

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**202292Orig1s000**

**CHEMISTRY REVIEW(S)**

## MEMORANDUM

**Date:** December 31, 2012

**To:** NDA 202-292

**From:** Terrance Ocheltree, Ph.D., R.Ph.  
Director  
Division of New Drug Quality Assessment II  
ONDQA

**Subject: Tertiary review of ONDQA recommendation for NDA 202-292, crofelemer, 125 mg delayed release tablets, Fulyzaq™.**

I have assessed the ONDQA reviews of NDA 202-292 by Nina Ni, Ph.D. (CMC review) and Mark Seggel, Ph.D. (Biopharmaceutics review). I concur with the determination that the information as provided in the NDA, along with the consideration that this drug product is for an unmet medical need (treatment of secretory diarrhea in patients with AIDS), is adequate to assure the identity, strength and quality of the drug product and the overall ONDQA recommendation of "Approval". I support the recommendation of a drug product shelf life of 24 months for the proposed commercial product when it is stored at controlled room temperature.

Crofelemer is for the indication of control and symptomatic relief of diarrhea in patients ages 18 years and over with HIV/AIDS on anti-retroviral therapy. It is thought to work locally by blocking chloride ion secretion and associated water loss in the small intestine. However, the structural feature(s) of the oligomers that contribute to its activity are currently unknown. Crofelemer is a new molecular entity (NME) extracted and purified from the crude plant latex (CPL) of *croton lechleri*. Crofelemer is a member of a class of compounds collectively referred to as proanthocyanidins, which are found as naturally occurring phenolic substances in a wide variety of plants. Crofelemer is an oligomeric/polymeric mixture made up of linked monomer units of varying chain lengths with a reported average molecular weight of approximately 2300 daltons (Da). The oligomers consist of from 3 to 30 monomers, with a reported average chain length of approximately 7 units. The monomer units are (+)-catechin, (-)-epicatechin, (+)-gallocatechin, and (-)-epigallocatechin or (b) (4). Crofelemer is highly soluble (18 - 20 mg/mL) in water over a range of pH (1.1 - 7.4).

The initial ONDQA CMC review was entered into DARRTS on July 13, 2012, with a recommendation for a Complete Response due to a lack of sufficient information to assure the identity, strength, purity, and quality of the drug product, an absence of a recommendation from the Office of Compliance on the manufacturing and testing sites acceptability and pending labeling issues. The ONDQA Biopharmaceutics review was entered into DARRTS on August 01, 2012, with a recommendation for Approval. An Environmental Impact was performed by Raanan Bloom with the finding of no adverse environmental impact is expected, no mitigation methods are addressed (entered into DARRTS on August 17, 2012). On December 31, 2012 the Office of Compliance entered an Overall Recommendation of "Acceptable" into EES. A second CMC review by Dr. Ni was entered into DARRTS on December 31, 2012 with an overall ONDQA recommendation of "Approval". There are related Post Marking Commitments that have been negotiated with the applicant (see below).

A methods validation was requested for the test method for Determination of Related Substance for Crofelemer Tablets. The method was found acceptable for quality control and regulatory purposes and the findings entered into DARRTS on September 11, 2012 by Michael Trehy, Ph.D.

Due to the extensive ONDQA concerns related to assurance of quality and the perceived medical need for this product, a CDER Center Director Briefing was held on August 6, 2012. The following three questions were put forward: 1) Is the benefit for public health of crofelemer greater than the potential risk that may originate due to unknown and inconsistent composition of the drug product? 2) Is there any concern if the commercial product may not be the same as that used in the clinical trials? 3) Is it sufficient to control identity and other quality attributes solely through the control of plant source and manufacturing process? During this meeting it was decided that a relevant bioassay may address many of the CMC concerns. Salix was then approached about developing such a bioassay. Salix submitted a draft description of the analytical procedures and validation protocol for Potency Determination of Crofelemer Drug Substance (API) and Drug Product (125 mg tablets) by (b) (4)

(b) (4) in November 2012, and the resulting data in December 2012. The methods and data were reviewed by Cristina Ausin-Moreno, Ph.D., Office of Biotechnology Products (OBP), Division of Therapeutic Proteins (DTP). The OBP review was entered into DARRTS on December 21, 2012 with a recommendation for "Approval" and Post Marking Commitments.

The proposed drug product, crofelemer delayed-release tablets, 125 mg, is a white, oval, plain, film-coated tablet for oral administration and will be manufactured by Patheon Pharmaceutical Inc. Commercial tablets will be printed with "125SLXP" in black ink on 1 side. The drug products will be packaged in 60-count, white, high density polyethylene bottles with (b) (4). Each bottle will contain 60 tablets. The formulation consists of microcrystalline cellulose (b) (4), croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, (b) (4), white dispersion (b) (4), talc- (b) (4), triethyl citrate, (b) (4). All excipients are compendial (USP/NF) and sufficient controls are in place.

