

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER:  
22-554**

**OTHER REVIEW(S)**

**MEMORANDUM**

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

**DATE:** March 24, 2010

**TO:** Division of Gastroenterology Products

**THROUGH :** Joyce Korvick, MD, MPH  
Deputy, Director of Safety

**FROM:** Hee (Sheila) Lianos, PharmD  
Project Manager

**SUBJECT:** PMRPMC negotiations log/history

**APPLICATION/DRUG:** NDA 022554

The following are documents to be filed as a negotiations log for the postmarketing requirements and commitments for NDA 022554 (XIFAXAN 550 mg Tablets)

**From:** Buck, Heather  
**Sent:** Monday, March 08, 2010 9:55 AM  
**To:** 'Glifort, Gail'; Lianos, Hee S  
**Subject:** 22-554: Xifaxan (rifaximin): PMRs/PMCs

Dear Gail,

**Reference is made to NDA 022554 for Xifaxan (rifaximin) 550mg Tablets. Please be advised that Salix Pharmaceuticals will be responsible for the following Post Marketing Requirements (PMRs):**

1. A randomized controlled clinical trial to evaluate safety of rifaximin in patients with Child-Pugh class C, MELD >19 and MELD  $\geq$ 25 hepatic impairment

(b) (4)

3. Conduct a chronic oral toxicology study that evaluates AUC exposure in animals that are comparable to the highest AUCs observed in cirrhotic patients. These AUC values must be achieved and maintained throughout the duration of the chronic toxicity study. In the event that sufficiently high AUC levels cannot be achieved from oral dosing, alternative routes of administration may be used.

**The following are studies that we request as Post Marketing Commitments (PMCs):**

1. A randomized controlled clinical trial to evaluate whether lactulose is required in combination with rifaximin to delay time to onset of episode of overt HE
2. Performance of an in vivo drug interaction study to evaluate the effect of P-glycoprotein inhibitor(s) of rifaximin pharmacokinetics
3. Performance of an in vitro study to evaluate the potential for rifaximin to inhibit P-glycoprotein transporter.

For each PMR/PMC, please submit, to your NDA, a timetable identifying the following milestones dates:

- Final Protocol Submission Date
- Study Completion Date
- Final Report Submission Date

At your convenience, please acknowledge receipt of this message.

Regards,  
Heather Buck (on behalf of Sheila Lianos)  
(301) 796-1413

Hee (Sheila) Lianos, RPh., PharmD.  
Regulatory Project Manager  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Phone: 301.796.4147

Fax: 301.796.9905

Email: [hee.lianos@fda.hhs.gov](mailto:hee.lianos@fda.hhs.gov)

**From:** Glifort, Gail [Gail.Glifort@Salix.com]

**Sent:** Tuesday, March 09, 2010 4:06 PM

**To:** Buck, Heather

**Cc:** Lianos, Hee S

**Subject:** NDA022554 PMR/PMC Timelines and Pgp Draft Report

**Attachments:** Post Marketing Timelines 030910.doc; (b)(4)-Salix-02\_draft report.doc; emfalert.txt

Dear Heather,

Attached please find our proposed timelines for the postmarketing requirements and commitments discussed with FDA yesterday. Please note that we have slightly reworded the first PMR to specify the population for the clinical study.

I have also included the draft report which we propose to fulfill PMC # 3 (An in vitro study to evaluate the potential for rifaximin to inhibit P-glycoprotein transporter). I have put the final protocol and study completion dates in italics because they may not be included in the final letter as they are already complete.

Please contact me if you have any questions.

Thank you,  
Gail

Gail Glifort, RAC  
Senior Manager, Regulatory  
Salix Pharmaceuticals, Inc.  
1700 Perimeter Park Drive  
Morrisville, NC 27560  
Phone: 919-862-1055  
Fax: 919-228-4255  
[Gail.Glifort@Salix.com](mailto:Gail.Glifort@Salix.com)

18 pp withheld in full immediately after this page as (b)(4) CCI/TS.

**From:** Lianos, Hee S  
**Sent:** Friday, March 12, 2010 2:05 PM  
**To:** 'Glifort, Gail'  
**Subject:** NDA 022554 Xifaxan: PMRPMC proposal amendment

**Importance:** High

**Attachments:** PMRPMC\_From FDA\_2010Mar12\_clean.doc

Dear Gail,

We have made an amendment to our correspondence dated March 8, 2010, which contained postmarketing requirements and commitments (PMR and PMCs, respectively) for NDA 022554. **Please be advised that Salix Pharmaceuticals will be responsible for the following additional PMRs** (the numbering below corresponds with the attachment to this email):

4. A randomized controlled trial to evaluate the effect of long term rifaximin treatment on the gut flora to include in vitro susceptibility testing to rifaximin and other antimicrobial drugs. Representative populations with a range of severity of disease represented by low to high MELD categories should be included. This may be conducted as a substudy of PMR #1 or PMC #2.

Final Protocol Submission Date:

Study Completion Date:

Final Report Submission Date:

5. A pharmacokinetic study in patients with MELD 19 - 25 and MELD > 25, This may be performed as a sub study in the ongoing Phase 3 trial, or as part of additional safety trials (PMR #1).

Final Protocol Submission Date:

Study Completion Date:

Final Report Submission Date:

6. A study pharmacokinetic study to assess the potential effect of concurrent renal insufficiency on the systemic exposure to rifaximin in cirrhotic patients; blood samples for PK analysis should be collected and the PK data should be analyzed by renal insufficiency (e.g. creatinine clearance) within a Child-Pugh class/and by MELD score. A population PK approach will be acceptable. This may be done as a sub-study.

Final Protocol Submission Date:

Study Completion Date:

Final Report Submission Date:

We will need your response by close of business Monday, March 15, 2010.

Thank you,

Sheila Lianos

Hee (Sheila) Lianos, RPh., PharmD.  
Regulatory Project Manager  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research  
Phone: 301.796.4147  
Fax: 301.796.9905  
Email: [hee.lianos@fda.hhs.gov](mailto:hee.lianos@fda.hhs.gov)

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## PROPOSED SUBMISSION AND COMPLETION DATES

### Post Marketing Requirements (PMRs):

1. A randomized controlled clinical trial to evaluate safety of rifaximin in patients with hepatic encephalopathy classified as Child-Pugh C, MELD > 19 and MELD  $\geq$  25 hepatic impairment

Final Protocol Submission Date: December 2010  
Study Completion Date: December 2013  
Final Report Submission Date: June 2014



3. A chronic oral toxicology study that evaluates AUC exposure in animals that is comparable to the highest AUCs observed in cirrhotic patients. These AUC values must be achieved and maintained throughout the duration of the chronic toxicity study. In the event that sufficiently high AUC levels cannot be achieved from oral dosing, alternative routes of administration may be used.

Final Protocol Submission Date: December 2010  
Study Completion Date: December 2012  
Final Report Submission Date: June 2013

4. A randomized controlled trial to evaluate the effect of long term rifaximin treatment on the gut flora to include *in vitro* susceptibility testing to rifaximin and other antimicrobial drugs.



Final Protocol Submission Date:  
Study Completion Date:  
Final Report Submission Date:

5. 
- (b) (4)

Final Protocol Submission Date:

Study Completion Date:

Final Report Submission Date:



Final Protocol Submission Date:

Study Completion Date:

Final Report Submission Date:

**Post Marketing Commitments (PMCs):**

1. A randomized controlled clinical trial to evaluate whether lactulose is required in combination with rifaximin to delay time to onset of episode of overt HE

Final Protocol Submission Date: December 2010

Study Completion Date: December 2013

Final Report Submission Date: June 2014

2. Ann in vivo drug interaction study to evaluate the effect of P-glycoprotein inhibitor(s) of rifaximin pharmacokinetics

Final Protocol Submission Date: December 2010

Study Completion Date: October 2011

Final Report Submission Date: April 2012

3. An in vitro study to evaluate the potential for rifaximin to inhibit P-glycoprotein transporter.  (b) (4)

*Final Protocol Submission Date: Report in draft*

*Study Completion Date: Completed*

Final Report Submission Date: June 2010

**From:** Glifort, Gail [Gail.Glifort@Salix.com]

**Sent:** Monday, March 15, 2010 12:03 PM

**To:** Lianos, Hee S

**Subject:** NDA022554 PMR/PMC

**Attachments:** PMRPMC\_15Mar2010\_clean.doc; PMRPMC\_15Mar2010\_edit.doc; emfalert.txt

Dear Sheila,

I am sending the latest draft of the PMR/PMC for XIFAXAN Tablets, 550 mg. I have attached clean and edited versions of the document so that you can see what changes were made from the previous version, including the wording changes discussed during today's telecom.

Please contact me if you have any questions.

Thanks,

Gail

Gail Glifort, RAC  
Senior Manager, Regulatory  
Salix Pharmaceuticals, Inc.  
1700 Perimeter Park Drive  
Morrisville, NC 27560  
Phone: 919-862-1055  
Fax: 919-228-4255  
[Gail.Glifort@Salix.com](mailto:Gail.Glifort@Salix.com)

**PROPOSED SUBMISSION AND COMPLETION DATES**

**Post Marketing Requirements (PMRs):**



(b) (4)

3. A chronic oral toxicology study that evaluates AUC exposure in animals that is comparable to the highest AUCs observed in cirrhotic patients. These AUC values must be achieved and maintained throughout the duration of the chronic toxicity study. In the event that sufficiently high AUC levels cannot be achieved from oral dosing, alternative routes of administration may be used.

Final Protocol Submission Date: December 2010  
Study Completion Date: December 2012  
Final Report Submission Date: June 2013



(b) (4)

(b) (4)

(b) (4)

**Post Marketing Commitments (PMCs):**

1. A randomized controlled clinical trial to evaluate whether lactulose is required in combination with rifaximin to delay time to onset of episode of overt HE

Final Protocol Submission Date: December 2010  
Study Completion Date: December 2013  
Final Report Submission Date: June 2014

2. Ann in vivo drug interaction study to evaluate the effect of P-glycoprotein inhibitor(s) of rifaximin pharmacokinetics

Final Protocol Submission Date: December 2010  
Study Completion Date: October 2011  
Final Report Submission Date: April 2012

3. An in vitro study to evaluate the potential for rifaximin to inhibit P-glycoprotein transporter. (b) (4)

*Final Protocol Submission Date: Report in draft*  
*Study Completion Date: Completed*  
Final Report Submission Date: June 2010

**From:** Lianos, Hee S  
**Sent:** Thursday, March 18, 2010 11:20 AM  
**To:** 'Glifort, Gail'  
**Subject:** RE: NDA 022554 XIFAXAN: PMR PMC negotiations letter

**Attachments:** PMRPMC\_From FDA\_2010Mar18.doc  
Please use this latest version.

Thank you,

Sheila Lianos

Hee (Sheila) Lianos, RPh., PharmD.  
Regulatory Project Manager  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research  
Phone: 301.796.4147  
Fax: 301.796.9905  
Email: [hee.lianos@fda.hhs.gov](mailto:hee.lianos@fda.hhs.gov)

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**From:** Lianos, Hee S  
**Sent:** Thursday, March 18, 2010 10:17 AM  
**To:** 'Glifort, Gail'  
**Subject:** NDA 022554 XIFAXAN: PMR PMC negotiations letter

Dear Gail,

Please send the following correspondence as an official submission for your PMRPMC agreements as soon as possible – call me and I will explain the best route in order to meet our PDUFA date. This copy incorporates all of the discussion we have had. The numbering must stay intact since these will be reflected in our final action letter.

Take care, Sheila

## PROPOSED SUBMISSION AND COMPLETION DATES

### Post Marketing Requirements (PMRs):



(b) (4)

2. A chronic oral toxicology study that evaluates AUC exposure in animals that is comparable to the highest AUCs observed in cirrhotic patients. These AUC values must be achieved and maintained throughout the duration of the chronic toxicity study. In the event that sufficiently high AUC levels cannot be achieved from oral dosing, alternative routes of administration may be used.

The timetable you submitted on March 15, 2010, states that you will conduct this study according to the following timetable:

Final Protocol Submission Date:	December 2010
Study Completion Date:	December 2012
Final Report Submission Date:	June 2013



(b) (4)



(b) (4)

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk of the potential development of antibiotic resistant organisms with chronic use of rifaximin, and hepatotoxicity in patients with severe hepatic impairment.

Therefore, based on appropriate scientific data, FDA has determined that you are required, to conduct the following:

5. A randomized controlled clinical trial to evaluate safety of rifaximin in patients with hepatic encephalopathy classified as Child-Pugh C, MELD > 19, and MELD  $\geq$  25 hepatic impairment.

