

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205613Orig1s000

CHEMISTRY REVIEW(S)

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

Application:	NDA 205613/000	Sponsor:	SALIX PHARMS
Code:	180		8510 COLONNADE CENTER DR
Priority:	3		RALEIGH, NC 27615
Stamp Date:	15-NOV-2013	Brand Name:	BUDESONIDE
PDUFA Date:	15-SEP-2014	Estab. Name:	
Action Goal:		Generic Name:	BUDESONIDE
District Goal:	17-JUL-2014	Product Number; Dosage Form; Ingredient; Strengths	001; EMULSION, AEROSOL FOAM; BUDESONIDE; 2MG

FDA Contacts:	T. MEHTA	Prod Qual Reviewer		3017961712
	C. TRAN-ZWANETZ	Product Quality PM	(HFD-800)	3017963877
	K. RICHARDS	Regulatory Project Mgr	(HFD-180)	2404024276
	M. KOWBLANSKY	Team Leader		3017961390

Overall Recommendation:	ACCEPTABLE	on 04-SEP-2014	by R. MOORE	()	2404029988
	PENDING	on 18-MAR-2014	by EES_PROD		
	PENDING	on 23-DEC-2013	by EES_PROD		

Establishment: **CFN:** 1628114 **FEI:** 1628114
DPT LABORATORIES, LTD.

Address: SAN ANTONIO, , UNITED STATES 78215

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile: NON-STERILE LIQUID (OTHER THAN SUSP & EMULSIONS) **AADA:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 17-JAN-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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

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

DMF No: AADA:

Responsibilities:

Profile: (b) (4) **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 19-MAR-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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

DMF No: AADA:

Responsibilities:

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 10-JUN-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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

DMF No: AADA:

Responsibilities:

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 23-DEC-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

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

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

DMF No: AADA:

Responsibilities:

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 27-DEC-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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

DMF No: AADA:

Responsibilities:

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 27-DEC-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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/s/

SHANNON J CREWS
10/14/2014

NDA 205613**Uceris (Budesonide) Rectal Foam
2mg/actuation****Salix Pharmaceuticals, Inc.****Tarun Mehta****Review Chemist****Office of New Drug Quality Assessment
Division of New Drug Quality Assessment II
Branch IV****CMC REVIEW OF NDA 205613
For the Division of Gastroenterology and Inborn Errors Products
(HFD-180)**

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Executive Summary Section

CMC Review Data Sheet

1. NDA 205613
2. REVIEW #: 1
3. REVIEW DATE: September 2, 2014
4. REVIEWER: Tarun Mehta
5. PREVIOUS DOCUMENTS: None
6. SUBMISSION(S) BEING REVIEWED:

Original Submission	November 15, 2013
Amendment 0008	February 14, 2014
Amendment 0016	March 26, 2014
Amendment 0017	April 09, 2014
Amendment 0025	June 03, 2014
Amendment 0031	July 07, 2014
Amendment 0032	July 10, 2014
Amendment 0039	July 22, 2014
Amendment 0046	August 18, 2014
Amendment 0050	August 28, 2014

7. NAME & ADDRESS OF APPLICANT:

Name: Salix Pharmaceuticals Inc.
Address: 8510 Colonnade Center Drive, Raleigh NC 27615
Representative: Jennifer Richards, Associate Director, Regulatory
Telephone: (919) 447-3465
Email: Jennifer.richards@salix.com

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Uceris
- b) Non-Proprietary Name (USAN): Budesonide
- c) Code Name/# (ONDQA only): None
- d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 3
 - Submission Priority: Standard

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

Executive Summary Section

(b) (4)	II	(b) (4)	(b) (4)	1	Adequate		No update since last review Reviewed by Tarun Mehta
(b) (4)	III	(b) (4)	(b) (4)	1	Adequate	5/2/ 2013	No update since last review
	III			3	Adequate	8/31/2009	Reviewed by Kim Chang, Ho No updated amendment since last adequate
	III			1	Adequate	08/15/2014	No update since last review Reviewed by Tarun

¹ Action codes for DMF Table:

1 – DMF Reviewed.

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

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	104725	Budesonide Foam 2mg

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	09/04/2014	R. Moore
Microbiology	Recommended for approval	12/02/2013	Pawar, Vinayak
CDRH	Satisfactory	08/18/2014	Brandan Reid
EA	Categorical exclusion granted	08/14/2014	Tarun Mehta

Executive Summary Section

The CMC Review for NDA 205613

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant of this NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product.

The label/labeling issues are fully resolved.

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

Therefore, from the ONDQA perspective, this NDA is recommended for **APPROVAL** with an expiration dating period of 24 months.