The drug substance, crofelemer, a reddish powder, was subjected to structural elucidation using elemental analysis (EA), a combination of various spectroscopic techniques including circular dichroism (CD), infrared (IR), ultraviolet (UV), nuclear magnetic resonance (NMR), mass (MS), and x-ray powder diffraction (XRPD). However, these spectroscopic structural data did not concretely define the identity of this reddish powder at the molecular level. The manufacturing process for crofelemer consists of three steps: (b) (4)

(b) (4) During the drug substance manufacturing, adequate in-process and controls are in place for each intermediate steps to reasonably maintain the batch to batch consistency. The proposed storage condition was changed from (b) (4) with excursions permitted to (b) (4). A proposed retest period of (b) (4) is granted. The BDS will be manufactured by (b) (4)

(b) (4)

The ownership and/or rights to the compound have been transferred to multiple companies over the years ending at the NDA phase with Salix Pharmaceutical possessing the rights to market in the US. (b) (4)

IND

51,818 was originally submitted in November 1996. An end of Phase II meeting was held with the sponsor in May 2004; however, no CMC issues were discussed. The company stated in the meeting request letter that a CMC meeting would be requested at a later date. This meeting never occurred. A pre-NDA meeting was requested in November 2010 and granted in January 2011. No CMC related questions were submitted by the sponsor. However, ONDQA and the Botanical Review Team (BRT) provided “additional comments” in the meeting responses, including a request for a CMC related meeting. A CMC related meeting was requested and granted in March 2011. The CMC responses were provided to Salix and a meeting was held in May 2011. Numerous CMC related issues were identified. A follow-up meeting was to occur, but Salix withdrew that request in June 2011. A new meeting request was granted in September 2011 following a verbal request for a teleconference. The NDA was submitted in December 2011.

The botanical drug substance (BDS) is derived from the latex of a tropical plant, *Croton lechleri* Müll. Arg. of Euphorbiaceae. *Croton lechleri* is a tree growing in Central and South America, including Mexico, Venezuela, Ecuador, Peru, Brazil, Colombia, Ecuador, and Bolivia. When the bark of the tree is cut or wounded, a reddish latex is released. The *Croton* genus is a relatively large with a total of approximately 750 species around the world. In addition to *Croton lechleri*, several other red resin-producing *Croton* species, such as *Croton draconoides* Müll. Arg., *Croton draco* Schlect & Cham., *Croton urucurana* Baill., *Croton xalapensis* Kunth, *Croton gossypifolium* Vahl, *Croton erythrochilus* Müll. Arg. and *Croton palanostigma* Klotzsch., have also been used as herbal medicines (see BRT review dated January 10, 2011 for additional information). From an ONDQA opinion, it is unclear if the various test methods proposed for this product will differentiate between these or other similar species. However, the BRT review did not identify safety or quality related issues for the botanical raw material (BRM) and state that the applicant’s Good Agricultural and Collection Practice (GACP) procedures are adequate and that *C. lechleri* can be correctly identified according to one or more morphological characteristics to prevent misuse and adulteration from other species (see BRT review dated August 8, 2012). The following BRT recommendation will be provided to the applicant following approval of the NDA: 1) tightening the contaminant specification for pesticides, aflatoxins, and heavy metals in the BDS and/or CPL batches; and 2) tightening the specification for taspine and total phenolics to include both upper and lower limits.

During the review process, ONDQA raised the concerns related to the source and availability of commercially available product. It appears, but is not confirmed, that much of the BDS testing that occurred during the review cycle was performed on (b) (4)

Since the determination of the GMP status of current or future drug product is an Office of Compliance (OC) issue, ONDQA has not requested further information related to this matter. Discussions were held between

ONDQA, BRT and OC to discuss the need to inspect or not inspect the source of the BRM. Since the primary assurance of BDS identity occurs at the source of the material, it was determined that the source of the BRM might be inspected post approval.

