

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-361

CHEMISTRY REVIEW(S)

NDA 21-361

Xifaxan (Rifaximin) Tablets, 200 mg.

Salix Pharmaceuticals, Inc.

**Ramesh Sood, Ph. D.
Division of Special Pathogen and Immunologic Drug
Products, HFD-590.**



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2 REVIEW # 3

3 REVIEW DATE 13-May-2004

4 REVIEWER Ramesh K Sood, Ph D

5 PREVIOUS DOCUMENTS

<u>Previous Documents</u>	<u>Document Date</u>
Original Submission	21-Dec-2001
BC	7-May-2002
BC	9-May-2002
Amendment	6-June-2002
IR Letter	20-June-2002
CMC Review #1	
Amendment	22-July-2002
Amendment	5-Aug-2002
Amendment (BC)	14-Aug-2002

6 SUBMISSION(S) BEING REVIEWED

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment (BC)	31-Oct-2003
Resubmission	25-Nov-2003
Amendment	12-April-2004
Amendment	21-Apr-2004
Amendment	26-Apr-2004

7 NAME & ADDRESS OF APPLICANT



CHEMISTRY REVIEW

Chemistry Review Data Sheet

Name Salix Pharmaceuticals, Inc
8540 Colonnade Center Drive
Suite 501
Address Raleigh, NC 27615
Ph 888-802-9956
Fax 919-862-1095

Representative —

Telephone —

8 DRUG PRODUCT NAME/CODE/TYPE

- a) Proprietary Name Xifaxan
- b) Non-Proprietary Name (USAN) rifaximin tablets
- c) Code Name/# (ONDC only) L-105
- d) Chem Type/Submission Priority (ONDC only)
 - Chem Type 1
 - Submission Priority S

9 LEGAL BASIS FOR SUBMISSION

NDA under 505(b)(1)

10 PHARMACOL CATEGORY

Antibacterial

11 DOSAGE FORM

Tablets

12 STRENGTH/POTENCY

200 mg

13 ROUTE OF ADMINISTRATION

Oral

14 Rx/OTC DISPENSED x Rx OTC



CHEMISTRY REVIEW



Chemistry Review Data Sheet

15 SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)

_____ SPOTS product – Form Completed

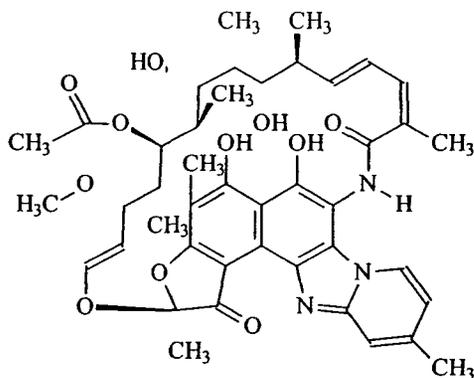
 x Not a SPOTS product

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

(2S,16Z,18E,20S,21S,22R,23R,24R,-
25S,26S,27S,28E)-5,6,21,23,25-
pentahydroxy-27-methoxy-2,4,11,16,-
20,22,24,26-octamethyl-2,7-(epoxy-
pentadeca[1,11,13]trienimino)-
benzofuro[4,5-e]pyrido[1,2- α]-
benzimidazole-1,15(2H)-dione,25-
acetate

Registry Number [80621-81-4]

C₄₃H₅₁N₃O₁₁ Formula Weight 785.89



17 RELATED/SUPPORTING DOCUMENTS

A DMFs

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
/	II	/	/	1	Adequate	3/1/04	Reviewed by R Sood
/	II	/	/	1	Adequate	3-Dec-2003	Reviewed by R Sood
/	III	/	/	1	Adequate	13-Feb-2004	Reviewed by



CHEMISTRY REVIEW



Chemistry Review Data Sheet

/	III	/	/	7	n/a		R. Sood DMF supports the use of as per review #1
/	III	/	/	7	n/a		DMF is adequate as per review #1
/	III	/	/	7	n/a		are satisfactory for as per review #1
/	III	/	/	3	n/a		DMF reviewed by R Sood and found adequate on 8/1/2002

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 N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18 STATUS

CONSULTS/ CMC RELATED	RECOMMENDATION	DATE	REVIEWER

Chemistry Review Data Sheet

REVIEWS			
Biometrics	N/A		
EES	Acceptable	3/11/2004	
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	Pending		
DMETS	Approved	4/28/2004	Alina R Mahmud
EA	Exclusion acceptable		O K in review 1
Microbiology	N/A		

The Chemistry Review for NDA 21-361

The Executive Summary

I. Recommendations

A Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls (CMC) standpoint, this NDA is recommended for approval. The firm has addressed all the CMC related questions in a satisfactory manner.