The timetable you submitted on March 15, 2010, states that you will conduct this trial according to the following timetable:

Final Protocol Submission Date:	April 2011
Study Completion Date:	June 2014
Final Report Submission Date:	December 2014

6. A randomized controlled trial to evaluate the effect of long term rifaximin treatment on the gut flora to include in vitro susceptibility testing to rifaximin and other antimicrobial drugs. (b) (4)

The timetable you submitted on March 15, 2010, states that you will conduct this trial according to the following timetable:

Final Protocol Submission Date:	April 2011
Study Completion Date:	June 2014
Final Report Submission Date:	December 2014

**Post Marketing Commitments (PMCs):**

7. A randomized controlled clinical trial to evaluate whether lactulose is required in combination with rifaximin to delay time to onset of episode of overt HE.

The timetable you submitted on March 15, 2010, states that you will conduct this trial according to the following timetable:

Final Protocol Submission Date:	December 2010
Study Completion Date:	December 2013
Final Report Submission Date:	June 2014

8. An in vivo drug interaction study to evaluate the effect of P-glycoprotein inhibitor(s) of rifaximin pharmacokinetics in healthy subjects.

The timetable you submitted on March 15, 2010, states that you will conduct this study according to the following timetable:

Final Protocol Submission Date:	December 2010
Study Completion Date:	October 2011
Final Report Submission Date:	April 2012

9. An in vitro study to evaluate the potential for rifaximin to inhibit P-glycoprotein transporter.

The timetable you submitted on March 15, 2010, states that you will conduct this study according to the following timetable:

Final Protocol Submission Date:	Report in draft
Study Completion Date:	Completed
Final Report Submission Date:	June 2010

**From:** Lianos, Hee S  
**Sent:** Tuesday, March 23, 2010 2:56 PM  
**To:** 'Glifort, Gail'  
**Subject:** FW: 22-554: Xifaxan (rifaximin): PMRs/PMCs

**Importance:** High

**Attachments:** PMRPMC\_From FDA\_2010Mar23.doc

Dear Gail,

**Reference is made to NDA 022554 for Xifaxan (rifaximin) 550mg Tablets. Please be advised that Salix Pharmaceuticals will be responsible for the following Post Marketing Requirements (PMRs):**

**The following are studies and trials that we request as Post Marketing Requirements (PMRs):**

1. A chronic oral nonclinical toxicology study that evaluates AUC exposure in animals that is comparable to the highest AUCs observed in cirrhotic patients. These AUC values must be achieved and maintained throughout the duration of the chronic toxicity study. In the event that sufficiently high AUC levels cannot be achieved from oral dosing, alternative routes of administration may be used.
2. A randomized, controlled clinical trial to evaluate safety of rifaximin in patients with hepatic encephalopathy classified as Child-Pugh C, MELD > 19 and MELD  $\geq$  25 hepatic impairment

(b) (4)

3. A pharmacokinetic trial in patients with severe hepatic impairment (MELD 19 - 25 and MELD > 25). This may be performed as a sub study in the ongoing Phase 3 trial (RFHE3002, "A multicenter, open label trial to evaluate the long term safety and tolerability of rifaximin 550 mg BID in subjects with a history of hepatic encephalopathy"), or as part of the required clinical trial described under PMR # 2.
4. A pharmacokinetic trial in patients with concurrent renal insufficiency and liver impairment to determine the extent of elevation of systemic exposure of rifaximin which may lead to worsening of hepatic function. The PK data should be collected and analyzed by the degree of renal insufficiency (e.g. creatinine clearance) within a Child-Pugh class/and by MELD score. A population PK approach would be acceptable.
5. A randomized controlled trial to evaluate the effect of long term rifaximin treatment on the gut flora. In vitro susceptibility testing to rifaximin and other antimicrobial drugs must be included.

**(Note to SALIX: this should be a comment and not a part of the title in response submission to your NDA: This study may be conducted as a substudy to PMR #2 or PMC #6)**

**The following are studies and trials that we request as Post Marketing Commitments (PMCs):**

6. A randomized controlled clinical trial to evaluate whether lactulose is required in combination with rifaximin to delay time to onset of episode of overt HE
7. An in vivo drug interaction study to evaluate the effect of P-glycoprotein inhibitor(s) on rifaximin pharmacokinetics in healthy subjects.
8. An in vitro study to evaluate the potential for rifaximin to inhibit P-glycoprotein transporter.

For each PMR/PMC, please submit, to your NDA, a timetable identifying the following milestones dates:

- Final Protocol Submission Date
- Study Completion Date
- Final Report Submission Date

At your convenience, you may make your revisions to the attached document.



PMRPMC\_From  
\\\_2010Mar23.doc

Thank you,

*Sheila Lianos*

Hee (Sheila) Lianos, RPh., PharmD.  
Regulatory Project Manager  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research  
Phone: 301.796.4147  
Fax: 301.796.9905  
Email: [hee.lianos@fda.hhs.gov](mailto:hee.lianos@fda.hhs.gov)

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## PROPOSED SUBMISSION AND COMPLETION DATES

### Post Marketing Requirements (PMRs):

1. A chronic oral nonclinical toxicology study that evaluates AUC exposure in animals that is comparable to the highest AUCs observed in cirrhotic patients. These AUC values must be achieved and maintained throughout the duration of the chronic toxicity study. In the event that sufficiently high AUC levels cannot be achieved from oral dosing, alternative routes of administration may be used.

Final Protocol Submission Date: 12/31/2010  
Study Completion Date: 12/31/2012  
Final Report Submission Date: 06/30/2013

2. A randomized, controlled clinical trial to evaluate safety of rifaximin in patients with hepatic encephalopathy classified as Child-Pugh C, MELD > 19 and MELD  $\geq$  25 hepatic impairment.

Final Protocol Submission Date: 04/30/2011  
Study Completion Date: 06/30/2014  
Final Report Submission Date: 12/31/2014

**Comment: A subset of patients' for this study (comparing a patients baseline ECG with that which would be obtained during the estimated Tmax of rifaximin) will be evaluated.**

3. A pharmacokinetic trial in patients with severe hepatic impairment (MELD 19 - 25 and MELD > 25). This may be performed as a sub study in the ongoing Phase 3 trial (RFHE3002, "A multicenter, open label trial to evaluate the long term safety and tolerability of rifaximin 550 mg BID in subjects with a history of hepatic encephalopathy"), or as part of the required clinical trial described under PMR # 2.

Final Protocol Submission Date: April 2011  
Study Completion Date: June 2014  
Final Report Submission Date: December 2014

4. A pharmacokinetic trial in patients with concurrent renal insufficiency and liver impairment to determine the extent of elevation of systemic exposure of rifaximin which may lead to worsening of hepatic function. The PK data should be collected and analyzed by the degree of renal insufficiency (e.g. creatinine clearance) within a Child-Pugh class/and by MELD score. A population PK approach would be acceptable.

Final Protocol Submission Date: 04/30/2011  
Study Completion Date: 06/30/2014

Final Report Submission Date: 12/31/2014

5. A randomized controlled trial to evaluate the effect of long term rifaximin treatment on the gut flora. In vitro susceptibility testing to rifaximin and other antimicrobial drugs must be included.

Final Protocol Submission Date: 04/30/2011

Study Completion Date: 06/30/2014

Final Report Submission Date: 12/31/2014

**Comment: This study may be conducted as a substudy to PMR #2 or PMC #6.**

**Post Marketing Commitments (PMCs):**

6. A randomized, controlled clinical trial to evaluate whether lactulose is required in combination with rifaximin to delay time to onset of episode of overt hepatic encephalopathy.

Final Protocol Submission Date: 12/31/2010

Study Completion Date: 12/31/2013

Final Report Submission Date: 06/30/2014

7. An in vivo drug interaction study to evaluate the effect of P-glycoprotein inhibitor(s) on rifaximin pharmacokinetics in healthy subjects.

Final Protocol Submission Date: 12/31/2010

Study Completion Date: 10/31/2011

Final Report Submission Date: 04/30/2012

8. An in vitro study to evaluate the potential for rifaximin to inhibit P-glycoprotein transporter.

Final Protocol Submission Date: Report in draft

Study Completion Date: Completed

Final Report Submission Date: 06/30/2010

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22554

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ORIG-1

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SALIX  
PHARMACEUTICA  
LS INC

-----  
XIFAXAN

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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HEE K LIANOS  
03/24/2010

**NDA/BLA REGULATORY FILING REVIEW**  
(Including Memo of Filing Meeting)

<b>Application Information</b>		
NDA # 22554 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: XIFAXAN Established/Proper Name: Rifaximin Dosage Form: Oral Tablets Strengths: 550 mg		
Applicant: Salix Pharmaceuticals Agent for Applicant (if applicable):		
Date of Application: June 24, 2009 Date of Receipt: June 24, 2009 Date clock started after UN:		
PDUFA Goal Date: <b>December 24, 2009</b>		Action Goal Date (if different): same
Filing Date: July 24, 2009 Date of Filing Meeting: July 22, 2009		
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed Indication(s): maintenance of remission of hepatic encephalopathy (18 years and older)		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<b>Refer to Appendix A for further information.</b>		
Review Classification:  <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>  <i>If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.</i>		<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority  <input type="checkbox"/> Tropical disease Priority review voucher submitted
Resubmission after withdrawal? <input type="checkbox"/> Resubmission after refuse to file? <input type="checkbox"/>		
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)	

Collaborative Review Division (if OTC product):	
List referenced IND Number(s):	(b) (4)
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <b><u>7/20/09 – emailed CDER-DRTL to request Orphan Designation marked in DFS</u></b>
<b>Application Integrity Policy</b>	
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ora/compliance_ref/aip.html">http://www.fda.gov/ora/compliance_ref/aip.html</a></i>  If yes, explain:  If yes, has OC/DMPQ been notified of the submission?  Comments:	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>User Fees</b>	
Form 3397 (User Fee Cover Sheet) submitted	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
User Fee Status  Comments:	<input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempt (e.g., business waiver, orphan exemption).</i>	
<b>Exclusivity</b>	

<p>Does another product have orphan exclusivity for the same indication? <i>Check the Electronic Orange Book at: <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a></i></p> <p><b>If yes</b>, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES # years requested: <input checked="" type="checkbox"/> NO <u><b>Applicant requested 7 yr ODE</b></u>
<p>If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>):</p> <p>Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>	<input checked="" type="checkbox"/> Not applicable  <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>505(b)(2) (NDAs/NDA Efficacy Supplements only)</b>	
<ol style="list-style-type: none"> <li>1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> <li>2. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).</li> <li>3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))?</li> </ol>	<input checked="" type="checkbox"/> <b>Not applicable</b>  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO

<p><i><b>Note:</b> If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i></p>	
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<p>4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? <b>Check the Electronic Orange Book at: <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a></b></p>		<input type="checkbox"/> YES <input type="checkbox"/> NO	
<p><b>If yes, please list below:</b></p>			
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>			
<b>Format and Content</b>			
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p> <p><b>Comments:</b></p>		<input type="checkbox"/> All paper (except for COL) <input type="checkbox"/> All electronic <input checked="" type="checkbox"/> Mixed (paper/electronic)  <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)	
<p><b>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</b></p>		<p>datasets as SAS transport data files</p>	
<p><b>If electronic submission:</b>  paper forms and certifications signed (non-CTD) or electronic forms and certifications signed (scanned or digital signature)(CTD)?</p> <p><i>Forms include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p> <p><b>Comments:</b></p>		<input type="checkbox"/> YES <input type="checkbox"/> NO	
<p><b>If electronic submission, does it follow the eCTD guidance?</b>  (<a href="http://www.fda.gov/cder/guidance/7087rev.pdf">http://www.fda.gov/cder/guidance/7087rev.pdf</a>)</p> <p><b>If not, explain (e.g., waiver granted):</b></p>		<input type="checkbox"/> YES <input type="checkbox"/> NO	

<p><b>Form 356h:</b> Is a signed form 356h included?</p> <p><i>If foreign applicant, <b>both</b> the applicant and the U.S. agent must sign the form.</i></p> <p>Are all establishments and their registration numbers listed on the form?</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>Index:</b> Does the submission contain an accurate comprehensive index?</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:</p> <p><input type="checkbox"/> legible  <input type="checkbox"/> English (or translated into English)  <input type="checkbox"/> pagination  <input type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>Controlled substance/Product with abuse potential:</b></p> <p>Abuse Liability Assessment, including a proposal for scheduling, submitted?</p> <p>Consult sent to the Controlled Substance Staff?</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>BLAs/BLA efficacy supplements only:</b></p> <p>Companion application received if a shared or divided manufacturing arrangement?</p> <p><b>If yes, BLA #</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	
<p>Patent information submitted on form FDA 3542a?</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Debarment Certification</b>	
<p>Correctly worded Debarment Certification with authorized signature?</p> <p><i>If foreign applicant, <b>both</b> the applicant and the U.S. Agent must</i></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><b>sign the certification.</b></p> <p><i>Note: Debarment Certification should use wording in FD&amp;C Act section 306(k)(l) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p> <p><b>Comments:</b></p>	
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	
<p>Field Copy Certification: that it is a true copy of the CMC technical section (<i>applies to paper submissions only</i>)</p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<p><input type="checkbox"/> Not Applicable (<i>electronic submission or no CMC technical section</i>)</p> <p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<b>Financial Disclosure</b>	
<p>Financial Disclosure forms included with authorized signature?</p> <p><i>Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<b>Pediatrics</b>	
<b>PREA</b>	
<p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	
<p>Are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES</p> <p><input checked="" type="checkbox"/> NO</p>
<p><b>If no</b>, is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included?</p>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>• <i>If no, request in 74-day letter.</i></li> <li>• <b>If yes</b>, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</li> </ul>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<p><b>Comments:</b> ODE granted in 1998</p>	