The following CMC related PMC was accepted by Salix:

1. An elemental analysis to identify the source and identity of potential [REDACTED] (b) (4) impurities in crofelemer.  
Final Report Submission: 12/2013
2. Characterize the [REDACTED] (b) (4) crofelemer [REDACTED] (b) (4).  
Final Report Submission: 12/2013
3. Revise the current HPLC methods for assay and related substances for the drug substance and drug product or develop new methods. The revised or new methods must be stability indicating and appropriately validated.  
Final Report Submission: 12/2013
4. Re-evaluate the specification and revise as needed for the crofelemer cell-based assay that uses [REDACTED] (b) (4) after one year of product lots of crofelemer (anticipated to be [REDACTED] (b) (4) lots) have been manufactured.  
Final Report Submission: February 28, 2014
5. To validate and implement a cell-based potency assay that uses [REDACTED] (b) (4).  
Final Report Submission: January 31, 2014

Manufactured for Salix Pharmaceuticals, Inc., Raleigh, NC 27615 by Patheon, Inc. FULYZAQ is distributed by Salix Pharmaceuticals, Inc. under license from Napo Pharmaceuticals, Inc. The active ingredient of FULYZAQ, crofelemer, is purified from *Croton lechleri* that is harvested in South America.

Secondary review of the CMC reviews was performed by Moo-Jhong Rhee, Ph.D.

Secondary review of the Biopharmaceutic review was performed by Angelica Dorantes, Ph.D.

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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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TERRANCE W OCHELTRIE  
12/31/2012

**NDA 202292**

**Fulyzaq™ (crofelemer) Delayed-Release Tablets  
125 mg**

**Salix Pharmaceuticals, Inc.**

**Nina Ni, Ph. D.**

**Review Chemist**

**Branch IV**

**Division of New Drug Quality Assessment II  
Office of New Drug Quality Assessment**

**CMC REVIEW**

**For the Division of Gastroenterology and Inborn Errors Products**

## CMC Review Data Sheet

**CMC Review Data Sheet**

1. NDA 202292
2. REVIEW #: 2
3. REVIEW DATE: 12/31/2012
4. REVIEWER: Nina Ni, Ph. D.
5. PREVIOUS DOCUMENTS:
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment (BC): 0015	06/29/2012
Amendment (BC): 0017	07/11/2012
Amendment (BC): 0020	07/31/2012
Amendment (BC): 0022	08/10/2012
Amendment (BC): 0023	08/15/2012
Amendment (BC): 0027	08/27/2012
Amendment (BC): 0028	08/27/2012
Amendment (BC): 0030	08/27/2012
Amendment (BC): 0031	09/05/2012
Amendment (BC): 0033	09/13/2012
Amendment (BC): 0034	10/15/2012
Amendment (BC): 0037	12/10/2012
Amendment (BC): 0038	12/12/2012
Amendment (BC): 0039	12/14/2012
Amendment (BC): 0040	12/19/2012
Amendment (BC): 0041	12/20/2012
Amendment (BC): 0042	12/20/2012

7. NAME & ADDRESS OF APPLICANT:

Name: Salix Pharmaceuticals, Inc.  
Address: 8510 Colonnade Center Drive, Raleigh, NC 27615  
Representative: Jennifer Richards  
Telephone: 1-919-447-3465

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Fulyzaq<sup>TM</sup> (crofelemer) delayed-release tablet
- b) Non-Proprietary Name (USAN): crofelemer

## CMC Review Data Sheet

c) Code Name/# (ONDQA only): NP-303; SP-303; TRN-002; (b) (4) Provir™;  
Virend™

d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1
- Submission Priority: Propriety

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

10. PHARMACOL. CATEGORY: Control and symptomatic relief of diarrhea in patients with human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) on anti-retroviral therapy (ART).

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 125 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

SPOTS product – Form Completed

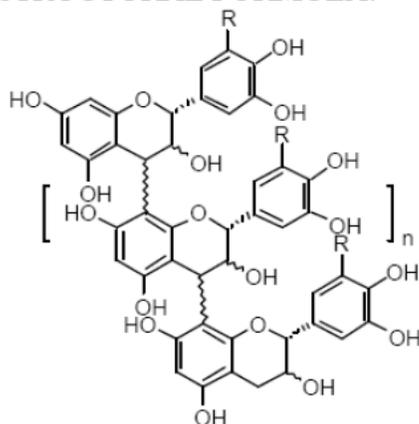
Not a SPOTS product

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

NAME: Crofelemer

CHEMICAL NAME: Oligomeric proanthocyanidin from the latex of *croton lechleri* with average molecular weight of approximately 2300 daltons (adopted from USAN).

