently, are considered acceptable. The CMC information which was found acceptable at the conclusion of review #2 continues to be acceptable. On April 10, 2010, however, the Office of Compliance issued a new overall recommendation of WITHHOLD for the proposed manufacturing facilities. Therefore, from the CMC perspective, this NDA is not recommended for approval until the acceptability of all manufacturing sites is established.

Chemistry Assessment Section

III. Administrative**A. Reviewer's Signature**

Signed electronically

B. Endorsement Block

Chemistry Reviewer: Marie Kowblansky, Ph.D.
Branch Chief: Moo-Jhong Rhee, Ph.D.

C. CC Block

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immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22205	ORIG-1	SALIX PHARMACEUTICA LS INC	BALSALAZIDE DISODIUM TABLETS

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/s/

MARIE KOWBLANSKY
04/14/2010

MOO JHONG RHEE
04/14/2010
Chief, Branch III

NDA 22-205

Giazo (balsalazide disodium) Tablets

Salix Pharmaceuticals

Maria Ysern, MSc.

Review Chemist

**Office of New Drug Quality Assessment
Division of Pre-marketing Assessment II
Branch III**

**CMC REVIEW OF NDA 22-205
For the Division of Division of Gastroenterology Products**

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CMC Review Data Sheet

CMC Review Data Sheet

1. NDA 22-205
2. REVIEW : #2
3. REVIEW DATE: Oct 14, 2008
4. REVIEWER: Maria Ysern, MSc.
5. PREVIOUS DOCUMENTS:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original Submission	16-JUL-2007
BZ amendment	21-NOV-2007
BL amendment	15-FEB-2008
BL amendment	10-MAR-2008
Amendment	20-MAR-2008

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Resubmission	30-JUN-2008
BL amendment	19-SEP-2008

7. NAME & ADDRESS OF APPLICANT:

Name: Salix Pharmaceuticals, Inc.
Address: 1700 Perimeter Park Drive, Morrisville, NC 27560
Representative: Benjamin Burgin
Telephone: (919) 447-3404
Fax: (919)-447-3410
e-mail: Benjamin.Burgin@salix.com

8. DRUG PRODUCT NAME/CODE/TYPE:

CMC Review Data Sheet

- a) Proprietary Name: Giazio (balsalazide disodium) Tablets
b) Non-Proprietary Name: Balsalazide disodium
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 3
 - Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Treatment of mildly to moderately active ulcerative colitis. Anti-inflammatory.

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 1.1 g / tablet

13. ROUTE OF ADMINISTRATION: Oral

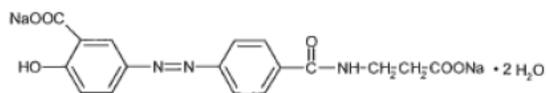
14. Rx/OTC DISPENSED: Rx

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____ SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Molecular formula: $C_{17}H_{13}N_3O_6 \cdot 2H_2O \cdot 2Na$

Molecular weight: 437.32

CMC Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Balsalazide disodium	3	II	April 14, 2006	Adequate
	II	(b) (4)	Balsalazide disodium	3	II	March 29, 2006	Adequate
	II	(b) (4)	Balsalazide disodium	3	II	October 1, 2004	Adequate
	III	(b) (4)	(b) (4)	4			(b) (4)

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	38,492	Pre-NDA meeting
NDA	20-610	Colazal

CMC Review Data Sheet

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Overall Acceptable	17-MAR-08	
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A, according to the current ONDQA policy		
DMETS	N/A		
EA	Categorical exclusion in accordance to 21CFR§25.31		
Microbiology	N/A		

Executive Summary Section

The CMC Review for NDA 22-205

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product and all facilities involved are in compliance with cGMP.

Therefore, from CMC perspective, this NDA is recommended for “Approval” pending corrections to the label

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.

N/A

II. Summary of CMC Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) **Drug Substance:** *See Review #1*

(2) **Drug Product:** *See Review #1*

In the resubmission, the sponsor submitted additional stability data to extend the originally proposed expiration dating period.

The new stability data support a 36 month expiration dating when balsalazide disodium tablets are stored at 15-30°C in 40 cc to 950 cc HDPE bottles with an induction seal closure system. Accelerated stability data at 40°C/75% RH indicate that the balsalazide disodium tablets are stable for up to 6 months under these conditions.