<b>BPCA (NDAs/NDA efficacy supplements only):</b>	
Is this submission a complete response to a pediatric Written Request?  <i>If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).</i>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<b>Comments:</b>	
<b>Prescription Labeling</b>	
Check all types of labeling submitted.  <b>Comments:</b> foil blister package	<input type="checkbox"/> <b>Not applicable</b> <input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use <input type="checkbox"/> MedGuide <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input checked="" type="checkbox"/> Other (specify)
Is electronic Content of Labeling submitted in SPL format?  <i>If no, request in 74-day letter.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b>	
Package insert (PI) submitted in PLR format?  <b>If no</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If before</b> , what is the status of the request?  <i>If no, request in 74-day letter.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b>	
All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <b><u>Need to send consult once labeling meetings have been scheduled</u></b>
<b>Comments:</b>	
MedGuide or PPI (plus PI) consulted to OSE/DRISK? ( <i>send WORD version if available</i> )	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b> no PPI or MedGuide	
REMS consulted to OSE/DRISK?	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<b>Comments:</b> No patient insert or med guide	
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP?	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b>	

<b>OTC Labeling</b>	
<p>Check all types of labeling submitted.</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> <b>Not Applicable</b> <input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)
<p>Is electronic content of labeling submitted?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Are annotated specifications submitted for all stock keeping units (SKUs)?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>If representative labeling is submitted, are all represented SKUs defined?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP?</p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<b>Meeting Minutes/SPA Agreements</b>	
<p>End-of Phase 2 meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p><b>Comments:</b> pre-Phase 3 clinical development</p>	<input checked="" type="checkbox"/> YES Date(s): December 13, 2004 <input type="checkbox"/> NO
<p>Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES Date(s): December 16, 2008 <input type="checkbox"/> NO
<p>Any Special Protocol Assessment (SPA) agreements?</p> <p><i>If yes, distribute letter and/or relevant minutes before filing meeting.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** July 22, 2009

**NDA/BLA #:** 022554

**PROPRIETARY/ESTABLISHED NAMES:** Xifaximin 550 mg Tablets

**APPLICANT:** Salix Pharmaceuticals

**BACKGROUND:** NDA 21-361 for Xifaxan (rifaximin) 200 mg Tablets is approved (2004 approval) for treatment in patients with travelers' diarrhea caused by noninvasive strains of *Escherichia coli* by OAP/DSPTP.

Salix Pharmaceuticals, the sponsor, met with the FDA for a pre-NDA meeting on December 16, 2008. At that meeting, the Agency conveyed concerns regarding the sponsor's proposed primary endpoints to support an NDA for the use of rifaximin tablets as maintenance therapy in patients with hepatic encephalopathy and suggested that a second Phase 3 study be performed prior to submitting an NDA. Salix submitted their NDA with one Phase 3 study and data from smaller studies (including foreign marketing history) that they believe supportive in lieu of a second Phase 3 study.

NDA 22-554 for Xifaxan 550 mg Tablets was submitted on June 24, 2009, for review by the Division of Gastroenterology Products as a Type 6 NDA (administrative split from NDA 21-361).

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Hee (Sheila) Lianos	Y
	CPMS/TL:	Brian Strongin; Cristi Stark (Acting)	Y
Cross-Discipline Team Leader (CDTL)	Hugo Gallo-Torres		Y
Clinical	Reviewer:	Lara Dimick	Y
	TL:	Hugo Gallo-Torres (Acting)	Y
Social Scientist Review (for OTC products)	Reviewer:		
	TL:		
Labeling Review (for OTC products)	Reviewer:		
	TL:		

OSE	Reviewer:	Phuong Nina Ton	Y
	TL:		
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:	Anne Purfield	N
	TL:		

Clinical Pharmacology	Reviewer:	Insook Kim	Y
	TL:	Sue Chih Lee	Y
Biostatistics	Reviewer:	Behrang Vali	Y
	TL:	Mike Welch	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Niraj Mehta	Y
	TL:	David Joseph	Y
Statistics, carcinogenicity	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	David Lewis	Y
	TL:		
Facility ( <i>for BLAs/BLA supplements</i> )	Reviewer:		
	TL:		
Microbiology, sterility ( <i>for NDAs/NDA efficacy supplements</i> )	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:	Khairy Malek	Y
	TL:		
Other reviewers	DMEPA - Kathleen Klemm		

**OTHER ATTENDEES:** Dr. Ranjit Mani, DNP MO consult/reviewer, June Germain (PM-DSPTP). NB: not present but will be performing simultaneous labeling review from DSPTP: Tafadzwa Vargas-Kasambira (clinical), Lynette Berkeley (micro), Stephen Hundley (PharmTox)

505(b)(2) filing issues?  <b>If yes, list issues:</b>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
Per reviewers, are all parts in English or English translation?  <b>If no, explain:</b>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><b>Electronic Submission comments</b></p> <p><b>List comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable
<p><b>CLINICAL</b></p> <p><b>Comments:</b> subjective endpoints. absence of 2nd P3 study (will need to review past studies for support of efficacy)</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b> clinical support of Conn and Asterixis</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li>○ <i>this drug/biologic is not the first in its class</i></li> <li>○ <i>the clinical study design was acceptable</i></li> <li>○ <i>the application did not raise significant safety or efficacy issues</i></li> <li>○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	<input checked="" type="checkbox"/> YES Date if known: <input type="checkbox"/> NO <input type="checkbox"/> To be determined  Reason: subjectiveness of primary endpoints
<ul style="list-style-type: none"> <li>• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b> Consult outstanding to assess safety in long-term use</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

<p><b>Comments:</b> dosing concern - appropriateness esp. in patients with shunts</p>	<input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b> potential clinical significance issues</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b> Pregnancy category decision may go to Repro Committee (DSPTP managed)</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b> facilities inspection req already sent</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Establishment(s) ready for inspection?</li> <li>Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?</li> </ul> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Sterile product?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO

<p><b>If yes, was Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>FACILITY (BLAs only)</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<b>REGULATORY PROJECT MANAGEMENT</b>	
<p><b>Signatory Authority:</b> Donna Griebel, DD</p> <p><b>GRMP Timeline Milestones:</b> September 24 (mid-cycle) December 24 (goal date)</p> <p><b>Comments:</b></p>	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <ul style="list-style-type: none"> <li><input type="checkbox"/> No review issues have been identified for the 74-day letter.</li> <li><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</li> <li><input type="checkbox"/> Standard Review</li> <li><input checked="" type="checkbox"/> Priority Review</li> </ul>
<b>ACTIONS ITEMS</b>	
<input checked="" type="checkbox"/>	Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.
<input type="checkbox"/>	If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	If BLA or priority review NDA, send 60-day letter.
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Other

## Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

-----  
NDA-22554

-----  
ORIG-1

-----  
SALIX  
PHARMACEUTICA  
LS INC

-----  
XIFAXAN

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

HEE K LIANOS  
03/18/2010

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications**

**\*\*\*\*Pre-decisional Agency Information\*\*\*\***

**Memorandum**

**Date:** March 17, 2010

**To:** Hee (Sheila) Lianos, Regulatory Project Manager  
Division of Gastroenterology Products (DGP)

**From:** Kathleen Klemm, Regulatory Review Officer  
Division of Drug Marketing, Advertising, and Communications (DDMAC)

**CC:** Lisa Hubbard, Professional Group Leader  
Shefali Doshi, Regulatory Review Officer  
Robert Dean, DTC Group Leader  
Wayne Amchin, Regulatory Health Project Manager  
DDMAC

**Subject:** NDA 22-554

DDMAC labeling comments for XIFAXAN<sup>®</sup> (rifaximin) Tablets

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In response to DGP's September 17, 2009, consult request, DDMAC has reviewed the draft product labeling (PI) for XIFAXAN<sup>®</sup> (rifaximin) Tablets (NDA 22-554). DDMAC's comments on the PI are based on the proposed draft marked-up labeling titled, "PI\_fromSalix\_2010Mar15.pdf" that was sent via email to DDMAC on March 16, 2010.

Thank you for the opportunity to comment on this proposed material.

If you have any questions, please contact Kathleen Klemm at 301.796.3946 or Kathleen.Klemm@fda.hhs.gov.

## Highlights

1. Please consider revising the Warnings and Precautions section to incorporate all of the important risk concepts discussed in the Full PI. Specifically, we note that risk information from sections 5.3 and 5.4 of the PI is not included in the Warnings and Precautions section of the Highlights.
2. The Adverse Reactions section states, “Most common adverse reactions ( $\geq 5\%$ ) were...” For clarity, we suggest adding context to convey that these were the most common adverse reactions seen in patients with Traveler’s Diarrhea.

## Full Prescribing Information (PI):

1. Section 6.1 includes the abbreviation (b) (4) in multiple locations. For clarity, we suggest deleting this and similar abbreviations (e.g., (b) (4)) throughout the PI and instead spelling out the text.
2. Section 6.1 (Hepatic Encephalopathy subsection) states, ‘(b) (4) and “Table 2: Adverse Reactions Occurring in  $\geq 5\%$  of Patients Receiving **XIFAXAN** and at a Higher Incidence Than Placebo.” (emphasis added) Section 8.4 also states, “The safety and effectiveness of **XIFAXAN Tablets** in pediatric patients with Traveler’s Diarrhea less than 12 years of age have not been established.” (emphasis added) Please consider adding context regarding the tablet strength (e.g., XIFAXAN 550 mg or XIFAXAN 200 mg) consistently throughout the PI as clinically appropriate.
3. Section 12.3 includes the text, “0.50 mg norgestimate” in more than one location. For clarity, we suggest deleting the trailing zero.
4. DDMAC is concerned that the presentation of section 13.2, which appears to present the more favorable risk information first, frames the subsequent risk information as less serious. Please consider revising.
5. Section 14.2 states, (b) (4) DDMAC is concerned that this text may be used promotionally to overstate the efficacy of the drug. Is there substantial evidence to support this claim? If not, please consider deleting.
6. Section 17 should contain information that a prescriber should discuss with the patient (e.g., most important safety issues from the main safety sections of the label, and/or any important information on proper dosing, registries, etc.) We recommend revising this section to incorporate all of these important concepts, as appropriate. Specifically, we note that risk information from section 5.4 is omitted from section 17.

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22554

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ORIG-1

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SALIX  
PHARMACEUTICA  
LS INC

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XIFAXAN

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/s/  
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KATHLEEN KLEMM

03/17/2010

# MEMORANDUM

**To:** Sheila Lianos, RPh, PharmD  
Division of Gastroenterology Products

**From:** Iris Masucci, PharmD, BCPS  
Division of Drug Marketing, Advertising, and Communications  
for the Study Endpoints and Label Development (SEALD) Team, OND

**Date:** March 16, 2010

**Re:** Comments on draft labeling for Xifaxan (rifaximin) tablets  
NDA 22-554

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We have reviewed the proposed label for Xifaxan (FDA version dated 3/15/10 accessed via the eRoom on 3/16/10) and offer the following comments. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, labeling Guidances, and FDA recommendations to provide for labeling quality and consistency across review divisions. We recognize that final labeling decisions rest with the Division after a full review of the submitted data.

Please see attached label for recommended changes.

18 pp of draft labeling are withheld in full immediately after this page as (b)(4) CCI/TS.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22554	ORIG-1	SALIX PHARMACEUTICA LS INC	XIFAXAN

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/s/

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IRIS P MASUCCI  
03/23/2010

LAURIE B BURKE  
04/01/2010

## CONSULTATION REVIEW

**Date:** February 3, 2010

**To:** Dr Donna Griebel, M.D.  
Director  
Division of Gastroenterology Products  
and  
Ms Hee (Sheila) Lianos, R.Ph., PharmD.  
Project Manager  
Division of Gastroenterology Products

**From:** Anne Purfield, Ph.D.  
Microbiology Reviewer  
Division of Special Pathogen and Transplant Products  
Office of Antimicrobial Products  
and  
Shukal Bala, Ph.D.  
Microbiology team Leader  
Division of Special Pathogen and Transplant Products  
Office of Antimicrobial Products

**Through:** Renata Albrecht, M.D.  
Director  
Division of Special Pathogen and Transplant Products  
Office of Antimicrobial Products  
and  
Edward Cox, M.D., M.P.H.  
Director  
Office of Antimicrobial Products

**Subject:** NDA 21-554  
Effect of long term use of rifaximin on safety including clinical impact of cross resistance

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### Background:

Rifaximin, a structural analog of rifampin, acts by binding to the beta-subunit of bacterial DNA dependent RNA polymerase resulting in inhibition of bacterial RNA synthesis. Rifaximin is approved for the treatment of travelers' diarrhea caused by noninvasive strains of *Escherichia coli*. The approved dose and duration of treatment (200 mg t.i.d. for 3 days) is short.