STRUCTURAL FORMULA:



CMC Review Data Sheet

R = H or OH

average n = 3 to 5.5

MOLECULAR FORMULA:  $C_{15 \cdot n}H_{12 \cdot n + 2}O_{6.5 \cdot n}$ , with an average length of 5 to 7.5 units, the monomer units are (+)-catechin, (-)-epicatechin, (+)-gallocatechin, and (-)-epigallocatechin.  
 MOLECULAR WEIGHT: average molecular weight ranges between 1500 and 2300 daltons

CAS NUMBER: [148465-45-6]

17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	1	Adequate	09/10/2012	By N. Ni, Ph. D.
	III			1	Adequate	03/21/2012	By G. Holbert, Ph. D.
	IV			4	Adequate		

<sup>1</sup> 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")

<sup>2</sup> 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	51,818	

## CMC Review Data Sheet

## 18. STATUS:

**ONDQA:**

<b>CONSULTS/ CMC RELATED REVIEWS</b>	<b>RECOMMENDATION</b>	<b>DATE</b>	<b>REVIEWER</b>
Biometrics	NA		
EES	Approval	12/31/2012	
Pharm/Tox	NA		
Biopharm	Acceptable	08/01/2012	Mark Seggel, Ph. D.
LNC	NA		
Methods Validation	Submitted		
DMEPA	NA		
EA	Acceptable	08/17/2012	Raanan A. Bloom, Ph. D.
Microbiology	NA		
Bioassay	Acceptable	12/21/2012	Cristina Ausin-Moreno, Ph. D.

## CMC Assessment Section

**The CMC Review for NDA 202292****The Executive Summary****I. Recommendations****A. Recommendation and Conclusion on Approvability**

The applicant of this NDA has provided adequate specifications to assure the identity, strength, purity, and quality of the drug substance and the drug product (**Attachment-1**).

The Office of Compliance has issued an overall “Acceptable” recommendation for the facilities involved in the NDA (**Attachment-2**).

Labels/labeling issues have been resolved satisfactorily (**Attachment-3**).

Therefore, from the ONDQA perspective, this NDA is recommended for **APPROVAL**.

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

ONDQA has requested the following post marketing commitments and that these studies be completed within one year after approval. The applicant has agreed and their commitment statement was provided in Amendment 0040, dated 12/19/2012.

- Elemental analysis: [REDACTED] (b) (4)
- Conversion yield: [REDACTED] (b) (4)
- HPLC analysis: Forced degradation studies showed a significant increase in the crofelemer peak area when the drug substance was subjected to strong oxidizing conditions or elevated temperatures, causing the crofelemer peak to increase by as much as [REDACTED] (b) (4). This increase in the crofelemer peak was evident in both HPLC methods (assay and related substances), suggesting that neither method is stability indicating. You will need to revise both methods

## CMC Assessment Section

(b) (4)

## II. Summary of CMC Assessments

### A. Description of Drug Product and Drug Substance

In CMC Review #1, dated 07-13-12, this NDA was recommended for “Complete Response” due to the unresolved issues delineated in the **List of Deficiencies in Review #1 (p.196)**.

The applicant has responded to these deficiencies via Amendments 0015, 0017, 0020, 0022, 0023, 0027, 0028, 0030, 0031, 0033, 0034, 0037, 0038, 0039, 0040, 0041, and 0042 dated 06/29/2012, 07/11/2012, 07/31/2012, 08/10/2012, 08/15/2012, 08/27/2012, 09/05/2012, 09/13/2012, 10/15/2012, 12/10/2012, 12/12/2012, 12/14/2012, 12/19/2012, and 12/20/2012 respectively. Based on this new information, the previously noted deficiencies have been re-evaluated. (Each deficiency is repeated below as originally cited and is followed by a summary of information submitted to resolve it.)

#### **1) Regarding Specifications for the Drug Substance and Drug Product**

##### **a) Identity**

- The specification of the drug substance does not have a reliable test for demonstrating consistent distribution of oligomers (b) (4) with an acceptance criterion for each oligomer.

##### ***Resolution:***

*The applicant updated the drug substance specification (see the Attachment-1) with the limits that define the oligomer distribution.*

(b) (4)

*These proposed limits are based on HPLC data obtained for 12 batches of drug substance. Replication of results for each batch was reasonable. Given the heterogeneity of this type of product, the proposed limits are considered acceptable.*

***The response is acceptable.***

- The IR spectroscopic test in the drug substance specification has not been demonstrated that the spectra obtained from testing samples are comparable to that obtained from the reference standard. Need to compare all available IR

## CMC Assessment Section

spectra generated from all clinical and stability batches of crofelemer drug substance with that of the reference standard.