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

N/A

II Summary of Chemistry Assessments

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

Drug Substance The active pharmaceutical ingredient (API), rifaximin, is an crystalline powder soluble in organic solvents and practically insoluble in water. The API is manufactured by _____

The quality of the incoming API is controlled through specification which include identification, assay, impurities, particle size and residual solvents. In this review cycle, we were able to negotiate more appropriate particle size acceptance criterion for the drug substance. The two DMFs explaining the detailed synthesis of the API have been reviewed and found adequate. _____

Drug Product The drug product is oral tablets that are formulated in 200 mg strength. The inactive ingredients include sodium starch glycolate, glycerol palmitostearate, silicon dioxide, microcrystalline cellulose, and talc. The tablets are coated with _____. All inactive ingredients, except glycerol palmitostearate, are compendial. Glycerol palmitostearate has a monograph in Food and Chemical Codex (FCC) and is listed as GRAS under 21 CFR 184.1329. The commercial batch size is _____ tablets.

In this review cycle, the firm has revised their degradation product acceptance criteria, developed and validated a new improved HPLC method for the degradation product determination after the Agency's recommendation.

Chemistry Assessment Section

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

For diarrhea the recommended dose is one 200 mg tablet taken three times a day for 3 days with or without food. The package insert in the latest amendment of 11/25/03 states that the commercial presentations for the drug product is 75 cc, HDPE bottles containing 30 tablets. In addition, the professional samples will be packaged as 1 tablet/blister in unit carton envelop. The DMETS had recommended in their earlier review dated 9/24/02 that the is inappropriate for out-patient use as . Based on this recommendation, the sponsor has removed the blister configuration completely except the physician samples. The storage conditions on the labels are "Store at 20-25°C (68-77°F), excursions permitted to 15-30°C (59-86°F) See USP Controlled Room Temperature". In this review cycle 24 month and 16 month expiration dates have been assigned to the product packaged in bottles and blisters, respectively, based on the submitted stability data and the statistical analysis. The requested extrapolation of for the product in bottles and blisters, respectively, were granted based on the statistical analysis of the available stability data.

C Basis for Approvability or Not-Approval Recommendation

N/A

III Administrative

A Reviewer's Signature

B Endorsement Block

HFD 590/Ramesh Sood, Ph D/
HFD 590/M Seggel, Ph D /
HFD 590/A Nabakowski/

C CC Block

Orig NDA 21-361	HFD-590/ANabakowski	HFD-590/HMahayni
HFD-590/Div File	HFD-590/RAIvistatos	HFD-590/CDixon
HFD-590/RSood	HFD-590/SKunder	HFD-830/DLin
HFD-590/MSeggel	HFD-590/PDionne	

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/s/

Ramesh Sood
5/13/04 02 04 03 PM
CHEMIST

Here is the final review

Mark Seggel
5/13/04 02 23 20 PM
CHEMIST

NDA 21-361

Rifaximin Tablets, 200 mg.

Salix Pharmaceuticals, Inc.

**Ramesh Sood, Ph. D.
Division of Special Pathogen and Immunologic Drug
Products, HFD-590.**

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C CC Block	10
Chemistry Assessment	12
I DRUG SUBSTANCE	12
II DRUG PRODUCT	12
1 Components/Composition Acceptable as per review # 1	12
2 Specifications & Methods For Drug Product Ingredients	12
4 Methods of Manufacturing And Packaging Acceptable	16
a Production Operations	16
b In Process Controls & Tests	16

5	Regulatory Specifications And Methods For Drug Product	17
b	Regulatory Specifications And Methods	17
6	Container/Closure System Acceptable	20
7	Microbiology	21
III	INVESTIGATIONAL FORMULATIONS	25
IV	ENVIRONMENTAL ASSESSMENT Acceptable as per review # 1	25
V	METHODS VALIDATION Pending	25
VI	LABELING	26
VII	ESTABLISHMENT INSPECTION Acceptable	28
VIII	DRAFT DEFICIENCY LETTER	28