The applicant had tested *in vitro* activity against a wide range of Gram positive and Gram negative bacterial pathogens. Rifaximin stays predominantly intraluminally. This makes it challenging to evaluate MICs in the usual fashion. The clinical trial results supported efficacy against *Escherichia coli* (enterotoxigenic and enteroaggregative strains) only.

The information from the clinical studies was not sufficient to interpret the *in vitro* susceptibility results for the other pathogens. Also, interpretative criteria and breakpoints could not be established for any of the pathogens in part because this is an intraluminal agent and stool cultures are difficult to work with for microbiologic evaluations. In the absence of interpretative criteria and breakpoints, the results of *in vitro* susceptibility (MIC) should be interpreted with caution. Although the word “resistance” is used below, this word is meant to denote an MIC value determined from susceptibility testing, but should be correlated with clinical outcome (i.e., failure) before the results can be interpreted that the organism is resistant to therapy.

On the basis of the preclinical and clinical information reviewed by microbiology reviewers (for details see microbiology reviews dated March 14, 2002 and April 13, 2004) the following information was included in the approved rifaximin package insert, including an acknowledgement that the clinical significance of the *in vitro* finding has not been studied:

*In Microbiology section:*

“*Escherichia coli* has been shown to develop resistance to rifaximin *in vitro*. However, the clinical significance of such an effect has not been studied.”

“Organisms with high rifaximin minimum inhibitory concentration (MIC) values also have elevated MIC values against rifampin. Cross-resistance between rifaximin and other classes of antimicrobials has not been studied.”

*In “Warnings and Precautions” section (Development of Drug Resistant Bacteria):<sup>1</sup>*

“Prescribing XIFAXAN Tablets in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.”

As noted above, the significance of an *in vitro* finding of “resistance” to an organism that is found in the gut lumen and acted upon by a product with low systemic absorption in the fasting and fed state (as noted in the XIFAXAN package insert) is unknown.

**Long Term Safety:**

There was no information on the long term safety of rifaximin available from the clinical studies reviewed previously for the treatment of travelers’ diarrhea; these studies were of 3 days duration.

**Effects of long term treatment on gut flora:**

For the treatment of hepatic encephalopathy (HE), [REDACTED] (b) (4). The currently approved regimen is short, only 3 days, and Dr. Anne Purfield, the Microbiology

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<sup>1</sup> 21 CFR 201.24 Labeling for Systemic Antibacterial Drug Products

Reviewer, found that no microbiology information was collected in the 6 month HE study or reported in the literature publications submitted by the applicant. In the absence of any microbiological data, the long term effects of rifaximin on gut flora and any change in the *in vitro* susceptibility of gut flora to rifaximin and other antimicrobial drugs within the rifamycin class cannot be evaluated.

Microorganisms can develop drug resistance during treatment (i.e., under drug pressure), and the same possibility exists with the use of rifaximin. It is important to note, however, that there are several drugs of the rifamycin class (e.g., rifampin, rifabutin, and rifapentine) that are currently approved, marketed and used in combination with other drugs for the long term treatment of tuberculosis. The role of these products on *in vitro* susceptibility of gut flora, and the additional impact of the long term use of rifaximin on gut flora have not been evaluated.

**Recommendation:**

If rifaximin is approved for the treatment of HE, post marketing studies should be considered to evaluate the effect of long term treatment with rifaximin on the gut flora and *in vitro* susceptibility to rifaximin and other rifamycin antimicrobial drugs, and depending on the outcome of such studies, consideration may need to be given to evaluating the clinical significance of *in vitro* “resistance” on the efficacy of rifaximin.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22554	ORIG-1	SALIX PHARMACEUTICA LS INC	XIFAXAN

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/s/

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ANNE E PURFIELD  
02/18/2010

SHUKAL BALA  
02/18/2010

RENATA ALBRECHT  
02/18/2010

EDWARD M COX  
02/20/2010



# Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: January 28, 2010

From: CDER DCRP QT Interdisciplinary Review Team

Through: Norman Stockbridge, M.D., Ph.D.  
Division Director  
Division of Cardiovascular and Renal Products /CDER

To: Hee (Sheela) Lianos/ Regulatory Project Manager  
Lara Dimick, MD, FACS/ Medical Officer  
Division of Gastroenterology Products (DGP)

Subject: QT-IRT Consult to NDA 22554

This memo responds to your consult to us dated Jan 14, 2010 regarding QT assessment for Xifaxan (rifaximin), sponsored by Salix Pharmaceuticals. The QT-IRT received and reviewed the following materials:

- Your consult request and review materials submitted by the division
- PI for Xifaxan

## Question from DGP

“DGP respectfully request your review of the data and expert opinion on the need for the thorough QT study and if this should be done preapproval for this indication or as a post-marketing study requirement.”

## *QT-IRT Response*

1. For drugs with systemic bioavailability, we typically recommend a thorough QT/QTc study. In this case, however, the bioavailability of rifaximin is low in healthy volunteers but increases in patients (mean unbound C<sub>max</sub>- 0.017  $\mu$ M in Child-Pugh C category). Potent inhibitors of hERG are typically active in the nM range. Rifaximin inhibited hERG expressed in a mammalian cell line quite weakly, with an IC<sub>50</sub> greater than 100  $\mu$ M. Therefore QT liability through hERG inhibition is unlikely. Nevertheless, standard practice is to do the clinical evaluation of QT or do close monitoring in phase 3 studies.

2. The sponsor should collect ECGs in their ongoing/planned studies as part of PMR or PMC to exclude large cardiovascular effects.

## **BACKGROUND**

Xifaxan (rifaximin) 550 mg Tablets has been submitted under NDA 022554 with the Division of Gastroenterology Products for the indication of prevention of episodes of recurrent hepatic encephalopathy (HE) in patients greater than 18 years of age. Rifaximin is a semi-synthetic rifamycin antibiotic and is largely not absorbed from the gastrointestinal tract. Rifaximin has previously been approved (NDA 021361) for the treatment of traveler's diarrhea in patients > 12 years of age. Under this new indication, rifaximin will be used long term (possibly for many years).

A thorough QT study has been requested of the sponsor in the past by DGP, however the sponsor has asserted that since the drug is poorly absorbed and systemic exposure is low, a TQT study was not required.

### Non-Clinical Experience

*Source: ChanTest Study 090413.TBM*

#### “Summary

The objective of this study was to examine the in vitro effects of Rifaximin on the hERG (human ether-à-go-go-related gene) channel current (a surrogate for IKr, the rapidly activating, delayed rectifier cardiac potassium current) at near-physiological temperature. Rifaximin inhibited hERG current by (Mean ± SEM) 6.7 ± 0.5% at 10 µM (n = 3), 16.8 ± 1.0% at 30 µM (n = 3), 34.5 ± 2.7% at 100 µM (n = 3) and 44.3 ± 4.9% at 300 µM (n = 3) versus 0.7 ± 0.1% (n = 3) in control. hERG inhibition at 30, 100 and 300 µM were statistically significant (P < 0.05) when compared to vehicle control values. Although there was increase in inhibition at 300 µM compared to the 100 µM, due to precipitation observed under the microscope during the 300 µM recordings (see section 9.2.1), the IC50 for the inhibitory effect of Rifaximin on hERG potassium current could only be estimated to be greater than 100 µM.

“Under identical conditions, the positive control (60 nM terfenadine) inhibited hERG potassium current by (Mean ± SD; n = 2) 81.6 ± 3.9%. This result confirms the sensitivity of the test system to hERG inhibition.

“Samples of the test article formulation solutions collected from the outflow of the perfusion apparatus were analyzed for concentration verification. The results from the sample analysis indicated that the measured concentrations of Rifaximin at all test concentrations were within (b) (4) RE of nominal concentrations, thereby meeting the acceptance criteria.

“The sample analysis indicated that all formulations were homogeneous at the beginning of testing.

“The stability of test article stock solutions (b) (4) and formulations ( (b) (4) ) were confirmed during the method validation study. All stock solutions and formulations prepared for the experiments were used and analyzed within the established stability windows.”

*Reviewer’s Comments: Rifaximin inhibited hERG expressed in a mammalian cell line quite weakly, with an IC50 greater than 100 micromolar. Assay sensitivity was adequate as demonstrated with a positive control (terfenadine). This nonclinical reviewer considers rifaximin to be a weak inhibitor, unlikely to be proarrhythmic.*

#### Previous Clinical Experience.

DGP reports that the sponsor has not performed ECG’s on any patients in the one pivotal Phase 3 controlled trial or in the treatment extension safety trial. Physical exams and vitals only were performed. There were cardiac incidents in the Phase 3 trials, but these are high risk patients, with multiple complications. The only study in which ECGs were collected at baseline and post-study was RFPK 1002 (a GI transit study in healthy volunteers) and no clinically relevant QT prolongation or ECG abnormalities were noted. However, this information is not very helpful since ECGs were obtained post-study and not at Tmax.

*Reviewer’s Comments: Ideally ECGs should have been collected in the phase 3 program since concentrations over 10-fold higher than healthy subjects (up to 52 mg/ml) are seen in subjects with hepatic encephalopathy.*

#### Clinical Pharmacology

*See Appendix for sponsor’s highlights of clinical pharmacology table*

The absorption of drug is very low (i.e., < 1% in healthy individuals). The absorption is increased 10- to 13-fold in patients with Child’s class A, B and C cirrhosis (Table 1).

#### **Table 1 Rifaximin and Rifampin Systemic Exposure Comparison**

### Rifaximin and Rifampin Systemic Exposure Comparison

Rifamycin	Free Fraction	MW	Therapeutic Dose	Total mean $C_{max}$ ( $\mu\text{g/mL}$ )	Unbound mean $C_{max}$ ( $\mu\text{M}$ )	Rifaximin fold exposure reduction versus rifampin
Rifaximin <sup>a</sup> (healthy subjects)	0.32	785.9	550 mg BID	0.0034	0.0014	1228.82
Rifaximin <sup>b</sup> (Child-Pugh A)	0.38	785.9	550 mg BID	0.0195	0.0094	180.43

Rifaximin <sup>b</sup> (Child-Pugh B)	0.38	785.9	550 mg BID	0.0251	0.0121	140.17
Rifaximin <sup>c</sup> (Child-Pugh C)	0.38	785.9	550 mg BID	0.0347	0.0168	101.39
Rifampin <sup>d</sup> (healthy subjects)	0.2	822.96	600 mg QD	7	1.7012	1.00

a: RFPK1007; b: RFHE3002PK; c: preliminary data, n=3, RFHE3002PK supplement; d: RIFADIN package insert;  $C_{max}$  is from single dose. Abbreviations: BID=twice daily;  $C_{max}$ =maximum plasma concentration; QD=once daily.

#### Reviewer's Comments:

1. Rifaximin exposure ( $C_{max}$ ) is anticipated to increase about 10- to 13-fold in patients with compromised hepatic function.
2. Rifaximin concentrations observed in patients and healthy subjects are below the concentration range associated with positive hERG channel results. The unbound mean  $C_{max}$  in patients with Child-Pugh C is 0.0168  $\mu\text{M}$ .

Thank you for requesting our input into the development of this product under IND. We welcome more discussion with you now and in the future. Please feel free to contact us via email at [cderderpqt@fda.hhs.gov](mailto:cderderpqt@fda.hhs.gov)

## APPENDIX

### Highlights of Clinical Pharmacology - Rifaximin

Therapeutic dose	Hepatic encephalopathy: 550 mg twice daily (1100 mg/day)
Maximum tolerated dose	Maximum dose tested: 800 mg three times daily (2400 mg/day) [RFHE9702]
Principal adverse events	Travelers' diarrhea (200 mg TID x 3 days): Adverse events occurred at similar rates between placebo- and rifaximin-treated subjects; the most common adverse events occurring in >10% of patients were flatulence and abdominal pain. Hepatic encephalopathy (550 mg BID): The overall profile of adverse events is consistent with the population under study, i.e., subjects with liver cirrhosis and a history of overt hepatic encephalopathy. The most common adverse events occurring in >10% of patients were peripheral edema, nausea, dizziness, fatigue, ascites, diarrhea, and headache, with similar rates in placebo- and rifaximin-treated subjects.