**Resolution:**

*The applicant has provided IR spectra from all lots of drug substance used for Phase 3 clinical trials and stability drug product batches:*

*The IR spectrum for each lot of drug substance was compared to that of the reference standard. The reference standard was prepared in the same manner as the drug substance sample, and its spectrum was recorded concomitantly with the same instrumental conditions as done for the sample. The resulting sample and standard spectra were compared visually for a general measure of similarity in the pattern of peak maxima. A computerized comparison of the sample and standard spectra were also performed which generates a correlation value. Correlation values of (b) (4) are considered as concordant spectra.*

*As the spectra show below, although minor batch to batch variations are observed in certain regions of the spectrum (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) the spectra are considered generally comparable to each other and to the reference standard. These minor differences can no doubt be attributed to the heterogeneity of the monomers that compose the oligomers.*

(b) (4)

(b) (4)

*All IR spectra submitted were reviewed, and a good correlation was found between a sample IR spectra and that of the reference standard.*

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## CMC Assessment Section

(b) (4)

*Although it is almost impossible to interpret quantitatively the IR spectra of different proanthocynadin products, it is apparent that differently sourced proanthocynadins have, qualitatively speaking, different overall fingerprint profiles allowing us to say that the IR spectra of crofelemer appear to be reasonably specific and show much more detailed fingerprint regions (b) (4) than those of other proanthocyanidins.*

*In summary, a reasonably concordant IR spectrum (exhibits comparable characteristic fingerprints) can be obtained from different lots of crofelemer when compared to the that of reference standard of crofelemer. At the same time, the IR spectra obtained from crofelemer appear to be reasonably specific and show a much more detailed and different fingerprints than those of other proanthocyanidins, making the IR measurement to be sufficiently enough to serve as a part of the identification tests.*

***The response is acceptable.***

- Satisfactory review of analytical procedure and its validation report for PC/PD ratio, mean degree of polymerization, conversion yield, and oligomer composition and distribution determination is needed.

## CMC Assessment Section

1) Analytical procedure and corresponding validation report for acid hydrolysis to determine PC/PD ratio, mean degree of polymerization (mDP), and conversion yield

**Resolution:**

*The applicant has informed us in their Amendment 0017, dated 07/11/2012 that the depolymerization (followed by HPLC) procedure from which PC/PD ratio, mean DP, and conversion yield are derived was unacceptable for a number of reasons, including poor reproducibility, and needed to be revised.*

(b) (4)

(b) (4)

*During the method validation studies, two analysts performed the intermediate precision study using two different HPLC systems and two different columns. The first analyst achieved a separation similar to that presented in Figure 1. The second chemist, however, achieved the separation presented in Figure 2, which shows*

(b) (4)

## CMC Assessment Section



The applicant states that the (b) (4) does not allow for the proper calculation of the individual monomers they represent and significantly affects the results for monomer ratio, average degree of polymerization, and conversion yield generated by the second chemist.

Therefore, later in Amendment 0020 dated 07/31/2012, the applicant informed us that the method has been successfully modified by

1. (b) (4)  
[Redacted]  
[Redacted]

After reviewing the validation data (see Attachment-4), the revised analytical method is deemed adequate.

**The response is acceptable.**

- 2) Analytical procedure and corresponding validation report for oligomer composition and distribution determination

**Resolution:**

The analytical procedure was provided in Salix QCTP-245 and the supporting validation report was provided in Salix QCTP-119, which were submitted in Amendment 0015 dated 06/29/2012. Both of them were reviewed and found adequate as summarized in Attachment-4.

## CMC Assessment Section

*The response is acceptable.*

- Even though all these issues are satisfactorily resolved, all identity tests as a whole will still be insufficient for fulfilling the statutory requirement for establishing the identity of a drug. This is a fundamental deficiency.

**Resolution:**

*At this time, the identity/structure for crofelemer is not fully established/defined.*

[REDACTED] (b) (4)

[REDACTED] (b) (4)

*To confirm their claim, the drug substance manufacturer is actively pursuing a new elemental analysis using current up-to-date technology. The applicant states that that information will be submitted upon completion of the analysis. The data have not yet been provided. Therefore, the following post approval commitment has conveyed to the applicant. The applicant has agreed and their commitment statement was provided in Amendment 0042, dated 12/20/2012.*

- *The source and identity of these [REDACTED] (b) (4) impurities need to be identified.*

*Despite the uncertainties regarding the structure of crofelemer, including the [REDACTED] (b) (4) of crofelemer, the updated tests and specifications for 1) oligomer distribution, 2) IR measurement, 3) monomer ratios, 4) mean degree of polymerization, and 5) conversion yield after hydrolysis, as described and discussed in their validation reports, is considered to be sufficient for establishing the identity of crofelemer, because a fully validated and clinically relevant bioassay has also been implemented as part of the drug substance and drug product specifications. In addition, the applicant has committed to characterizing the [REDACTED] (b) (4) material as a post marketing commitment.*