B. Description of How the Drug Product is Intended to be Used

The proposed dosage and administration is three 1.1 g tablets twice daily (BID) for a total daily dose of 6.6 g for 8 weeks.

C. Basis for Approvability Recommendation

Executive Summary Section

This NDA provided adequate information on the raw material controls, manufacturing process specifications, and containers/closure. It also provided sufficient stability data to assure identity, strength, purity and quality of the drug product during the 36 month of expiration dating period. The Office of Compliance has issued an “Acceptable” overall recommendation for all the facilities involved.

III. Administrative**A. Reviewer’s Signature:**

(See appended electronic signature page)

Maria Ysem, MSc., Review Chemist.

B. Endorsement Block:

(See appended electronic signature page)

Moo-Jhong Rhee, Ph.D., Branch Chief, Branch 3, ONDQA

C. CC Block: entered electronically in DFS

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immediately following this page

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this page is the manifestation of the electronic signature.**

/s/

Maria Ysern
11/21/2008 01:39:06 PM
CHEMIST

Moo-Jhong Rhee
11/21/2008 01:41:06 PM
CHEMIST
Chief, Branch III

NDA 22-205

Giazo (balsalazide disodium) Tablets

Salix Pharmaceuticals

Maria Ysern, MSc.

Review Chemist

**Office of New Drug Quality Assessment
Division of Pre-marketing Assessment II
Branch III**

**CMC REVIEW OF NDA 22-205
For the Division of Division of Gastroenterology Products**

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CMC Review Data Sheet

CMC Review Data Sheet

1. NDA 22-205
2. REVIEW #: 1
3. REVIEW DATE: 16-ABR-2008
4. REVIEWER: Maria Ysern, MSc.
5. PREVIOUS DOCUMENTS: None
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original Submission	16-JUL-2007
BZ amendment	21-NOV-2007
BL amendment	15-FEB-2008
BL amendment	10-MAR-2008
Amendment	20-MAR-2008

7. NAME & ADDRESS OF APPLICANT:

Name: Salix Pharmaceuticals, Inc.
Address: 1700 Perimeter Park Drive, Morrisville, NC 27560
Representative: Benjamin Burgin
Telephone: (919) 447-3404
Fax: (919)-447-3410
e-mail: Benjamin.Burgin@salix.com

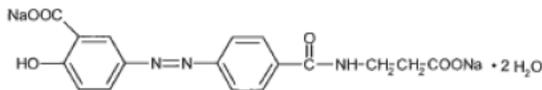
8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Giazio (balsalazide disodium) Tablets
- b) Non-Proprietary Name: Balsalazide disodium
- c) Code Name/# (ONDQA only): N/A
- d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 3
 - Submission Priority: standard

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

CMC Review Data Sheet

10. PHARMACOL. CATEGORY: Treatment of mildly to moderately active ulcerative colitis. Anti-inflammatory.
11. DOSAGE FORM: Tablets
12. STRENGTH/POTENCY: 1.1 g (3 tablets twice daily for a total daily dose of 6.6 g for eight weeks).
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: Rx
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____ SPOTS product – Form Completed
✓ Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Molecular formula: C₁₇H₁₃N₃O₆ · 2H₂O · 2 Na
Molecular weight: 437.32

CMC Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

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	II	(b) (4)	Balsalazide disodium	3	II	March 29, 2006	Adequate
	II	(b) (4)	Balsalazide disodium	3	II	October 1, 2004	Adequate
	III	(b) (4)	(b) (4)	4			(b) (4)

¹ Action codes for DMF Table:

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6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	38,492	Pre-NDA meeting
NDA	20-610	Colazal

CMC Review Data Sheet

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Overall Acceptable	17-MAR-08	
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A, according to the current ONDQA policy		
DMETS	N/A		
EA	Categorical exclusion in accordance to 21CFR§25.31		
Microbiology	N/A		

Executive Summary Section

The CMC Review for NDA 22-205

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. All facilities involved are in compliance with cGMP. From a CMC perspective, this NDA is recommended for "Approval" pending corrections to the label.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.

N/A

II. Summary of CMC Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Substance:

Information concerning the procedures and controls for assuring the proper identification, quality, purity and strength of the drug substance, balsalazide disodium, are incorporated by reference to (b) (4) and DMF (b) (4) for the information on the drug substance characteristics and to NDA 20610/S-004 approved 12 January 2004 and NDA 20-610/S-005 approved 04 March 2004.