Maximum dose tested	Single Dose	<ul style="list-style-type: none"> <li>• 550 mg in healthy subjects [RFPK1007]</li> <li>• 550 mg in IBS subjects [RFPK1010]</li> <li>• 800 mg in HE subjects [RFHE9702]</li> </ul>												
	Multiple Dose	<ul style="list-style-type: none"> <li>• 550 mg TID for 14 days (1650 mg daily dose) in healthy subjects [RFPK1007]</li> <li>• 550 mg TID for 14 days (1650 mg daily dose) in IBS subjects [RFPK1010]</li> <li>• 550 mg BID for at least 7 days (1100 mg daily dose) in mild to moderate HE subjects [RFHE3002PK]</li> <li>• 800 mg TID for 7 days (2400 mg daily dose) in HE subjects [no traditional exposure estimates; RFHE9702]</li> </ul>												
Exposures Achieved at Maximum Tested Dose	Single Dose	<p>Healthy subjects (550 mg):  Mean C<sub>max</sub>: 4.04 ng/mL (37.4%CV)  Mean AUC<sub>∞</sub>: 11.1 ng•h/mL (37.4 %CV)</p> <p>IBS subjects (550 mg):  Mean C<sub>max</sub>: 3.49 ng/mL (39.0%CV)  Mean AUC<sub>∞</sub>: 15.5 ng•h/mL (43.4%CV)</p> <p>HE subjects (800 mg):  Mean 3-h concentration: 13.5 ng/mL</p>												
	Multiple Dose	<p>Healthy subjects (550 mg TID):  Mean C<sub>max</sub>: 2.39 ng/mL (53.6%CV)  Mean AUC<sub>tau</sub>: 9.30 ng•h/mL (29.0 %CV)</p> <p>IBS subjects (550 mg TID):  Mean C<sub>max</sub>: 4.22 ng/mL (63.0%CV)  Mean AUC<sub>tau</sub>: 16.0 ng•h/mL (59.9%CV)</p> <p>HE subjects (550 mg BID):  Mean C<sub>max</sub>: 21.1 ng/mL (55.9%CV)  Mean AUC<sub>tau</sub>: 130 ng•h/mL (59.7 %CV)</p>												
Range of linear PK	<p>While the linearity of rifaximin PK has not been assessed in a single clinical study, the following single-dose data [mean (SD)] are available:</p> <table border="1"> <thead> <tr> <th>Dose</th> <th>AUC (ng.h/mL)</th> <th>C<sub>max</sub> (ng/mL)</th> </tr> </thead> <tbody> <tr> <td>400 mg (2 x 200)</td> <td>12.73 (7.13)</td> <td>3.48 (2.15)</td> </tr> <tr> <td>400 mg (2 x 200)</td> <td>18.35 (9.48)</td> <td>3.80 (1.32)</td> </tr> <tr> <td>550 mg</td> <td>11.1 (4.15)</td> <td>4.04 (1.51)</td> </tr> </tbody> </table> <p>The data suggest no proportional dose-exposure relationship across the dosage range of 400 to 550 mg, in keeping with the solubility- and permeability limited absorption of rifaximin.</p>		Dose	AUC (ng.h/mL)	C <sub>max</sub> (ng/mL)	400 mg (2 x 200)	12.73 (7.13)	3.48 (2.15)	400 mg (2 x 200)	18.35 (9.48)	3.80 (1.32)	550 mg	11.1 (4.15)	4.04 (1.51)
Dose	AUC (ng.h/mL)	C <sub>max</sub> (ng/mL)												
400 mg (2 x 200)	12.73 (7.13)	3.48 (2.15)												
400 mg (2 x 200)	18.35 (9.48)	3.80 (1.32)												
550 mg	11.1 (4.15)	4.04 (1.51)												
Accumulation at steady state	550 mg BID for 7 days in healthy volunteers [RFPK1007]: Mean accumulation ratio: 1.37 (42.5%CV);													
Metabolites	25-desacetylrifaximin: <ul style="list-style-type: none"> <li>• &lt;1% of dose appears in feces, &lt;0.01% in urine, undetectable in plasma following 400 mg <sup>14</sup>C-rifaximin oral dose [RFPK9801]</li> <li>• Biological activity not determined</li> </ul>													
Absorption	Absolute/Relative Bioavailability	The systemic absorption of rifaximin is low, accounting for <0.4% of the dose following oral administration [RFPK9801]. Absolute												

		bioavailability and relative bioavailability studies have not been conducted.
	T <sub>max</sub>	Based on 550 mg BID dose: <ul style="list-style-type: none"> <li>• In healthy subjects [RFPK1007]: Median T<sub>max</sub>: 0.76 h (range 0.5 - 4.0 h)</li> <li>• In subjects with mild to moderate HE [RFHE3002PK]: Median T<sub>max</sub>: 1.00 h (range 0.933 to 10.0 h)</li> <li>• Median (range) for metabolites - Not applicable</li> </ul>
Distribution	V <sub>d</sub> /F or V <sub>d</sub>	Based on 550 mg BID dose: No V <sub>d</sub> information available; the V <sub>d</sub> /F results are inflated by the drug's low and variable bioavailability. <ul style="list-style-type: none"> <li>• In healthy subjects [RFPK1007]: Mean V<sub>d</sub>/F: 400,000 L (53.6 %CV)</li> <li>• In subjects with mild to moderate HE [RFHE3002PK]: Mean V<sub>d</sub>/F: 83,000 L (87.8 %CV)</li> </ul>
	% bound	Mean (%CV) [MC09M-0004]: In vitro (5 ng/mL): 65.8 (7.36) In vitro (10 ng/mL): 66.5 (2.68) Ex vivo (healthy subjects): 67.5 (5.50) Ex vivo (liver impaired): 62.0 (7.06)
Elimination	Route	<ul style="list-style-type: none"> <li>• Primary route: feces; of ~97% recovered, 96.62% in feces [RFPK9801]</li> <li>• Other routes: renal (0.025%), biliary, metabolic</li> </ul>
	Terminal t <sub>1/2</sub>	Based on 550 mg BID dose: <ul style="list-style-type: none"> <li>• In healthy subjects [RFPK1007]: Mean t<sub>1/2</sub>: 4.17 h (79.1 %CV)</li> <li>• In subjects with mild to moderate HE [RFHE3002PK]: Mean t<sub>1/2</sub>: 8.64 h (42.0 %CV)</li> <li>• Mean (%CV) for metabolites - Not applicable</li> </ul>
	CL/F or CL	Based on 550 mg BID dose: No CL information available; the CL/F results are inflated by the drug's low and variable bioavailability. <ul style="list-style-type: none"> <li>• In healthy subjects [RFPK1007]: Mean CL/F: 863 L/min (42.2 %CV)</li> <li>• In subjects with mild to moderate HE [RFHE3002PK]: Mean CL/F: 109 L/min (82.7 %CV)</li> </ul>
Intrinsic Factors	Age	Geriatrics: Healthy subjects: Not available (not assessed in subjects >65 years of age) Liver-impaired subjects: Insufficient number of subjects >65 years of age (n=2) to detect a difference in pharmacokinetics Pediatrics: The pharmacokinetics of rifaximin has not been

		studied in pediatric patients of any age.
	Sex	<p>No sex-related statistically significant differences were observed:</p> <p>In healthy subjects (550 mg BID [RFPK1007]):</p> <p>Female: Mean <math>C_{max}</math>: 3.67 ng/mL  Mean <math>AUC_{tau}</math>: 13.09 ng•h/mL</p> <p>Male: Mean <math>C_{max}</math>: 3.06 ng/mL  Mean <math>AUC_{tau}</math>: 11.20 ng•h/mL</p> <p>In liver impaired subjects (550 mg BID [RFHE3002PK]):</p> <p>Female: Mean <math>C_{max}</math>: 22.2 ng/mL  Mean <math>AUC_{tau}</math>: 150 ng•h/mL</p> <p>Male: Mean <math>C_{max}</math>: 20.5 ng/mL  Mean <math>AUC_{tau}</math>: 118 ng•h/mL</p>
	Race	<p>No race-related statistically significant differences were observed:</p> <p>In healthy subjects (550 mg BID [RFPK1007]):</p> <p>Non-white: Mean <math>C_{max}</math>: 3.80 ng/mL  Mean <math>AUC_{tau}</math>: 12.11 ng•h/mL</p> <p>White: Mean <math>C_{max}</math>: 3.19 ng/mL  Mean <math>AUC_{tau}</math>: 12.37 ng•h/mL</p> <p>In liver impaired subjects (550 mg BID [RFHE3002PK]):</p> <p>Black or African-American: Mean <math>C_{max}</math>: 17.6 ng/mL  Mean <math>AUC_{tau}</math>: 102 ng•h/mL</p> <p>White: Mean <math>C_{max}</math>: 21.5 ng/mL  Mean <math>AUC_{tau}</math>: 134 ng•h/mL</p>
	Hepatic & Renal Impairment	<p>Hepatic impairment:</p> <p><b><math>AUC_{tau}</math> (ng h/mL):</b></p> <p>Healthy: 12.3  Child-Pugh A: 118  Child-Pugh B: 161  Child-Pugh C: 246</p> <p><b><math>C_{max}</math> (ng/mL):</b></p> <p>Healthy: 3.41  Child-Pugh A: 19.5  Child-Pugh B: 25.1  Child-Pugh C: 35.5</p> <p>Following 550 mg BID rifaximin, rifaximin mean <math>AUC_{tau}</math> in subjects with Child-Pugh A, B, and C were approximately 9.6, 13.1, and 20-fold higher, respectively, than those observed in healthy subjects. Corresponding mean <math>C_{max}</math> values were 5.7, 7.4, and 10.4-fold higher, respectively. The increase in systemic exposure to rifaximin in subjects with hepatic impairment should be interpreted in light of rifaximin gastrointestinal local action and its low systemic bioavailability, as well as the available rifaximin safety data in subjects with cirrhosis</p>