*The response is acceptable.*

*In summary, although no single test can give a unequivocal identity of crofelemer, it is believed that when all the tests are combined, the composite results are expected to provide a reasonable insight into the nature of the identity of crofelemer.*

*Therefore, the following holistic approach to controlling this extremely complicated drug substance will assure the identity of the drug product and thereby assure that a therapeutically consistent drug product can be produced:*

1. *Strict controls on the raw material (see the Botanical Review by J. Dou, Ph. D.)*
2. *Robust manufacturing process controls (see CMC Review #1 by N. Ni, Ph. D.)*

## CMC Assessment Section

3. Adequate specifications are in placed with:
  - i. Validated chemical and physical tests as discussed above
  - ii. A validated clinically relevant bioassay (see the Bioassay Review by Cristina Ausin-Moreno, Ph. D.)

**b, c) Purity and Strength**

- [REDACTED] (b) (4)

**Resolution:**

[REDACTED] (b) (4)

*The response is satisfactory.*

- Satisfactory review of analytical procedure and its validation report for [REDACTED] (b) (4) is needed.

**Resolution:**

*Analytical procedure and the corresponding validation report for [REDACTED] (b) (4) were reviewed and found adequate as summarized below in this review.*

*A typical headspace GC method equipped with [REDACTED] (b) (4) is used to determine [REDACTED] (b) (4). The following table summarized the validation study for the GC method to determine [REDACTED] (b) (4)*

**CMC Assessment Section**

Sr. No.	Validation Parameter	Observations	Acceptance Criteria
1	Specificity	Method found specific for (b) (4)	(b) (4) should be well resolved along with the diluent.
2A	Limit of Detection	The (b) (4) (b) (4) and the % RSD is within the acceptance criteria	(b) (4) should be above (b) (4) and %RSD for six injections at this concentration should be less than (b) (4)
2B	Limit of Quantification	The (b) (4) (b) (4) and the % RSD is within the acceptance criteria.	(b) (4) should be above (b) (4) and %RSD for six injections at this concentration should be less than (b) (4)
3	Linearity	The method is linear over concentration range of LOQ, and (b) (4) concentration for (b) (4) with correlation coefficient greater than (b) (4)	Correlation coefficient greater than or equal to (b) (4)
4	Accuracy	Recovery is within the prescribed limit of (b) (4) for (b) (4)	Mean recovery should lie within (b) (4)
5	Precision		
	System Precision	%RSD is within desired limits.	%RSD should not be more than (b) (4)
	Method Precision	%RSD is within desired limits.	%RSD should not be more than (b) (4)
	Ruggedness	%RSD is within desired limits.	%RSD should not be more than (b) (4)
6	Robustness	Method is unaffected by small changes in experimental conditions. %RSD is within desired limits.	RSD should not be more than (b) (4)

*Therefore, the GC method found to be specific, precise, accurate, linear, and robust. It is suitable for determination of (b) (4) in crofelemer.*

***The response is satisfactory.***

- The proposed acceptance criterion of NMT (b) (4) for heavy metals should be tightened to (b) (4)

***Resolution:***

*The proposed acceptance criterion for heavy metals has been tightened from NMT (b) (4). See Attachment-1.*

***The response is satisfactory.***

## CMC Assessment Section

- The applicant needs to commit to develop, within one year of the approval date of this NDA, a stability indicating analytical methods for Related Substances in the drug substance and drug product.

**Resolution:**

*The applicant has committed to develop, within one year of the approval date of this NDA, stability indicating analytical methods for assay and related substances in the drug substance and drug product. This requirement was reaffirmed and conveyed to and agreed by the applicant as the post approval commitment as listed on page of 6 of this review.*

*The response is satisfactory.*

**d) Quality**

- The proposed dissolution test and acceptance criterion should be revised as follows:
  - o Acid Stage: no individual unit exceeds (b) (4) dissolved at 2 hours, rather than (b) (4) as proposed.
  - o Buffer Stage: Q = (b) (4) at 45 minutes, rather than Q = (b) (4)

**Resolution:**

*The test and acceptance criteria are revised accordingly. The biopharmaceutics reviewer, M. Seggel, Ph. D., has recommended approval of this NDA.*

*The response is satisfactory.*

**e) Others:**

- The drug product specification should be updated with the acceptance criterion for 'Appearance' to reflect the imprint on the tablets.

**Resolution:**

*The drug product specification has been updated as requested. See Attachment-1.*

*The response is satisfactory.*

**2) Regarding Stability:**

- Revise the proposed storage condition for the drug substance to (b) (4) with excursion permitting to (b) (4).