Also refer to (b) (4)

(b) (4)

(b) (4)

Balsalazide disodium is a pro-drug composed of 5-amino salicylic acid (mesalamine) and carrier, 4-amino benzoyl- β -alanine (4-ABA), linked by an azo bond. When administered orally, balsalazide is delivered intact to the colon where bacterial azoreductases cleave the azo bond releasing mesalamine, the active moiety) and 4-ABA. The mechanism of action of mesalamine is unknown but appears to be local to the gastrointestinal mucosa rather than systemic. It is believed that 5-ASA diminishes inflammation by blocking cyclooxygenase and inhibiting prostaglandin production in the colon.

Executive Summary Section

The manufacturing process and process controls utilized to assure the identification, quality, purity and strength of the drug substance for use in the tablet dosage form are (b) (4) for the treatment of mildly to moderately active ulcerative colitis.

(2) Drug Product:

The characteristics of the drug product were identified during development and goals of obtaining a higher drug load than that of the current capsule formulation, and obtaining (b) (4)

Studies were conducted to identify the appropriate excipients for this formulation. No overages are included in the balsalazide disodium tablet formulation.

Balsalazide disodium will be provided as a solid oral tablet dosage form. Each tablet contains 1100 mg of balsalazide disodium, hypromellose and magnesium stearate.

The commercial batch size approximately (b) (4) and the manufacturing process consists of (b) (4)

All excipients used in the manufacture of basalazide disodium tablets are compendial and are tested in accordance to their respective compendial monographs. Regulatory specifications for the drug product are provided and include: appearance, identification, IR, HPLC, assay, individual unspecified impurities, total impurities, dissolution, (b) (4) uniformity of dosage units and microbial limits.

An overall absence of degradation products was found and is consistent with the capsule dosage form and the drug substance, both of which do not exhibit degradation.

The Reference Standard Batch 061610344 is being used and was previously qualified and characterized for use under NDA 20-610.

Bulk balsalazide disodium tablets are packaged into (b) (4)

Balsalazide disodium tablets will be packaged for commercial distribution in 40cc (oblong), 500cc and 950cc high density polyethylene white pharmaceutical bottles with a

(b) (4) child resistant closure (CRC) with an induction seal liner. The primary stability for balsalazide disodium tablets is based on data from 3 bulk tablet batches packaged in the 40 cc, 500 cc and 950 cc HDPE containers. Salix has used a bracketing matrix stability design to support the stability of the single, 1100 mg dosage strength of balsalazide disodium tablets.

The stability data support a 24-month expiration date when balsalazide disodium tablets are stored at 15-30°C in 40 cc to 950 cc HDPE bottles with an induction

Executive Summary Section

seal closure system. Stress studies showed that balsalazide disodium tablets do not need protection from light.

Salix certifies that the approval of this application does not significantly increase the use of the active moiety so no environmental assessment is required.

B. Description of How the Drug Product is Intended to be Used

The proposed dosage and administration is three 1.1 g tablets twice daily (BID) for a total daily dose of 6.6 g for 8 weeks.

C. Basis for Approvability Recommendation

This NDA provided adequate information on the raw material controls, manufacturing process specifications, and containers/closure. It also provided sufficient stability data to assure identity, strength, purity and quality of the drug product during the shelf life.

Since it will be an “Approvable” action for clinical issues, corrections to the label will be notified to the applicant and the package insert content will be discussed at a later time.

The Office of Compliance has issued an “Acceptable” overall recommendation for all the facilities involved.

III. Administrative**A. Reviewer’s Signature:**

(See appended electronic signature page)

Maria Ysem, MSc., Review Chemist.