		<p>(RFHE3001 and RFHE3002). As a result, no dosing adjustment should be required in individuals with hepatic impairment.</p> <p>Renal impairment: The pharmacokinetics in subjects with renal impairment has not been studied; however, rifaximin renal clearance is very low since less than 0.4% of the dose is recovered in urine.</p>																																																																														
Extrinsic Factors	Drug interactions	<p>In clinical drug-drug interaction studies, no clinically significant effects of rifaximin on the pharmacokinetics of midazolam or oral contraceptives were observed.</p> <p>MIDAZOLAM:</p> <ul style="list-style-type: none"> <li>• Rifaximin 550 mg TID x 7 and 14 d: effect on oral midazolam (2 mg PO) pharmacokinetics [RFDI1008]:</li> </ul> <table> <tr> <td><math>C_{max}</math> (ng/mL):</td> <td>Day 1 (no rifaximin)</td> <td>10.8</td> </tr> <tr> <td></td> <td>7 d rifaximin</td> <td>10.1</td> </tr> <tr> <td></td> <td>14 d rifaximin</td> <td>10.1</td> </tr> </table> <ul style="list-style-type: none"> <li>• Rifaximin 550 mg TID x 7 and 14 d: effect on oral midazolam (2 mg PO) pharmacokinetics [RFDI1008]:</li> </ul> <table> <tr> <td><math>AUC_{\infty}</math> (ng.h/mL):</td> <td>Day 1 (no rifaximin)</td> <td>24.7</td> </tr> <tr> <td></td> <td>7 d rifaximin</td> <td>23.4</td> </tr> <tr> <td></td> <td>14 d rifaximin</td> <td>22.2</td> </tr> </table> <ul style="list-style-type: none"> <li>• Rifaximin 200 mg TID x 3 and 9 d: effect on oral midazolam (6 mg PO) pharmacokinetics [RFDI1002]:</li> </ul> <table> <tr> <td><math>C_{max}</math> (ng/mL):</td> <td>Day 1 (no rifaximin)</td> <td>32.4</td> </tr> <tr> <td></td> <td>3 d rifaximin</td> <td>29.1</td> </tr> <tr> <td></td> <td>9 d rifaximin</td> <td>31.9</td> </tr> </table> <ul style="list-style-type: none"> <li>• Rifaximin 200 mg TID x 3 and 9 d: effect on oral midazolam (6 mg PO) pharmacokinetics [RFDI1002]:</li> </ul> <table> <tr> <td><math>AUC_{\infty}</math> (ng.h/mL):</td> <td>Day 1 (no rifaximin)</td> <td>77.8</td> </tr> <tr> <td></td> <td>3 d rifaximin</td> <td>72.3</td> </tr> <tr> <td></td> <td>9 d rifaximin</td> <td>68.6</td> </tr> </table> <ul style="list-style-type: none"> <li>• Rifaximin 200 mg TID x 3 and 9 d: effect on intravenous midazolam (2 mg IV) pharmacokinetics [RFDI1002]:</li> </ul> <table> <tr> <td><math>C_{max}</math> (ng/mL):</td> <td>Day 1 (no rifaximin)</td> <td>29.6</td> </tr> <tr> <td></td> <td>3 d rifaximin</td> <td>29.6</td> </tr> <tr> <td></td> <td>9 d rifaximin</td> <td>31.0</td> </tr> </table> <ul style="list-style-type: none"> <li>• Rifaximin 200 mg TID x 3 and 9 d: effect on intravenous midazolam (2 mg IV) pharmacokinetics [RFDI1002]:</li> </ul> <table> <tr> <td><math>AUC_{\infty}</math> (ng.h/mL):</td> <td>Day 1 (no rifaximin)</td> <td>84.8</td> </tr> <tr> <td></td> <td>3 d rifaximin</td> <td>83.5</td> </tr> <tr> <td></td> <td>9 d rifaximin</td> <td>84.3</td> </tr> </table> <p>ORAL CONTRACEPTIVES:</p> <ul style="list-style-type: none"> <li>• Rifaximin 550 mg TID x 7 d: effect on estradiol and norgestimate (Ortho Tri-Cyclen Lo) pharmacokinetics [RFDI1009]:</li> </ul> <p>Ethinyl Estradiol:</p> <table> <tr> <td><math>C_{max}</math> (pg/mL):</td> <td>Day 1 (no rifaximin)</td> <td>74.9</td> </tr> <tr> <td></td> <td>7 d rifaximin</td> <td>56.4</td> </tr> </table> <ul style="list-style-type: none"> <li>• Rifaximin 550 mg TID x 7 d: effect on estradiol and norgestimate (Ortho Tri-Cyclen Lo) pharmacokinetics [RFDI1009]:</li> </ul> <table> <tr> <td><math>AUC_{\infty}</math> (pg.h/mL):</td> <td>Day 1 (no rifaximin)</td> <td>656</td> </tr> <tr> <td></td> <td>7 d rifaximin</td> <td>661</td> </tr> </table> <p>Norgestrel:</p> <table> <tr> <td><math>C_{max}</math> (pg/mL):</td> <td>Day 1 (no rifaximin)</td> <td>560</td> </tr> <tr> <td></td> <td>7 d rifaximin</td> <td>494</td> </tr> </table> <ul style="list-style-type: none"> <li>• Rifaximin 550 mg TID x 7 d: effect on estradiol and norgestimate (Ortho Tri-Cyclen Lo) pharmacokinetics [RFDI1009]:</li> </ul> <table> <tr> <td><math>AUC_{\infty}</math> (pg.h/mL):</td> <td>Day 1 (no rifaximin)</td> <td>19500</td> </tr> <tr> <td></td> <td>7 d rifaximin</td> <td>17700</td> </tr> </table>	$C_{max}$ (ng/mL):	Day 1 (no rifaximin)	10.8		7 d rifaximin	10.1		14 d rifaximin	10.1	$AUC_{\infty}$ (ng.h/mL):	Day 1 (no rifaximin)	24.7		7 d rifaximin	23.4		14 d rifaximin	22.2	$C_{max}$ (ng/mL):	Day 1 (no rifaximin)	32.4		3 d rifaximin	29.1		9 d rifaximin	31.9	$AUC_{\infty}$ (ng.h/mL):	Day 1 (no rifaximin)	77.8		3 d rifaximin	72.3		9 d rifaximin	68.6	$C_{max}$ (ng/mL):	Day 1 (no rifaximin)	29.6		3 d rifaximin	29.6		9 d rifaximin	31.0	$AUC_{\infty}$ (ng.h/mL):	Day 1 (no rifaximin)	84.8		3 d rifaximin	83.5		9 d rifaximin	84.3	$C_{max}$ (pg/mL):	Day 1 (no rifaximin)	74.9		7 d rifaximin	56.4	$AUC_{\infty}$ (pg.h/mL):	Day 1 (no rifaximin)	656		7 d rifaximin	661	$C_{max}$ (pg/mL):	Day 1 (no rifaximin)	560		7 d rifaximin	494	$AUC_{\infty}$ (pg.h/mL):	Day 1 (no rifaximin)	19500		7 d rifaximin	17700
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		<p>17-Deacetyl Norgestimate:</p> <p><math>C_{max}</math> (pg/mL): Day 1 (no rifaximin) 1770 7 d rifaximin 1550</p> <p><math>AUC_{\infty}</math> (pg.h/mL): Day 1 (no rifaximin) 19400 7 d rifaximin 17900</p> <ul style="list-style-type: none"> <li>• Rifaximin 200 mg TID x 3 d: effect on estradiol and norgestimate (Ortho-Cyclen) pharmacokinetics [RFDI1001]:</li> </ul> <p>Ethinyl Estradiol:</p> <p><math>C_{max}</math> (ng/mL): Day 1 (no rifaximin) 0.20 3 d rifaximin 0.19</p> <p><math>AUC_{\infty}</math> (ng.h/mL): Day 1 (no rifaximin) 1.95 3 d rifaximin 1.85</p> <p>Norgestrel:</p> <p><math>C_{max}</math> (ng/mL): Day 1 (no rifaximin) 1.03 3 d rifaximin 1.09</p> <p><math>AUC_{\infty}</math> (ng.h/mL): Day 1 (no rifaximin) 41.4 3 d rifaximin 46.1</p> <p>17-Deacetyl Norgestimate:</p> <p><math>C_{max}</math> (ng/mL): Day 1 (no rifaximin) 3.48 3 d rifaximin 3.40</p> <p><math>AUC_{\infty}</math> (ng.h/mL): Day 1 (no rifaximin) 38.0 3 d rifaximin 39.3</p> <p>IN VITRO:</p> <ul style="list-style-type: none"> <li>• No significant inhibition of human CYPs 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, 3A4 [N2271] or human BSEP [RFDM0105]</li> <li>• 1.8-fold induction of hepatocyte CYP3A4 activity by rifaximin 10 <math>\mu</math>M [N2246], with no clinically significant induction of CYP3A4 substrates observed in vivo.</li> </ul>
	Food Effects	<p>Food significantly delayed 550 mg rifaximin absorption following a high-fat meal (median <math>T_{max}</math> increased from 0.75 h fasted to 1.5 h fed), and increased rifaximin systemic exposure by approximately 2-fold as determined by AUC (11.1 to 22.5 ng•h/mL); this increase was not reflected in <math>C_{max}</math>. In an earlier study, administration of rifaximin 400 mg with a high-fat meal increased <math>C_{max}</math> and AUC approximately 2-fold. However, since the absolute systemic bioavailability of rifaximin is relatively low and the drug works locally in the gastrointestinal tract, rifaximin can be given with or without food.</p>
Expected High Clinical Exposure Scenario		<p>In instances of liver function impairment, a <math>C_{max}</math> change of approximately 10-fold and an AUC change of approximately 20-fold, consistent with data from RFHE3002PK, would be anticipated; the highest exposure observed in RFHE3002PK was <math>C_{max}=52.2</math> ng/mL. Exposures exceeding this have been observed at an 800 mg three times daily dose in a previous study in human subjects [RFHE9702].</p>

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22554	ORIG-1	SALIX PHARMACEUTICA LS INC	XIFAXAN

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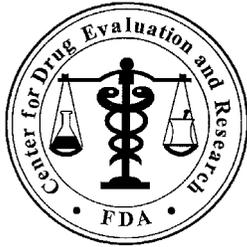
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SUCHITRA M BALAKRISHNAN  
01/28/2010

JOHN E KOERNER  
01/28/2010

HAO ZHU  
01/28/2010

NORMAN L STOCKBRIDGE  
01/29/2010



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: December 14, 2009

To: Donna J. Griebel, MD, Director  
Division of Gastroenterology Products

Through: Kellie Taylor, PharmD, Team Leader  
Denise Toyer, PharmD, Deputy Director  
Carol Holquist, RPh, Director  
Division of Medication Error Prevention and Analysis

From: Cathy A. Miller, MPH, RN, Safety Evaluator  
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Xifaxan (Rifaximin) Tablets  
550 mg

Application Type/Number: NDA 22-554

Applicant/sponsor: Salix Pharmaceuticals, Inc.

OSE RCM #: 2009-1397

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## **EXECUTIVE SUMMARY**

The Division of Medication Error Prevention and Analysis evaluated the container labels, carton and insert labeling for Xifaxan (Rifaximin) tablets (NDA 22-554) and identified vulnerabilities that could lead to medication errors. Specifically, we raise concern with the close proximity of the strength (550 mg) to the net quantity (6 tablets and 60 tablets) as presented on the principal display panel of container labels and carton labeling. We also ask that the Applicant consider increasing the prominence of the 550 mg strength on the unit dose foil pack container to provide added differentiation from the 200 mg strength foil pack container. We believe these vulnerabilities can be revised prior to approval and we have provided our recommendations in Section 5.2 (*Comments to the Applicant*) that aim at reducing the risk of medication errors with regards to the proposed labels and labeling.

Lastly, we note that the container label for the currently marketed Xifaxan 200 mg strength 100-count size is presented with a different color scheme (b) (4) than all other labels and labeling for the 200 mg strength, presented in (b) (4). DMEPA has concerns that the differentiation of the quantity of tablets between the 30-count and 100-count size is not necessary and may cause wrong strength selection errors once the 550 mg strength is available. We believe these vulnerabilities can be remedied through revisions to current labels and labeling submitted by the Applicant as a prior approval supplement to new drug application (NDA 21361) and we have provided recommendations in Section 5.1 (*Comments to the Sponsor*).

## **1 BACKGROUND**

### **1.1 INTRODUCTION**

This review is in response to an August 4, 2009 request from the Division of Gastroenterology Products for an assessment of the labels and labeling for the proposed new strength (550 mg) of Xifaxan (Rifaximin) tablets for evaluation to identify areas that could lead to medication errors.

Xifaxan (Rifaximin) is currently an approved product (NDA 21-361) for the treatment of traveler's diarrhea in a 200 mg strength tablet. On June 24, 2009, the Applicant submitted efficacy supplement (S-010) to the NDA (NDA 21-361) for a proposed new strength (550 mg) and indication (maintenance of remission and prevention of recurrent hepatic encephalopathy). The Applicant requested priority review for the efficacy supplement based on the claims of providing a safe and effective therapy to maintain patients' remission from hepatic encephalopathy (HE) for which there is no satisfactory alternative therapy. This application is being reviewed by the Division of Gastroenterology Products for the new indication and therefore, a separate new drug application number (NDA 22-554) was assigned for administrative purposes.

### **1.2 PRODUCT INFORMATION**

Xifaxan (Rifaximin) was originally granted orphan drug designation on February 10, 1998 for the indication of treatment of hepatic encephalopathy. Xifaxan 200 mg tablets were approved on May 25, 2004 for the indication of treatment of traveler's diarrhea

under new drug application (NDA 21-361) under the Division of Special Pathogens and Transplant Products. The recommended dose for the indication of traveler's diarrhea is one 200 mg tablet taken three times daily for three days. The 200 mg strength is available in a pink round non-scored tablet with the letters 'SX' embossed on the front of the tablet. Xifaxan 200 mg tablets are supplied in single blister unit professional samples, bottles of 30-count and 100-count tablets, and cartons of 100-count unit dose tablets.

The proposed new Xifaxan 550 mg strength is indicated for the treatment of hepatic encephalopathy and the recommended dose is one 550 mg tablet taken two times a day. The proposed 550 mg strength will be available in a pink oval-shaped (b) (4) tablet with the letters 'rfx' embossed on the front of the tablet. Xifaxan 550 mg tablets will be supplied in bottles of six tablet professional samples, bottles of 60-count tablets and cartons of 60-count unit dose tablets.

## **2 MATERIALS REVIEWED**

### **2.1 ADVERSE EVENTS REPORTING SYSTEM (AERS) DATABASE**

Xifaxan 200 mg tablets are currently marketed, therefore, DMEPA conducted a search of the Adverse Events Reporting System (AERS) on October 14, 2009 using the product name "Xifaxan", the active ingredient name "Rifaximin" and the verbatim terms "Xifaxan%" and "Rifaximin%" along with the MedDRA reaction terms "Medication Errors" (HLGT), "Product Quality Issue" (PT) and "Product Label Issue" (HLT).

The reports were manually reviewed to determine if a medication error occurred. Duplicate reports were grouped together into cases. If an error occurred, the staff reviewed the cases to determine if the root cause could be associated with the labels, labeling, or packaging configuration of the product, and thus pertinent to this review. Those cases that did not describe a medication error were excluded from further analysis. The cases that did describe a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors.

### **2.2 LABELS AND LABELING**

For this product the Applicant submitted labels and labeling as part of the June 24, 2009 original submission. (See Appendix A through D for images of proposed container label and carton labeling for Xifaxan 550 mg tablets).