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

The applicant has agreed via an amendment 0046 dated August 20, 2014 to complete the following extraction study, and submit the data in first annual report.

1) To perform forced extraction studies as follow:

- Typical Sample preparation: 5g test article/ 200mL extraction solvent
- Expose cut or crushed pieces of the valve Housing and Stem using 57% propylene glycol, 30% alcohol at elevated temperature (55⁰C) for longer exposure times (such as 2-3 days).
- Reflux cut or crushed pieces of the valve Housing and Stem for 30 minutes in n-heptane.

2) To list the specific composition of the Housing and Stem components and report the extraction profiles (qualitative and quantitative).

3) To provide leachable data for the drug product stored in the proposed container closure for expiry period at the long term storage condition.

II. Summary of CMC Assessments

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

(1) Drug Substance

Executive Summary Section

The drug substance budesonide is a compendial (USP) material. It has been used as an active drug substance in previously approved prescription drug products. The DMF (b) (4) for the drug substance was reviewed and found adequate. Based on available stability data, a retest period of (b) (4) months for budesonide drug substance is granted, when stored as follows: (b) (4)

(b) (4) The retest period may be extended when additional real-time stability data are available.

(2) Drug Product

The proposed formulation is a non-sterile emulsion consisting of budesonide as an active ingredient. The emulsion is pressurized using a propellant mixture to deliver it as a foam. Each multi-dose canister delivers fourteen (14) 1.35-mL doses (equivalent to 2 mg budesonide per dose). (b) (4)

(b) (4) The drug substance, excipients, and propellant gases (n-butane, iso-butane and propane) used in the formulation are compendial (USP) grade.

(b) (4)

The proposed regulatory specification is deemed adequate to assure the drug product quality at release and on stability. Physical attributes are controlled using compendial monograph (USP <601>) for "Aerosols metered dose products" monograph. Foam characterization and property were tested using validated in-house method. Potency and impurities of the active ingredient are monitored using validated chromatographic methods. The impurity specification is based on the compendial (USP) monograph for the budesonide.

The primary container closer system for the drug product is a (b) (4) aluminum canister (b) (4). The canister is filled with the emulsion and propellant mixture. Canister is fitted with 1-inch metering valve which houses 1.35mL of metering head. The size of valve housing and metering valve determines the amount of emulsion and expansion of the foam with each actuation.

The registration batches demonstrate the chemical, physical, and microbiological stability of Budesonide 2 mg Rectal Foam stored through 12 months at 25°C/60% RH and 6 months at 40°C/75% RH. All results met the proposed acceptance criteria under both storage conditions. Stability samples were stored in horizontal and vertical

Executive Summary Section

orientations. The supporting stability batches demonstrate up to 36 months of stability at the long term condition. Based on the adequate stability data, the proposed expiration dating period of 24 months for Budesonide 2 mg Rectal Foam is granted, when stored as follows: “Store at 20–25°C (68–77°F) [see USP Controlled Room Temperature]; excursions permitted to 15–30°C”.

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

Prior to the first dose, the “safety tab” provided on the foam shield of the canister will be removed by the user. After shaking the canister, the user will attach an applicator to the delivery nozzle of the dosing valve, invert the canister and depress the pump dome. The user will then insert the applicator into the rectum and release the pump dome to deliver the foam product. After delivery of the foam, the user will remove the applicator and place it in a plastic disposal bag. A new applicator will be used for each dose.

C. Basis for Approval Recommendation

The sponsor has provided sufficient information on raw material controls, manufacturing process and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The NDA has also provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product during the expiration dating period of 24 months..

All the facilities have **ACCEPTABLE** site recommendations.
All labels/labeling have required information.

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

(See appended electronic signature page)

Tarun Mehta, M.Sc., Branch IV, ONDQA Division II

B. Endorsement Block:

(See appended electronic signature page)

Moo-Jhong Rhee, Ph.D. Branch Chief, Branch IV, ONDQA Division II

C. CC Block: entered electronically in DFS

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immediately following this page

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/s/

TARUN D MEHTA
09/04/2014

MOO JHONG RHEE
09/04/2014
Chief, Branch IV

ONDQA Initial Quality Assessment (IQA) and Filing Review

IQA and Filing Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: **205613**

2. DATES AND GOALS:

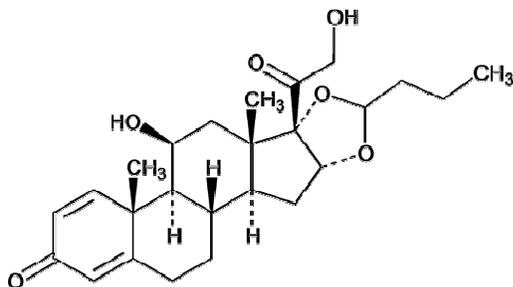
Letter Date:	Submission Received Date : 11/15/2013
PDUFA Goal Date: 9/15/2014	Filing Date: 1/14/2014