Chemistry Review Data Sheet

1 NDA 21-361

2 REVIEW # 2

3 REVIEW DATE 26-Oct-2002

4 REVIEWER Ramesh K Sood, Ph D

5 PREVIOUS DOCUMENTS

<u>Previous Documents</u>	<u>Document Date</u>
Original Submission	21-Dec-2001
BC	7-May-2002
BC	9-May-2002
Amendment	6-June-2002
IR Letter	20-June-2002
CMC Review #1	

6 SUBMISSION(S) BEING REVIEWED

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment	22-July-2002
Amendment	5-Aug-2002
Amendment (BC)	14-Aug-2002

7 NAME & ADDRESS OF APPLICANT

Name Salix Pharmaceuticals, Inc

CHEMISTRY REVIEW

Chemistry Review Data Sheet

Address 3600 W Bayshore Road
Suite 205
Palo Alto, CA 94303

Representative

Telephone

8 DRUG PRODUCT NAME/CODE/TYPE

- a) Proprietary Name acceptable by DMRTS at this point)
- b) Non-Proprietary Name (USAN) rifaximin tablets
- c) Code Name/# (ONDC only) L-105
- d) Chem Type/Submission Priority (ONDC only)
- Chem Type 1
 - Submission Priority S

9 LEGAL BASIS FOR SUBMISSION

10 PHARMACOL CATEGORY

Antibacterial

11 DOSAGE FORM

Tablets

12 STRENGTH/POTENCY

200 mg

13 ROUTE OF ADMINISTRATION

Oral

14 Rx/OTC DISPENSED Rx OTC

15 SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note26]

SPOTS product – Form Completed

Not a SPOTS product

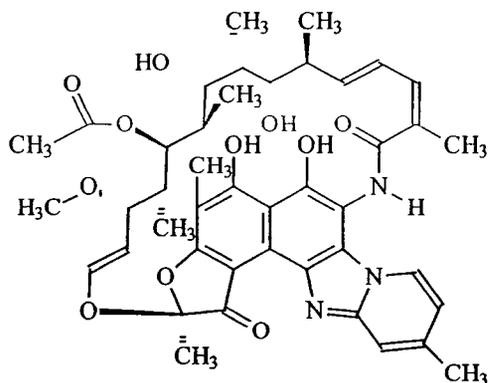
Chemistry Review Data Sheet

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

(2S,16Z,18E,20S,21S,22R,23R,24R,-
25S,26S,27S,28E)-5,6,21,23,25-
pentahydroxy-27-methoxy-2,4,11,16,-
20,22,24,26-octamethyl-2,7-(epoxy-
pentadeca[1,11,13]trienimino)-
benzofuro[4,5-e]pyrido[1,2- α]-
benzimidazole-1,15(2H)-dione,25-
acetate

Registry Number [80621-81-4]

C₄₃H₅₁N₃O₁₁ Formula Weight 785.89



17 RELATED/SUPPORTING DOCUMENTS

A DMFs

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
✓	II		/	3	Adequate	23-Jan-2002	Reviewed by G Lunn
✓	II			3	Adequate	10-Sep-2002	Reviewed by G Lunn
✓	III			1	Adequate	26-Aug-2002	Reviewed by R Sood
✓	III			3	Adequate	17-Nov-1995	DMF supports

Chemistry Review Data Sheet

/	III			3	Adequate	16-Aug-2001	tablets Components comply with 21CFR, Indirect Food Additives
/	III			3	Adequate	6-Feb-2000	DMF is adequate
/	III			3	Adequate	20-Aug-2001	— are satisfactory for —
/	III			1	Inadequate	5-Aug-2002	Reviewed by R Sood and letter sent on 9/4/02
/	III			1	Adequate	1-Aug-2002	Reviewed by R Sood
/	III			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 N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

Chemistry Review Data Sheet

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Overall pending		
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	Pending		
DMETS	Proprietary name acceptable at this point	24-Sep-2002	Nora Roselle
EA	N/A		
Microbiology	N/A		

The Chemistry Review for NDA 21-361

The Executive Summary

I. Recommendations

A Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls (CMC) standpoint, this NDA is not approvable until satisfactory resolution of the CMC-related deficiencies. The three CMC approvability issues relate to the drug substance particle size control, drug product impurity specification and stability data.