B. Endorsement Block:

(See appended electronic signature page)

Moo-Jhong Rhee, Ph.D., Branch Chief, Branch 3, ONDQA

C. CC Block: entered electronically in DFS

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/s/

Maria Ysern
4/24/2008 04:03:13 PM
CHEMIST

Moo-Jhong Rhee
4/24/2008 04:05:00 PM
CHEMIST
Chief, Branch III

Initial Quality Assessment
Branch 3
Pre-Marketing Assessment Division 2

OND Division: Division of Gastroenterology Products
NDA: 22-205
Applicant: Salix Pharmaceuticals
Stamp Date: 7/17/2007
Received by PAL: 7/24/2007
Review Date: 8/24/2007
PDUFA Date: 5/17/2008
Filing Meeting: 8/27/2007
Proposed Trademark: To be determined
Established Name: Balsalazide disodium
Dosage Form: Immediate release tablets
Route of Administration: oral
Indication: Ulcerative colitis

P.A.L.: Marie Kowblansky, PhD

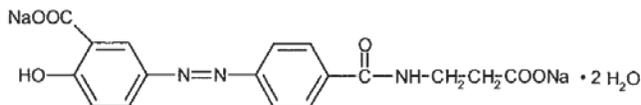
	YES	NO
ONDQA Fileability:	<input checked="" type="checkbox"/>	
Comments for 74-Day Letter		<input checked="" type="checkbox"/>

A. Summary

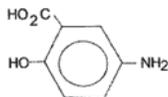
Balsalazide disodium Tablets is an immediate release tablet formulation intended for the treatment of ulcerative colitis in adults. Each tablet contains 1100 mg balsalazide disodium with instructions to administer three tablets twice daily (for a total dose of 6.6 g/day), over an eight week period. Balsalazide disodium is a prodrug of 5-amino salicylic acid (mesalamine); both have been approved separately for use in a number of other products. This application is being filed under 505(b)(1) and references Salix's NDA 20-610 (balsalazide disodium capsules) and IND 38,492 for information not provided directly to this application.

Drug Substance

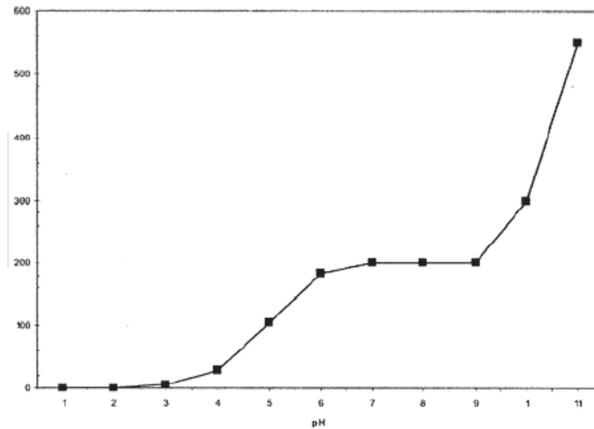
The drug substance in the product is balsalazide disodium dihydrate



When administered orally, balsalazide is delivered to the colon where bacterial enzymes cleave the azo bond, releasing the active drug mesalamine



According to the applicant, the mesalamine is locally acting in the GI tract, with only minimal systemic absorption. Due to the solubility profile of balsalazide (as reproduced below from the submission)



it remains relatively insoluble as it passes through the low pH regions of the stomach and upper intestine until it reaches the required site of action.

Balsalazide disodium will be manufactured at three alternate sites: (b) (4). Information regarding the manufacturing process and characterization of the drug substance from each site is referenced to the respective DMFs (b) (4).

The specification includes testing for appearance, solubility, sodium, water content (b) (4), heavy metals, residual solvents (b) (4), tapped density, assay, five identified impurities (NMT (b) (4) each), unidentified impurities (NMT (b) (4) for each), and total impurities (NMT (b) (4)). The applicant argues that based on Decision Tree 3 of ICH Q6A, drug substance particle size acceptance criteria are not required.

Test results for four batches of drug substance showed that four of the identified potential impurities were not detected in any of the batches, with the fifth one being present at a level of only (b) (4), and unidentified impurities were reported to be present at levels below (b) (4). The (b) (4) content in these batches ranged between (b) (4) content ranged between (b) (4).

Drug Product

Balsalazide Disodium Tablets will be marketed as a coated immediate-release tablet containing 1100 mg balsalazide disodium, debossed with BZT on one side. The to-be-marketed formulation is the same as the one that was used in Phase 3 clinical trials. The composition will be as given below, with all excipients being compendial:

Component	Reference to Quality Standard	Function	mg/tablet
(b) (4) Tablet			
Balsalazide disodium ^a	In-house standard	Active ingredient	1100
Hypromellose	USP	(b) (4)	(b) (4)
Magnesium stearate	USP		
(b) (4)	USP		
(b) (4)			
(b) (4)	USP	Coating	~4.32
(b) (4)	USP	Solvent	qs
(b) (4)	USP	Solvent	qs
Opadry II Yellow	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	USP	(b) (4)
Total Tablet Weight			1192.32
(b) (4)			

The manufacturing process for the tablets involves (b) (4). In-process testing includes measurement of: (b) (4) (b) (4) tablet weight, thickness, hardness, friability, and disintegration.