Using Failure Mode and Effects Analysis (FMEA),<sup>1</sup> the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the packaging, container labels, carton labeling and insert labeling and identified the following vulnerabilities that could lead to medication errors

Additionally, DMEPA evaluated container labels and carton labeling for the currently approved Xifaxan 200 mg strength tablet to assess whether the addition of labels and labeling for a new strength presents any potential for product confusion between the 200

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

mg and 550 mg strength tablets. (See Appendix E through J for images of currently approved contain labels and carton labeling for Xifaxan 200 mg tablets).

### **3 RESULTS**

#### **3.1 FDA ADVERSE EVENTS REPORTING SYSTEM (AERS) DATABASE**

Our search retrieved a total of 12 cases occurring between August 2005 and August 2009. Four of the cases were excluded as irrelevant to our review because they did not appear to describe a medication error. These four cases involved product complaints that the drug was ‘ineffective’ with additional adverse event reports of abdominal pain and diarrhea. The remaining eight cases were considered relevant to our labels and labeling review (see below).

##### ***3.1.1 Wrong Dose Medication Errors (n=2)***

Two of the eight relevant medication error cases involved Xifaxan overdoses. In the first case (ISR 5057785-3 dated 6/27/06), a consumer reported she was prescribed Xifaxan 1200 mg daily for ten days for irritable bowel syndrome (unlabeled indication). The report did not provide information about the rationale for the treating physician’s order therefore, it is not possible to conclude whether the physician intentionally prescribed this dose (off-label) for the indication or made an error in dosing and/or frequency. The patient experienced chronic headache and acute onsets of diarrhea. She discussed the unusually high dose with her physician after reading information about the recommended daily dose of 200 mg daily for three days. At the time of the report, however, it was not known if the patient continued the medication or received additional directives from the treating physician. It was also unclear from the report whether the physician did prescribe the dose as ‘1200 mg for ten days’. In the second case (ISR 5505890-1 dated 6/26/06), a physician reported that a patient being prepped for a colonoscopy accidentally took 21 Xifaxan tablets instead of the colonoscopy prep (name of drug not reported) she was prescribed. The patient had been prescribed Xifaxan for an intestinal bacterial growth (unlabeled indication) and misunderstood the instructions provided for the colonoscopy prep which resulted in a wrong dose medication error. At the time of the event, patient experienced slight nausea but no other symptoms were reported. DMEPA notes that Salix Pharmaceuticals (Xifaxan manufacturer) does market a colonoscopy prep medication named Osomprep however, the name of the preparation used in the reported case was not identified. The case does not specify whether the patient was given verbal instructions by the provider and/or the dispensing pharmacist regarding administration of either drug, nor does it state whether both prescriptions were dispensed at the same time. In neither case, however, were their contributing factors reported that identified labels or labeling deficiencies with Xifaxan.

##### ***3.1.2 Wrong Drug Medication Errors (n=6)***

Six of the eight cases were wrong drug errors related to established and proprietary name confusion.

### ***3.1.2.1 Rifaximin versus Rifampin Name Confusion***

Three of the six name confusion medication errors involved Rifaximin versus Rifampin. In the first case (ISR 4738453 dated 8/8/05), a pharmacist unfamiliar with the non-formulary drug Rifaximin received an order for “Rifaximin 400 mg per NG TID” intended for the treatment of hepatic encephalopathy symptoms (orphan drug indication). Because he was unfamiliar with the non-formulary drug or indication, he mistakenly compounded and filled the prescription with Rifampin suspension 400 mg per NG instead. The error was caught the next day by another pharmacist and the treating nurse. The patient had received three doses of the wrong drug however, no adverse events were reported. The reporter added that the unusual dose of Rifampin 400 mg should have prompted further investigation by the dispensing pharmacist. The remaining two cases (ISR 6332855-5 dated 2/3/2009) occurred in the same institution and were reported in the same case number. They involved errors during computer entry (‘RIF’ confusion during drug name entry) that lead to wrong drug dispensing medication errors. In the first case, a nurse who was calling to reschedule the time of the Rifampin dose asked the practitioner ‘what Rifampin was used for’ and subsequently discovered that the patient did not have tuberculosis or any other indication for which the drug is used. This prompted the nurse to investigate and discover that the root cause of the error occurred during order entry in the pharmacy at the time of dispensing. The second case describes the same type of order entry error and explains that a pharmacist discovered the wrong drug medication error while reviewing a patient’s medication profile. In both cases, the reporter explains that they use Horizon Meds Manager and at the time of the order entry, the pharmacist enters ‘RIFA’ to search the drug and only sees brand names that start with RIFA which includes Rifampin capsules and Rifampin compounded suspension. The reports also explain that if the pharmacist had typed ‘RIFAX’ instead of ‘RIFA’ no brand name would have matched the default display would have been all the ‘R’ drug names or the pharmacist could have selected a ‘generic’ button to search the drug name. The reporter also adds that in both cases, the written prescriptions were legible.

### ***3.1.2.2 Rifaximin versus Repraxain Name Confusion***

One medication error case (ISR 4923308 dated 2/22/06) involved Rifaximin versus Repraxain. The case was reported as a near miss when the wrong drug name was transcribed on a prescription order and error was caught before the drug was dispensed. The reporter added that contributing factors included similarities in the drug names.

### ***3.1.2.3 Rifaximin versus Ribavirin Name Confusion***

One medication error case (ISR 5984279 dated 12/4/2008) involved Rifaximin versus Ribavirin. A written prescription for Rifaximin 200 mg but it was misinterpreted as Ribavirin, and the wrong medication was subsequently processed, adjudicated and dispensed. The pharmacist was notified by the treating physician approximately one month after the incident, however, it was not reported whether the patient experience adverse events as a result of taking the wrong medication. No additional information was reported about the root cause of the wrong medication misinterpretation error.

### ***3.1.2.4 Xifaxan versus Skelaxin Name Confusion***

One medication error case (ISR 5013528 dated 5/26/06) involving Xifaxan versus Skelaxin. This error occurred when an order for Xifaxan was incorrectly spelled as 'Zyfazan' when written, and was subsequently misinterpreted as 'Skelaxin' when transcribed and dispensed. The patient took the wrong medication for three days before the error was discovered however, the report did not provide any details about the patient outcome. The reporter stated that illegibility of the drug name and unfamiliarity with Xifaxan were contributing factors to the medication error occurrence.

## **4 DISCUSSION**

Our evaluation considered how the introduction of a new 550 mg strength may or may not contribute to errors. To evaluate this, we considered current postmarketing errors reported with the use of Xifaxan. DMEPA found that none of the wrong dose medication errors identified in our AERS searches cited label or labeling vulnerabilities that contributed to the medication error occurrences.

Although six cases of name confusion medication errors retrieved in our search raise potential concerns about wrong drug medication errors, in no case did labels and labeling for Xifaxan 200 mg contribute to the medication errors that occurred. Additionally, the medication errors related to name confusion primarily involved the established name, Rifaximin, and therefore, labels and labeling did not necessarily contribute to the errors. We concluded that knowledge deficit with the new Xifaxan product, name similarities between the product's brand name and other drugs, as well as established name and other drug names, illegible handwriting, spelling errors, computer systems knowledge deficits and performance deficits lead to all of the wrong drug medication errors identified in our search. These errors occurred due to the practitioners' failure to refer to product information, failure to spell the drug name correctly, failure to investigate untraditional prescribed dosing, failure to utilize computer systems using comprehensive approaches provided with the system and general human factor errors due to lack of familiarity with a product or indication.

Although DMEPA recognizes that similar wrong drug name medication errors could occur in the future, we see no evidence that the addition of a new 550 mg strength will exacerbate such errors. Conversely, the addition of a second strength may provide an added differentiating feature that will prompt health care practitioners to verify the correct strength when selecting the drug product, and errors such as those identified with the computer entry systems may actually be averted since practitioners will need to search not only the drug name (RIF) but also the strength (200 mg versus 550 mg) when selecting the correct product. DMEPA provides an ongoing evaluation of medication errors through routine post-marketing surveillance efforts and if needed, to will re-evaluate these and other errors in the future.

Our review of the labels and labeling noted areas of needed improvement. These are discussed in detail below.

#### 4.1 PRESENTATION OF STRENGTH AND QUANTITY OF CONTAINER LABEL AND CARTON LABELING

DMEPA understands that there is minimal chance that the strength ‘550 mg’ will be confused or misinterpreted as the quantity ‘6 or 60’ as currently displayed adjacent to the strength on labels and labeling, especially since the Xifaxan is not available in a 6 mg or 60 mg tablet. However, because the proposed new strength and indication introduce a second Xifaxan product strength to the market, presenting the strength separately from the quantity will maximize the prominence of the strength and minimize any potential numeric confusion which may help avert wrong strength medication errors.

#### 4.2 DIFFERENTIATION OF 200 MG VERSUS 550 MG STRENGTHS

The Sponsor has provided several elements in the design of the proposed Xifaxan 550 mg labels and labeling that provide differentiation from the currently available 200 mg strength. The 200 mg versus 550 mg container labels and carton labeling have different color combination schemes and design. Additionally, the proposed new 550 mg strength has a distinguishing circular target with a green arrow design on the principal display panel (b) (4) (See Appendices A through H). While DMEPA agrees that this carton and container design differentiates the proposed 550 mg strength from the currently marketed 200 mg strength, (b) (4)

We agree that this feature may provide added distinction to practitioners during drug selection and dispensing (b) (4)

DMEPA also notes that, although the unit dose foil blister packs for the 200 mg and 550 mg strengths have inherent similarities given the packaging configuration and identical layout of information, the font colors provide differentiation with (b) (4) font color used on the 200 mg strength versus (b) (4) font color used on the 550 mg strength. However, added differentiation can be provided to distinguish the 200 mg blister from the 550 mg blister by increasing the size of the strength on the proposed ‘550 mg’ strength blister.

Lastly, DMEPA notes features on the currently marketed 200 mg strength container label that may introduce vulnerabilities that could lead to wrong strength medication errors. The Applicant has provided two different color schemes for the 30-count (b) (4) versus 100-count (b) (4) size container labels. Only the 100-count container label is presented in (b) (4) with all other container labels and carton labeling presented in (b) (4). We understand that this feature was likely implemented to differentiate the two size bottles however, DMEPA is concerned that practitioners may misinterpret this as a ‘strength’ differentiating feature, especially with the introduction of the new 550 mg strength. We also note that the strength on the currently marketed 200 mg strength container labels and carton labeling is not prominently displayed. With the introduction of a second Xifaxan strength, it will be even more important to provide strength differentiation for the 200 mg versus 550 mg products. Improvements can be made to the presentation of the 200 mg strength on currently marketed container labels and will provide comments to the Division in Section 5.1.

## 5 CONCLUSION AND RECOMMENDATIONS

Our evaluation noted areas where information on the label and labeling can be improved to minimize the potential for medication errors. We provide recommendations on revisions to the currently marketed container label for Xifaxan 200 mg strength in Section 5.1 (*Comments to the Division*). Section 5.2 (*Comments to the Applicant*) contains our recommendations for the container labels and carton labeling. We request the recommendations in Section 5.2 be communicated to the Applicant prior to approval.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have questions or need clarifications, please contact Nina Ton , OSE Regulatory Project manager, at 301-796-1648.

### 5.1 COMMENTS TO THE DIVISION

DMEPA limited our review to the proposed labels and labeling for Xifaxan 550 mg tablet and have provided our recommendations in Section 5.2. DMEPA notes, however, that while reviewing differentiating product characteristics between the proposed 550 mg strength and the currently marketed 200 mg strength, certain vulnerabilities were identified with container labels and carton labeling for the 200 mg strength product. We note that the strength on the currently marketed 200 mg strength container labels and carton labeling is not prominently displayed. With the introduction of a second Xifaxan strength, it will be even more important to provide strength differentiation for the 200 mg versus 550 mg products. Secondly, we note that the currently marketed Xifaxan 200 mg container labels have two different color schemes for the 30-count ( (b) (4) ) versus 100-count ( (b) (4) ) size container labels. Only the 100-count container label is presented in (b) (4) with all other container labels and carton labeling presented in (b) (4) . We understand that this feature was likely implemented by the Applicant to differentiate the two size bottles (30-count versus 100-count), however, DMEPA is concerned that practitioners may misinterpret this as a ‘strength’ differentiating feature, especially with the introduction of the new 550 mg strength.

DMEPA asks that the Applicant submit a prior approval supplement to the application (NDA 21361) with the following revisions to labels and labeling:

- 1) Increase the prominence of the strength presentation (200 mg) on the principal display panel of all container labels and carton labeling.
- 2) Revise the (b) (4) color scheme of the 100-count container label to align with the (b) (4) color scheme of all of the other Xifaxan 200 mg container labels and carton labeling.