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

N/A

II Summary of Chemistry Assessments

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

The active pharmaceutical ingredient (API), rifaximin, is an _____ crystalline powder soluble in organic solvents and practically insoluble in water. The API is manufactured by _____

_____ The quality of the incoming API is controlled through specification which include identification, assay, impurities, particle size and residual solvents. The two DMFs explaining the _____ have been reviewed and found adequate.

The drug product is oral tablets that are formulated in 200 mg strength. The inactive ingredients include sodium starch glycolate, glycerol palmitostearate, silicon dioxide, microcrystalline cellulose, and talc. The tablets are coated with _____. All inactive ingredients, except glycerol palmitostearate, are compendial. Glycerol palmitostearate has a monograph in Food and Chemical Codex (FCC) and is listed as GRAS under 21 CFR 184.1329. The commercial batch size is _____ tablets.

The commercial product will be manufactured and packaged at _____. The product will be packaged as 30 count in 75 cc, HDPE bottles, _____ and professional samples will be packed as _____.

The analytical methods used for the drug product were transferred from _____ (where they were validated and validation was found acceptable as per review # 1) to the commercial manufacturing site at _____ under methods transfer protocol. During the _____ establishment inspection, the inspectors noted that the related substance, assay and dissolution methods were not adequately validated.

Executive Summary Section

The firm has agreed with the inspector to validate these methods and submit the validation report to the agency

The DMETS has reviewed the suggested proprietary names and recommends the use of _____ as the proprietary name at this point

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

For _____ diarrhea the recommended dose is one 200 mg tablet taken three times a day for 3 days with or without food The latest amendment of 8/14/02 states that the commercial presentations for the drug product are 75 cc, HDPE bottles containing 30 tablets _____

professional samples will be packaged as _____ In addition, the _____ The DMETS has recommended in their review dated 9/24/02 that the _____ is inappropriate for out-patient use as it _____

They have recommended _____ The storage conditions on the labels are "Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F) See USP Controlled Room Temperature" No expiration dating period can be assigned because of deficiencies in the stability data

C Basis for Approvability or Not-Approval Recommendation

The firm has provided limited stability data The stability data provided for the product packaged in _____ HDPE bottles are _____ RT and _____ accelerated data The product is packaged in HDPE bottles as _____

These stability data are not sufficient to provide any expiration date for the product packaged in commercial container/closure systems The firm should provide adequate stability data before any expiration date could be assigned The other two approvability issues relate to the drug substance particle size and the drug product impurity specification

III Administrative

A Reviewer's Signature

B Endorsement Block

HFD 590/Ramesh Sood, Ph D/Date
 HFD 590/Norman Schmuff, Ph D /
 HFD 590/Diana Willard/

C CC Block

Orig NDA 21-361	HFD-590/DWillard	HFD-590/HMahayni
HFD-590/Div File	HFD-590/RAIhivistatos	HFD-590/CDixon
HFD-530/GLunn	HFD-590/SKunder	HFD-830/CChen
HFD-590/NSchmuff	HFD-590/PDionne	

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/s/

Ramesh Sood
10/28/02 08 10 14 AM
CHEMIST

Norman Schmuff
10/28/02 09 10 46 AM
CHEMIST

NDA 21-361

LUMENAX™ (rifaximin) Tablets, 200 mg.

Salix Pharmaceuticals, Inc.

**George Lunn, Ph.D.
Division of Antiviral Drug Products, HFD-530**

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c Microbiology	30
7 Container/Closure System For Drug Substance Storage	30
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II DRUG PRODUCT	31
1 Components/Composition Acceptable	31
2 Specifications & Methods For Drug Product Ingredients Not Acceptable	32
a Active Ingredient	32
b Inactive Ingredients	33
3 Manufacturer Acceptable	34
4 Methods Of Manufacturing And Packaging Acceptable	35
a Production Operations ..	35
b In-Process Controls & Tests ..	40
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Chemistry Review Data Sheet