**Resolution:**

*The proposed storage condition for the drug substance has been revised to (b) (4) with excursions permitting to (b) (4).*

## CMC Assessment Section

*The response is satisfactory.*

-  (b) (4)

**Resolution:**

 (b) (4)

*The response is satisfactory.*

- Insufficient stability data is provided to justify the proposed shelf life of 24 months for drug product.

**Resolution:**

*24-month stability data was provided in Amendment 0027 to support the proposed expiration dating period of 24 months for the drug product.*

*The response is satisfactory.*

**3) Regarding DMF**  (b) (4)

*Issues with the holder of DMF  (b) (4) have been successfully resolved.*

*The response is satisfactory.*

**4) Regarding Labels and Labeling**

**a) “Full Prescribing Information” Section**

1. Strength needs to be provided.
2. Word of  (b) (4) needs to be changed to imprinted.

**b) “Description” Section**

1. Describe pharmacological/ therapeutic class.
2. Delete the structural formula.
3. Delete the statement of “ (b) (4)

**c) “How Supplied” Section**

## CMC Assessment Section

1. Add the strength of dosage form.
2. Add the identification of dosage form.
3. Add storage condition.

**d) “Carton Label”**

1. Need to provide carton label.
2. Need to revise the dosage form to delayed-release tablets.

***Resolution:***

*A final label was submitted in Amendment 0037, 0038, and 0040, dated 12/10/2012 12/12/2012, and 12/19/2012, respectively with all above issues being corrected. The applicant also confirmed that there is no carton label via email through K. Bugin, RPM for this NDA, dated 09/04/2012.*

*Labeling is satisfactory.*

**5) Environmental Assessment:**

*A final recommendation of “A Finding of No Significant Impact (FONSI)” on environmental assessment is recommended by R. Bloom, Ph. D.*

*The response is satisfactory.*

**6) Biopharmaceutics:**

*M. Seggal, Ph. D. of the ONDQA biopharmaceutics group has recommended approval for this NDA.*

*The response is satisfactory.*

**7) Botanic Review on Raw Material:**

*J. Dou, Ph. D. of the botanic has recommended approval for this NDA.*

*The response is satisfactory.*

**8) Bioassay Review:**

*Cristina Ausin-Moreno, Ph. D. of OBP has judged the bioassay to be acceptable.*

*The response is satisfactory.*

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

See Review #1.

**C. Basis for Approvability**

The botanical raw materials are well controlled. Manufacturing process and in-process controls are deemed adequate. Specifications for the botanical drug substance and botanical drug product are considered adequately validated (**Attachment-4**) to assure the identity, strength, purity and quality of the drug product. Clinically relevant bioassays for

## CMC Assessment Section

the drug substance and drug product are also considered to be acceptable for assuring therapeutic consistency of the drug product (see OBP's Review dated 12/18/2012). Stability of the drug product is reasonably demonstrated to be adequate for assuring a 24-month expiration dating period.

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

*(See appended electronic signature page)*

Nina Ni, Ph. D., CMC Reviewer, Branch IV, ONDQA

**B. Endorsement Block:**

*(See appended electronic signature page)*

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

**C. CC Block:** entered electronically in DFS

Marie Kowblansky, Ph. D., CMC Lead, Branch IV, ONDQA

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/s/  
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XUHONG LI

12/31/2012

Check in primary review on behalf of Nina Ni.

DONNA F CHRISTNER on behalf of MOO JHONG RHEE

12/31/2012



Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research

Office of Biotechnology Products  
Division of Therapeutic Proteins  
Bethesda, MD 20892  
Tel. 301-827-1790

---

### Memorandum of Review

**Date:** December 18, 2012  
**To:** DGIEP Review Team for NDA 202292  
**From:** Cristina Ausin-Moreno, PhD DTP, OBP  
**Through:** Emanuela Lacana, PhD and Susan Kirshner, PhD, DTP, OBP  
**Subject:** Consult regarding NDA 202292 - Bioassay Validation Results  
**Applicant:** Salix Pharmaceuticals Inc.  
**Product:** Fulyzaq (crofelemer)

---

### RECOMMENDATION

The Division of Therapeutic Proteins recommends approval of the cell-based assay for crofelemer, pending a favorable inspection of the testing facility and a favorable recommendation from the Office of Compliance.

The validation report provided by the sponsor indicates that the assay is of sufficient accuracy and precision and the data support the suitability of the assay for release and stability testing of crofelemer. The proposed specification of (b) (4) relative potency is also acceptable. We suggest conducting improvement to the assay and acceptance criteria through Post-Marketing Commitment, as follows:

1. Re-evaluate the specification and revise as needed for the crofelemer cell-based assay that uses (b) (4) after one year of product lots of crofelemer (anticipated to be (b) (4) lots) have been manufactured.