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	not provided
Established or Non-Proprietary Name (USAN):	budesonide
Dosage Form:	foam
Route of Administration	rectal
Strength/Potency	2 mg
Rx/OTC Dispensed:	Rx

4. INDICATION: ulcerative colitis

5. DRUG SUBSTANCE STRUCTURAL FORMULA:



Budesonide is a mixture of two epimeric forms, epimer A ^{(b) (4)}22S) and epimer B ^{(b) (4)}22R). It contains between ^{(b) (4)}% and ^{(b) (4)}% of epimer A, with the remainder being epimer B.

6. NAME OF APPLICANT (as indicated on Form 356h): **Salix Pharmaceuticals**

7. SUBMISSION PROPERTIES:

Review Priority:	Standard
Submission Classification (Chemical Classification Code):	Type 3 (New Dosage Form)
Application Type:	505(b)(1)
Breakthrough Therapy	No
Orphan Drug Designation	No

ONDQA Initial Quality Assessment (IQA) and Filing Review

Responsible Organization (Clinical Division):	Division of Gastrointestinal and Inborn Error Products (HFD-180)
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8. CONSULTS:

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Establishment Evaluation Request (EER)	x		12/20/2013
Methods Validation		x	
Environmental Assessment	x		Request for categorical exclusion
CDRH		x	
Other		x	

Overall Filing Conclusions and Recommendations

CMC:

Is the Product Quality Section of the application fileable from a CMC perspective?

Yes No

Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter?

Yes No

CMC Comments for 74-Day Letter: **none**

Biopharmaceutics:

Is the Product Quality Section of the application fileable from a Biopharmaceutics perspective?

Yes No

Biopharmaceutics Filing Issues: **none**

Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with the 74-Day letter?

Yes No

Biopharmaceutics Comments for 74-Day Letter:

We suggest that you propose an in vitro release acceptance criterion (range) based on a developed in vitro release test (IVRT) methodology for your product at release and during stability as a quality control parameter. Your proposed acceptance criterion should be based on generated data on the final to be marketed batches.

Microbiology:

Is the Product Quality Section of the application fileable from a Microbiology perspective?

Yes No

Microbiology Filing Issues:

See Microbiology Filing Review for details and for any potential Microbiology review issues.

ONDQA Initial Quality Assessment (IQA) and Filing Review

Summary of Initial Quality Assessment

Does the submission contain any of the following elements?			
Nanotechnology	QbD Elements	PET	Other, please explain
no	no	no	no

Is a team review recommended?		Yes
Reviewers assigned:	CMC: Tarun Mehta Biopharmaceutics: Kelly Kitchen, Ph.D Micro: Vinayak Pawar Ph.D	

Summary of Critical Issues and Complexities
Probably the most critical issue for this type of dosage form is to determine if the controls for this product are sufficient to ensure that the metered dose can be delivered with sufficient accuracy to ensure the efficacy and safety of the product.

ONDQA Initial Quality Assessment (IQA) and Filing Review

Product Summary

BRAND NAME (budesonide) **rectal foam** is a rectally administered aerosol foam indicated for patients with ulcerative colitis, with a recommended dose of 2 mg of budesonide administered twice daily for 2 weeks. A metered dose of the foam is delivered by a disposable, (b) (4), dose-metering, multi-dose canister. The product formulation is a non-sterile emulsion consisting of budesonide, propylene glycol, cetyl alcohol, emulsifying wax, polyoxyl (10) stearyl ether, purified water, edetate disodium, citric acid monohydrate, and a propellant consisting of propane, isobutane, and butane.

Each multi-dose canister delivers fourteen 1.35-mL doses of foam product (equivalent to 2 mg budesonide per dose) and is provided with 14 single-use, disposable rectal applicators. Each metered dose expands from 1.35 mL to approximately (b) (4)

(b) (4)

(b) (4)

The product includes testing for assay, impurities, delivered dose uniformity, foam actuation weight, foam volume (per actuation), duration of foam expansion, pH and microbial examination

Twelve months of long term stability data and six months of accelerated data have been submitted for three registration batches to support expiration dating.