The proposed regulatory specification for the finished product is reproduced from the submission:

Table 2.3.P-13. Balsalazide Disodium Tablets Regulatory Specifications

Attribute	Method Number	Specification
Appearance	Visual	(b) (4) yellow coated oval shaped tablet (approximately 0.370" x 0.748"), debossed with BZT on one side and plain on the other
Identification		(b) (4)
IR		(b) (4)
HPLC		
Assay		
Individual unspecified impurities		
Total impurities		
Dissolution		
(b) (4)		
Uniformity of dosage units		

(The specification also includes microbial limit testing that does not appear in the above tabulation.)

While this specification includes limits for individual unidentified impurities (referred to as “unspecified impurities”) and total impurities, no acceptance criteria have been defined for identified impurities. The submission identifies 8 possible impurities, but no data for these impurities are reported in the batch analysis data.

An acceptance criterion for (b) (4) is also absent from the specification (although the batch analysis data indicate that such testing was performed, this was only for information purposes). The (b) (4) acceptance criterion for (b) (4) in the balsalazide disodium drug substance indicates that the drug substance i (b) (4).

While the above specification appropriately calls for testing of (b) (4) content (b) (4) (b) (4) the batch analysis data do not include any results of such testing. In the absence of these test results, the appropriateness of the proposed (b) (4) (b) (4) limit cannot be evaluated.

Dissolution is measured in unbuffered water and is slower than is usually observed in immediate release dosage forms. This is illustrated by the comparative dissolution profiles of the more typical Colazal capsules (upper curve) and the proposed Balsalazide tablet (lower curve)



The relatively slow dissolution rate is not a concern since the dissolution profile is not a measure of *in vivo* performance, rather a manufacturing control. In view of the long dissolution test, it may be appropriate to add an acceptance criterion at 30 minutes, in addition to the proposed 90-minute requirement; batch analysis data (obtained only for informational purposes) showed (b) (4) (b) (4) dissolution in 30 minutes.

The product will be packaged in 40 cc to 950 cc containers containing 6 to 500 tablets. Stability studies were conducted using a matrix bracketing approach to include the different packaging configurations. Up to 12 months of real-time stability data and 6 months of accelerated data have been submitted in the application. However, the stability specification only defines acceptance criteria for assay and dissolution. Although it also requires testing for impurities and (b) (4) (b) (4) no acceptance criteria are defined; the only requirement is to “record result”.

Salix appropriately claims categorical exclusion from filing an environmental assessment on the basis that the estimated concentration of the substance at the point of entry into the aquatic environment will be below one part per billion.

Inspection requests for the facilities involved in the manufacture of the drug substance and drug product have been entered into EES. (See appended list.)

At the time of this review, the applicant has not yet proposed a product name. Once a name is submitted, it will need to be evaluated for conformance to current FDA naming practice.

B. Critical issues for review

- Although the submission states that the decision to exclude particle size testing from the drug substance specification was based on ICH Q6A, Decision Tree 3, actual data to support this decision do not appear to have been submitted.
- Based on the batch analysis data, the proposed acceptance criterion for (b) (4) in the drug substance appears too high. This should be carefully assessed.
- The drug product registration specification will need to be closely evaluated to determine 1) if additional testing attributes (as discussed above) need to be added and 2) if (b) (4) is too liberal a limit for (b) (4).
- The stability specification is quite different from the registration specification. It will need revision to include limits for impurities and other attributes, as necessary.
- When evaluating the applicant's proposed 24-month expiration for the product, the acceptability of the matrix bracketing stability design will need to be closely scrutinized.

C. Comments for 74-Day Letter -- None

Marie Kowblansky, PhD
Pharmaceutical Assessment Lead

8/28/2007
Date

Moo-Jhong Rhee, PhD
Branch Chief

8/28/2007
Date

MANUFACTURING SITES

NDA 22-205

Drug Substance



Drug Product Manufacture

Nexgen Pharma
Irvine, CA:
CFN 2011194

Contact: (949) 260-3770

Stability Testing:



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/s/

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