1 NDA 21-361

2 REVIEW # 1

3 REVIEW DATE 9-Sep-2002

4 REVIEWER George Lunn, Ph D

5 PREVIOUS DOCUMENTS

Previous Documents

Document Date

None

6 SUBMISSION(S) BEING REVIEWED

Submission(s) Reviewed

Document Date

Original Submission

21-Dec-2001

BC

7-May-2002

BC

9-May-2002

7 NAME & ADDRESS OF APPLICANT

Name Salix Pharmaceuticals, Inc

3600 W Bayshore Road

Address Suite 205

Palo Alto, CA 94303

Representative

—

Telephone

—

Chemistry Review Data Sheet

8 DRUG PRODUCT NAME/CODE/TYPE

- a) Proprietary Name LUMENAX™
b) Non-Proprietary Name (USAN) rifaximin tablets
c) Code Name/# (ONDC only) L-105
d) Chem Type/Submission Priority (ONDC only)
- Chem Type 1
 - Submission Priority S

9 LEGAL BASIS FOR SUBMISSION

10 PHARMACOL CATEGORY

Antibacterial

11 DOSAGE FORM

Tablets

12 STRENGTH/POTENCY

200 mg

13 ROUTE OF ADMINISTRATION

Oral

14 Rx/OTC DISPENSED Rx OTC15 SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM) SPOTS product – Form Completed Not a SPOTS product

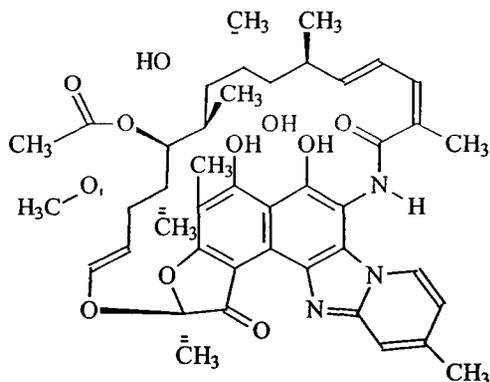
Chemistry Review Data Sheet

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

(2S,16Z,18E,20S,21S,22R,23R,24R,-
25S,26S,27S,28E)-5,6,21,23,25-
pentahydroxy-27-methoxy-2,4,11,16,-
20,22,24,26-octamethyl-2,7-(epoxy-
pentadeca[1,11,13]trienimino)-
benzofuro[4,5-e]pyrido[1,2- α]-
benzimidazole-1,15(2H)-dione,25-
acetate

Registry Number [80621-81-4]

$C_{43}H_{51}N_3O_{11}$ Formula Weight 785.89



Chemistry Review Data Sheet

17 RELATED/SUPPORTING DOCUMENTS

A DMFs

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
—	II			1	Adequate	23-Jan-2002	Reviewed by G Lunn
—	II			1	Adequate	10-Sep-2002	Reviewed by G Lunn
—	III			1	Adequate	26-Aug-2002	Reviewed by R Sood
—	III			3	Adequate	17-Nov-1995	DMF supports the use of
—	III			3	Adequate	16-Aug-2001	Components comply with
—	III			3	Adequate	6-Feb-2000	DMF is adequate
—	III			3	Adequate	20-Aug-2001	CRCs are satisfactory for
—	III			7	Pending		Comments communicated to firm 8/5/02
—	III			1	Adequate	1-Aug-2002	Reviewed by R Sood
—	III			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")

CHEMISTRY REVIEW**Chemistry Review Data Sheet**

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
None		

18 STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Overall pending		
Pharm/Tox			
Biopharm			
LNC			
Methods Validation	Pending		
OPDRA			
EA			
Microbiology			

The Chemistry Review for NDA 21-361

The Executive Summary

I. Recommendations

A Recommendation and Conclusion on Approvability

Not approvable until the deficiencies that have been identified are resolved. These deficiencies concern the particle size distributions of the drug substance lots used for the clinical trials and for the commercial product, the analytical methods that are to be used for incoming drug substance lots, validation of the drug product analytical methods, confirmation that all bottle configurations will be marketed commercially, data to show that the for each bottle container-closure system are similar, stability data concerning batches made at the commercial site, data for individual impurities/degradants, and a

I See the Deficiency Letter

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

N/A

II Summary of Chemistry Assessments

A Description of the Drug Substance and Drug Product

The drug substance, rifaximin, is manufactured by . This manufacturing process is covered by DMF . This DMF was reviewed and rifaximin manufactured by was found to be suitable for use as a drug substance in oral dosage forms. Rifaximin is produced from . The manufacture of is covered by DMF . This DMF was reviewed and was found to be suitable for use as an in the manufacture of rifaximin. Based on these reviews of the DMFs the drug substance was found to be acceptable.