### 5.2 COMMENTS TO THE APPLICANT

#### A. Container Labels and Carton Labeling

- 1) Relocate the net quantity of tablets (6 tablets and 60 tablets) away from the strength. Currently, the strength and quantity are presented adjacent to one another inside a ‘green arrow’ on container labels and carton labeling. DMEPA understands that there is minimal chance that the strength ‘550 mg’ will be

confused or misinterpreted as the quantity ‘6 or 60’, especially since the Xifaxan is not available in a 6 mg or 60 mg tablet. However, because the proposed new 550 mg strength and indication introduce a second Xifaxan product to the market, the presentation of this new strength while minimize any potential numeric confusion may help avert wrong strength medication errors.

- 2) Decrease the size of the graphic ‘target’ that appears adjacent to the strength ‘550 mg’ on the principal display panel of container labels and carton labeling. While DMEPA agrees that this carton and container design differentiates the proposed 550 mg strength from the currently marketed 200 mg strength, the graphic ‘target’ appears larger than the proprietary name, the established name and the strength, which should be the most prominent information on the principal display panel of the label.
- 3) If space permits, consider increasing the size of the 550 mg strength presentation on the unit dose foil blister pack to help provide differentiation from the 200 mg unit dose foil pack label.

## **6 REFERENCES**

### ***1. Adverse Events Reporting System (AERS)***

AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufactures that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential post-marketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

6 pages of draft labeling withheld in full immediately after this page as (b)(4) CCI/TS.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22554	ORIG-1	SALIX PHARMACEUTICA LS INC	XIFAXAN

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/s/

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CATHY A MILLER  
12/14/2009

KELLIE A TAYLOR  
12/14/2009

DENISE P TOYER  
12/15/2009

CAROL A HOLQUIST  
12/16/2009

**MEMORANDUM**

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

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**CLINICAL INSPECTION SUMMARY**

DATE: 11/2/09

TO: Hee (Sheila) Lianos, Regulatory Project Manager  
Lara Dimick, Medical Officer  
Division of Gastroenterology Products

FROM: Khairy Malek, Medical Officer  
Good Clinical Practice Branch 2  
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.  
Branch Chief  
Good Clinical Practice Branch 2  
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA or BLA: 22-554

APPLICANT: Salix Pharmaceuticals, Inc.

DRUG: Xifaxan (rifaximin)

NME: No

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATIONS: 1. Maintenance of remission of hepatic encephalopathy

CONSULTATION REQUEST DATE: July 23, 2009

DIVISION ACTION GOAL DATE: December 24, 2009  
PDUFA DATE: December 24, 2009

## **I. BACKGROUND:**

Hepatic encephalopathy (HE) is caused by a reversible decrease in neurologic function associated with liver failure and portosystemic venous shunting. It is associated with fulminant hepatic failure, end-stage liver disease and liver cirrhosis. Nitrogenous substances derived from the gut, most notably ammonia, are normally detoxified by the liver. As a result of decreased liver function, these compounds gain access to the circulation and brain and produce alteration in consciousness and behavior.

The new study drug, rifaximin is a broad spectrum oral antibiotic which is practically not absorbed (only <0.4% absorbed). It inhibits bacterial RNA synthesis in the gut. Rifaximin is approved in many countries including the US.

Two Protocols were conducted to support this NDA:

1. RFHE3001-“A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial To Evaluate The Efficacy, Safety And Tolerability of Rifaximin 550 mg BID For 6 Months In Preventing Hepatic Encephalopathy.”
2. RFHE3002-“A Multicenter, Open-Label Trial to Evaluate The Long-Term Safety And Tolerability Of Rifaximin 550 Mg BID In Subjects With A History Of Hepatic Encephalopathy”

Efficacy Assessment (Protocol 3001):

The primary efficacy endpoint was the time to the first breakthrough HE episode. A breakthrough HE episode was defined as an increase of the Conn score to Grade  $\geq 2$  or a Conn and asterixis score increase of one grade each for those subjects that have a baseline Conn score of 0. The time to the first breakthrough HE episode was defined as the duration between the first dose of the study drug and the date of the first breakthrough HE episode.

1. Conn Score
2. Asterixis Grades
3. Ammonia Concentration:  
At Days 0, 28, 84, and 168.
4. CLDQ; ESS; SF-36 (optional); daily lactulose intake are used for tertiary efficacy analysis.

**II. Results (by Site):**

<b>Name of CI Location</b>	<b>Protocol #: and # of Subjects:</b>	<b>Inspection Date</b>	<b>Final Classification</b>
Fred Poordad, M.D. Site 351. LA, CA	Protocol 1: # 3001-15 subjects Protocol 2: # 3002-10 subjects	9/28-10/8/09	Pending  (Preliminary Classification: VAI)
Muhammad Sheikh, M.D. Site 799, Fresno, CA	Protocol 1: # 3001-14 subjects Protocol 2: # 3002-6 subjects	9/14-9/22/09	Pending  (Preliminary Classification: NAI)
Olga Alexeeva, M.D. Site 938-Novgorod, Russia	Protocol 1: #3001-12 subjects Protocol 2: #3002-10 subjects	EIR Pending	Pending  (Preliminary Classification: NAI)
Vladimir Gorbakov, M.D. Moscow, Russia	Protocol 1: #3001-10 subjects Protocol 2: #3002- 2 subjects	EIR Pending	Pending  (Preliminary Classification: VAI)
Vladimir Rafalsky, M.D. Smolensk, Russia	Protocol 1: #3001-9 subjects Protocol 2: #3002-5 subjects	EIR Pending	Pending  (Preliminary Classification: NAI)

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and/or complete review of EIR is pending.

**1. Name of CI: Fred Poordad, M.D.-Site 351**

8635 West Third Street, Los Angeles, CA 90048

- a. The field investigator reviewed the records of all subjects in the 2 protocols  
Protocol 3001: 15 subjects enrolled in the study and 8 completed the study.  
Protocol 3002: 10 subjects enrolled in the study and it is still ongoing.

For Protocol 3001, the ORA Investigator mentioned that 15 were enrolled but 8 completed the study. The rationale for discontinuation was not discussed in the EIR.

- b. General observations/commentary:  
In general, the study appears to have been conducted appropriately at the site. No significant issues were noted, and a Form FDA 483 was not issued to the investigator. Items were discussed where subjects were not re-consented with updated consent forms in a timely manner. There was no under-reporting of adverse events, and no discrepancies were noted with primary and secondary endpoint verification.
- c. Assessment of data integrity: The data obtained from this site can be used in support of the NDA.

**2. Muhammad Sheikh, M.D. - Site 799**  
445 S. Cedar, Fresno, CA 93702

- a. What was inspected: The field investigator reviewed the records of 6 subjects in Protocol 3001. There were 6 subjects enrolled in Protocol 3002; 2 of them died, two had liver transplants and 2 remain in the study which is still ongoing.
- b. General observations/commentary: In general, the study appears to have been conducted adequately.
  - The field investigator did not report any violations or SAEs.
  - The field investigator reported that he reviewed the AEs and the SAEs and stated that they were accurately reported.
  - There was no mention of a review of the efficacy parameters, including ammonia, except that “he compared the source documents to CRFs and data listings” and no significant discrepancies were noted.
  - The field investigator did not review the lab reports, although he mentioned that they were in the records.
  - Regarding Protocol 3002, the Investigator stated that 2 subjects expired during the study and 2 subjects had liver transplant but did not mention the cause of death.

Although the EIR didn't specifically discuss data listings that were reviewed, there did not appear to be any significant discrepancies. A Form FDA 483 was not issued.

- c. Assessment of data integrity: The data from this site appear reliable and can be used in support of the NDA.

**3. Olga Alexeeva, M.D.**  
190 Rodionova Street, Nizhny Novgorod, 603126, Russia

- a. The field investigator and DSI reviewer, Dr. Khairy Malek, reviewed the records of all subjects in the study, 12 in Protocol 3001, and 10 in Protocol 3002. They compared the source documents with the data listings for the efficacy parameters and adverse events and found few differences. In Protocol 3001, five subjects on placebo, # 005, 006, 009, 010, and 012, had HE

breakthrough episodes. Adverse events observed in the rifaximin group were: headache and one day of retching for Subject # 011, higher liver enzymes for Subject # 004 from V2 (ALT 25, AST 42 and Gamma GT 56) to V15 (ALT 35, AST 201 and Gamma GT 2727). Subject # 013 (on placebo), died after 2 weeks due to liver cirrhosis in decompensation stage.

In Protocol 3002, there were 3 HE breakthrough episodes noted: Subject# 006, after a year, Subject#007 after 10 months on the drug and Subject 012 (were not reported by the sponsor with an excuse that the study is still going). There were higher liver enzymes in Subjects # 004, 007, 009, and 012. Two subjects had high bilirubin; # 012, and 014 which required hospitalization. Subjects # 4 and 14 had increase in their uric acid. Subjects # 007 and 012 withdrew from the study because of progressive liver cirrhosis and Subjects # 001, 004, 005, 008, 009, 010, and 014 are continuing in the study.

- b. General observations/commentary: The study was properly done, adequately recorded and we found no departure from federal regulations or from the protocol requirements. No Form FDA 483 was issued.
- c. Assessment of data integrity: The data from this site are considered reliable and can be used in support of the NDA.

#### **4. Vladimir Gorbakov, M.D.- Site # 905**

LLC, Clinical of Modern Medicine, 2/5 Build 1, Pobedi Sq., Moscow, 121293, Russia.

- a. The field investigator and DSI reviewer, Dr. Khairy Malek, reviewed the records of all subjects in the study, 10 in study protocol 3001 and 2 in study protocol 3002. They reviewed also the source documents, the laboratory reports and the adverse reactions.
- b. General observations/commentary: The study was adequately recorded. We observed one protocol violation in that 8 subjects used some herbal and other over the counter medications which were prohibited by the protocol. The CI defended himself by stating that these herbal medicines are ineffective, he was unaware of the situation, and that all other aspects of the study were done properly, which we observed. These drugs were for “Heptral” (or SAM-E) taken by Subjects # 001, 003, 006, 008, 009, and 011, “Hepa-Merz” or (L-ornithine-L-aspartate) taken by Subjects # 012 and 002. Subjects # 001, 003, 006, and 008 were on placebo while Subjects # 002, 009, and 011 were on rifaximin. Subjects # 002 and 012 had early termination; # 002 due to HE episode (on rifaximin) after about 2 months on the drug; # 012 was discontinued due to use of prohibited drugs after screening. Subject # 009 (on rifaximin), died after about 6 months on the drug due to GI bleeding from esophageal varices. There were no HE episodes in the placebo group.
- c. Assessment of Data Integrity: The violation with respect to concomitant use of an herbal medication, is not considered to have a significant impact on the validity of the data, especially as it was equally noted in subjects on placebo and those on rifaximin;

however, the review division may choose to consider the impact of this finding in their evaluation of study results. The data from this site can be used in support of the NDA.

**5. Vladimir Rafalsky, M.D.-Site 894**

27, Gagarina Ave., Smolensk, 214018, Russia

- a. The field investigator and DSI reviewer, Dr. Khairy Malek, reviewed all the subjects' records at this site, 9 in Protocol 3001, and 5 in Protocol 3002. They reviewed the lab reports, the adverse reactions and the data listings presented to the FDA.

In Protocol 3001: Subject # 005 suffered diarrhea for 1 day; Subject # 007 withdrew consent after Visit 6 because she had work outside the city.

In Protocol 3002: Subject # 002 had elevated glucose level and peripheral arterial disease attributed to diabetes and atherosclerosis. Subject # 009, died after about 6 months on the drug due to GI bleeding after hospitalization.

- b. General observations/commentary:

The study was properly conducted at this site and records were well maintained. No regulatory violations were noted and a Form FDA 483 was not issued.

- c. Assessment of data integrity:

The data from this site are reliable and can be used in support of the NDA

**IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS**

Five sites were inspected in support of this NDA. Although minor issues were noted at Dr. Poordad's and Dr. Gorbakov's sites, the findings are unlikely to impact data integrity. The data from the 5 sites detailed above are acceptable in support of the NDA.

***Note: Observations noted above for Drs. Alexeeva, Gorbakov, and Rafalsky are based on the participation in the inspection by the DSI reviewer; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.***

{ See appended electronic signature page }

Khairy W. Malek, Medical Officer  
Good Clinical Practice Branch II  
Division of Scientific Investigations

CONCURRENCE:

{ See appended electronic signature page }

Tejashri Purohit-Sheth, M.D.

Branch Chief

Good Clinical Practice Branch II

Division of Scientific Investigations

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22554	ORIG-1	SALIX PHARMACEUTICA LS INC	XIFAXAN

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/s/

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TEJASHRI S PUROHIT-SHETH

11/05/2009

Entered on behalf of Dr. Khairy Malek. My signature denotes supervisory concurrence.