ONDQA Initial Quality Assessment (IQA) and Filing Review

FILING REVIEW CHECKLIST

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	√		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	√		
3.	Are all the pages in the CMC section legible?	√		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		

B. FACILITIES*				
* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a <i>potential filing issue</i> or a <i>potential review issue</i>.				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	√		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			NA. (synthetic drug substance)

ONDQA Initial Quality Assessment (IQA) and Filing Review

	Parameter	Yes	No	Comment
7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	√		
8.	<p>Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	√		

ONDQA Initial Quality Assessment (IQA) and Filing Review

	Parameter	Yes	No	Comment
9.	Are additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	√		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	√		

C. ENVIRONMENTAL ASSESMENT

	Parameter	Yes	No	Comment
11.	Has an environmental assessment or claim of categorical exclusion been provided?	√		Claim of categorical exclusion

ONDQA Initial Quality Assessment (IQA) and Filing Review

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?		√	referenced to DMF (b) (4)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?		√	referenced to DMF (b) (4)
14.	Does the section contain information regarding the characterization of the DS?		√	referenced to DMF (b) (4)
15.	Does the section contain controls for the DS?		√	referenced to DMF (b) (4)
16.	Has stability data and analysis been provided for the drug substance?		√	referenced to DMF (b) (4)
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		√	Not required
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		√	Not required

ONDQA Initial Quality Assessment (IQA) and Filing Review

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	√		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	√		
21.	Is there a batch production record and a proposed master batch record?	√		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	√		
23.	Have any biowaivers been requested?		√	
24.	Does the section contain description of to-be-marketed container/closure system and presentations?	√		
25.	Does the section contain controls of the final drug product?	√		
26.	Has stability data and analysis been provided to support the requested expiration date?	√		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		√	Not required
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		√	Not required

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?		√	Not required; electronic submission

ONDQA Initial Quality Assessment (IQA) and Filing Review

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product			A micro biology reviewer has been assigned

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	√		drug substance information has been referenced to DMF (b) (4) and packaging DMFs (b) (4)

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	√		
33.	Have the immediate container and carton labels been provided?	√		

{See appended electronic signature page}
 Marie Kowblansky, PhD
 CMC-Lead
 Division II
 Office of New Drug Quality Assessment

{See appended electronic signature page}
 Kelly Kitchens, Ph.D.
 Biopharmaceutics Reviewer
 Office of New Drug Quality Assessment

{See appended electronic signature page}
 Tapash Ghosh, Ph.D.
 Biopharmaceutics Team Leader
 Office of New Drug Quality Assessment

{See appended electronic signature page}
 Moo-Jhong Rhee, PhD
 Branch Chief
 Division II
 Office of New Drug Quality Assessment

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/s/

MARIE KOWBLANSKY
01/16/2014

KELLY M KITCHENS
01/16/2014

TAPASH K GHOSH
01/16/2014

MOO JHONG RHEE
01/17/2014
Chief, Branch IV

Initial Manufacturing (CGMP/Facilities) Assessment (IMA) and Filing Review for Pre- Marketing Applications (Original)

- I. Review Cover Sheet
- II. Application Detail
- III. Filing Checklist
- IV. Manufacturing Summary
- V. Overall Conclusions and Recommendations

I. Review Cover Sheet

- 1. OMPQ Reviewer: Christina Capacci-Daniel
- 2. NDA/BLA Number: NDA 205613
 Submission Date: Nov. 15, 2013
 21st C. Review Goal Date:
 PDUFA Goal Date: Sept. 15, 2014

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	<i>Pending</i>
Established or Non-Proprietary Name (USAN) and strength:	Budesonide, 2mg
Dosage Form:	Topical (Rectal) foam

4. SUBMISSION PROPERTIES:

Review Priority :	STANDARD
Applicant Name:	Salix Pharmaceuticals
Responsible Organization (OND Division):	DGIEP

II. Application Detail

1. INDICATION: Treatment of active mild to moderate ulcerative colitis (b) (4)
2. ROUTE OF ADMINISTRATION: Topical/Rectal
3. STRENGTH/POTENCY: 2mg (as a metered 1.35mL volume of foam)
4. Rx/OTC DISPENSED: Rx OTC
5. ELECTRONIC SUBMISSION (yes/no)? YES
6. PRIORITY CONSIDERATIONS:

	Parameter	Yes	No	Unk	Comment
1.	NME / PDUFA V		<input checked="" type="checkbox"/>		
2.	Breakthrough Therapy Designation		<input checked="" type="checkbox"/>		
3.	Orphan Drug Designation		<input checked="" type="checkbox"/>		
4.	Unapproved New Drug		<input checked="" type="checkbox"/>		
5.	Medically Necessary Determination		<input checked="" type="checkbox"/>		
6.	Potential Shortage Issues [either alleviating or non-approval may cause a shortage]		<input checked="" type="checkbox"/>		
7.	Rolling Submission		<input checked="" type="checkbox"/>		
8.	Drug/device combination product with consult		<input checked="" type="checkbox"/>		
9.	Complex manufacturing		<input checked="" type="checkbox"/>		
10.	Other (e.g., expedited for an unlisted reason)		<input checked="" type="checkbox"/>		