The drug product consists of pink, film-coated, 10 mm, circular biconvex tablets. Each tablet contains 200 mg rifaximin and is .

The first commercial drug substance lots that are received by the drug product manufacturer and per year thereafter will be subject to complete release testing by the drug product manufacturer. However, not every lot of drug substance that is received will be assayed. Additionally the analytical methods are not described.

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The particle size distributions of the drug substance lots used for the clinical trials and for the commercial product remain unknown. There is clearly some variation amongst manufacturers and there is no evidence that batch to batch variations do not occur.

The inactive ingredients are sodium starch glycolate, NF, glycerol palmitostearate, FCC, colloidal silicon dioxide, NF, microcrystalline cellulose, NF, talc, USP,

USP, _____, disodium edetate, USP, propylene glycol, USP, and red iron oxide, NF. With the exception of glycerol palmitostearate all inactive ingredients are compendial. Glycerol palmitostearate is FCC grade and is adequately described.

Manufacturing, packaging, labeling, quality control testing for release, and stability testing will take place at _____ a. Quality control testing for release and stability testing will take place at _____.

The tablets are manufactured using a _____ using conventional equipment.

_____ is planned. No _____ scale batches have yet been manufactured at _____. The production process is adequately described and the controls are appropriate. Tablets in the _____ batch produced at the proposed commercial manufacturing site _____ are similar in dissolution profile ($f_2 > 50$) to tablets in the batches used in the clinical studies.

The specifications are reasonable and the analytical methods are well described. The validation of the analytical methods by _____ is acceptable. However, these methods have not been validated by the tablet manufacturer, _____. Full details should be supplied to show that the methods have been validated at _____ facilities.

The tablets will be packaged in _____ HDPE bottles. The sponsor should confirm that all four configurations will be marketed commercially. The sponsor should also provide data to show that the _____ rates for each container-closure system are similar. The bottles do not have secondary packaging. The tablets will also be packaged in blister packs. Different (but similar) materials were used for the stability lots packaged by Alfa Wassermann. Except for the closures from _____ the packaging materials are acceptable.

For the _____ lot manufactured at the commercial site, _____, on _____ scale and packaged in _____ satisfactory stability data are provided. Three lots manufactured by Alfa Wassermann, Italy on about _____ of the

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proposed commercial scale are claimed as primary stability batches with — of satisfactory stability data. They are each packaged in —. There are no obvious trends except for a possible — at 40°C/75% RH.

The three batches manufactured by Alfa Wassermann cannot be accepted as primary stability batches. Q1A(R) states that "stability testing should be conducted on the dosage form packaged in the container closure system proposed for marketing." However, the Alfa Wassermann batches are packaged in —. Also, the — materials used at Alfa Wassermann are not identical to those used at — and the — packaging equipment is not described. The sponsor should send any updated stability data concerning batches made at the commercial site, — so that a decision concerning the expiry date can be made. The sponsor should also supply data for individual impurities/degradants. Additionally, the sponsor —.

The Sponsor claims a categorical exclusion under 21 CFR 25.31(b) from the requirements for an Environmental Assessment. The estimated aquatic concentration is — ppb which is less than the 1 ppb specified in the regulations.

A Methods Validation package is provided. Validation is not expected prior to approval.

The container labels are acceptable. However, the trade name of Lumenax has not yet been agreed with the sponsor.

An Establishment Evaluation Request was submitted and is pending.

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

For — diarrhea the recommended dose is one 200 mg tablet taken three times a day for 3 days with or without food. The tablets are supplied in blister packs in — count samples and a — and are packaged in a —. The tablets are also packaged in —.

— HDPE bottles. The bottles do not have secondary packaging. The storage conditions on the labels are "Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F) See USP Controlled Room Temperature." No expiration dating period can be assigned because of deficiencies in the stability data.

C Basis for Approvability or Not-Approval Recommendation

Not approvable because of the numerous deficiencies noted above.

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III. Administrative

A Reviewer's Signature

B Endorsement Block

ChemistName/Date George Lunn/9-Sep-2002
ChemistryTeamLeaderName/Date Norman Schmuff
ProjectManagerName/Date Diana Willard

C CC Block

44 Page(s) Withheld