III. FILING CHECKLIST

The following parameters are necessary in order to initiate a full review (i.e., the application is complete enough to start review but may have deficiencies). On **initial** review of the NDA application:

A. COMPLETENESS OF FACILITY INFORMATION				
	Parameter	Yes	No	Comment
11.	Is all site information complete (e.g., contact information, responsibilities, address)?	<input checked="" type="checkbox"/>		
12.	Do all sites indicate they are ready to be inspected (on 356h)?	<input checked="" type="checkbox"/>		356h updated during filing period with complete information
13.	Is a single comprehensive list of all involved facilities available in one location in the application?	<input checked="" type="checkbox"/>		DS and DP Manufacturing sections
14.	For testing labs, is complete information provided regarding which specific test is performed at each facility and what stage of manufacturing?	<input checked="" type="checkbox"/>		Drug substance release and stability testing performed at non-manufacturing facilities
15.	Additional notes (non-filing issue)	<input checked="" type="checkbox"/>		
	1. Are all sites registered or have FEI #?			
	2. Do comments in EES indicate a request to participate on inspection(s)?		<input checked="" type="checkbox"/>	
	3. Is this first application by the applicant?		<input checked="" type="checkbox"/>	Several approved solid oral dosage forms & one topical formulation

*If any information regarding the facilities is missing/omitted, communicate to OPS/ONDQA regarding missing information and copy EESQuestions. Notify OMPQ management if problems are not resolved within 3 days and it can be a *potential* filing issue.

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B. DRUG SUBSTANCE (DS) / DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
16.	Have any Comparability Protocols been requested?		<input checked="" type="checkbox"/>	

IMA CONCLUSION				
	Parameter	Yes	No	Comment
17.	Does this application fit one of the EES Product Specific Categories?		<input checked="" type="checkbox"/>	
18.	Have EERs been cross referenced against the 356h and product specific profile for accuracy and completion? Have all EERs been updated with final PAI recommendation?	<input checked="" type="checkbox"/>		
19.	From a CGMP/facilities perspective, is the application fileable? If the NDA is not fileable from a product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	<input checked="" type="checkbox"/>		

IV. Manufacturing Summary: Critical Issues and Complexities

Does the submission contain any of the following elements?			
Nanotechnology <input type="checkbox"/>	RTRT Proposal <input type="checkbox"/>	PAT <input type="checkbox"/>	Drug/Device Combo <input type="checkbox"/>
PET <input type="checkbox"/>	Design Space <input type="checkbox"/>	Continuous Mfg <input type="checkbox"/>	Naturally derived API <input type="checkbox"/>
Other (explain):			

Manufacturing Highlights

1. Drug Substance

	Parameter	Yes	No	Comment
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		<input checked="" type="checkbox"/>	<ul style="list-style-type: none"> • See DMF (b) (4) • Last reviewed 2012 after several updates were submitted; found to be acceptable



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2. Drug Product

	Parameter	Yes	No	Comment
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		<input checked="" type="checkbox"/>	<ul style="list-style-type: none">• (b) (4)• (b) (4)• Packaged in an aerosol container

(b) (4)



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3. Facility-Related Risks (e.g., expected in-process testing not being performed, questionable development, unexplained stability failures, data integrity issues, etc.). Describe any potential 21CFR 211 compliance issues.

- No facility-related issues at this time.

4. Drug Product Facility Inspectional History that could impact the manufacturing of this product

- (b) (4) Both facilities are operated by the same company (DPT Laboratories) and have acceptable inspectional histories for these respective operations.

Additional information not covered above

V. Overall Conclusions and Recommendations

Is the application fileable? (yes/no, Yes to questions 11-12) YES
Based on Section IV, is a KTM warranted for any PAI? (yes/no). If yes, please identify the sites in the above chart. <ul style="list-style-type: none">No KT memos or briefings are anticipated at this time.
Are there comments/issues to be included in the 74 day letter, including appropriate identification of facilities? (yes/no) NO
Comments for 74 Day Letter
1.
2.
3.

REVIEW AND APPROVAL (DARRTS)

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

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

/s/

CHRISTINA A CAPACCI-DANIEL
01/13/2014

MAHESH R RAMANADHAM
01/13/2014