Final report provided by: February 28, 2014

2. To validate and implement a cell-based potency assay that uses (b) (4)

Final report provided by: January 31, 2014

### REVIEW

#### 1. Introduction

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/s/  
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HOWARD A ANDERSON  
12/21/2012

EMANUELA LACANA  
12/21/2012

SUSAN L KIRSHNER  
12/21/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research

**METHODS VALIDATION REPORT SUMMARY**

**TO:** Nina Ni, Ph.D., CMC Reviewer  
Office of New Drug Quality Assessment (ONDQA)  
E-mail Address: nina.ni@fda.hhs.gov  
Phone: (301) 796-5296  
Fax: (301) 796-9745

**FROM:** FDA  
Division of Pharmaceutical Analysis  
Michael Trehy, MVP Coordinator  
Suite 1002  
1114 Market Street  
St. Louis, MO 63101  
Phone: (314) 539-3815

**Through:** Benjamin J. Westenberger, Deputy Director  
Phone: (314) 539-3869

**SUBJECT:** Methods Validation Report Summary

---

Application Number: 202-292

Name of Product: Crofelemer, 125 mg tablets

Applicant: Salix Pharmaceuticals, Inc.

Applicant's Contact Person: Jennifer Richards

Address: 8510 Colonnade Center Drive, Raleigh, NC 27615

Telephone: (919) 447-3465 Fax: NA

---

Date Methods Validation Consult Request Form Received by DPA: 6-5-2012

Date Methods Validation Package Received by DPA: 6-5-2012

Date Samples Received by DPA: 6-27-2012

Date Analytical Completed by DPA: 9-11-2012

---

Laboratory Classification: **1.** Methods are acceptable for control and regulatory purposes.   
**2.** Methods are acceptable with modifications (as stated in accompanying report).   
**3.** Methods are unacceptable for regulatory purposes.

Comments:  
See attached memo for comments.



Date: August 22, 2012  
To: Nina Ni, Ph. D., CMC Reviewer, ONDQA  
From: Jeffrey T. Woodruff, Chemist (HFD-920)  
Subject: Evaluation of NDA 202-292  
Crofelemer, 125mg Tablets  
Salix Pharmaceutical, Inc.

The following method was evaluated and found acceptable for quality control and regulatory purposes:

- Determination of Related Substances for Crofelemer Tablets; (Document No. QCTP-234)

**Summary of Analysis for NDA 202-292**

**Determination of Related Substances for Crofelemer Tablets**

No impurities were seen in the determination of related substances for the Crofelemer Tablets.

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/s/  
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MICHAEL L TREHY  
09/11/2012

BENJAMIN J WESTENBERGER  
09/11/2012

# **NDA 202-292**

**Verdera<sup>TM</sup> (crofelemer) Delayed-Release Tablets  
125 mg**

**Salix Pharmaceuticals, Inc.**

**Nina Ni, Ph. D.**

**Review Chemist**

**Branch IV**

**Division of New Drug Quality Assessment II  
Office of New Drug Quality Assessment**

**CMC REVIEW**

**For the Division of Gastroenterology and Inborn Errors Products**

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## CMC Review Data Sheet

# CMC Review Data Sheet

1. NDA 202-292
2. REVIEW #: 1
3. REVIEW DATE: 07/05/2012
4. REVIEWER: Nina Ni, Ph. D.
5. PREVIOUS DOCUMENTS:
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original Submission	12/05/2011
Correspondence (C): 0000	
Amendment (BC): 0002	01/05/2012
Amendment (BC): 0004	02/24/2012
Amendment (BC): 0009	04/06/2012
Amendment (BC): 0011	04/30/2012
Amendment (BC): 0013	06/01/2012
Amendment (BC): 0014	06/27/2012

7. NAME & ADDRESS OF APPLICANT:

Name: Salix Pharmaceuticals, Inc.  
Address: 8510 Colonnade Center Drive, Raleigh, NC 27615  
Representative: Jennifer Richards  
Telephone: 1-919-447-3465

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: (b) (4)
- b) Non-Proprietary Name (USAN): crofelemer
- c) Code Name/# (ONDQA only): NP-303; SP-303; TRN-002; (b) (4); Provir™, Virend™
- d) Chem. Type/Submission Priority (ONDQA only):
  - Chem. Type: 1
  - Submission Priority: Priority

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

## CMC Review Data Sheet

10. PHARMACOL. CATEGORY: Control and symptomatic relief of diarrhea in patients with human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) on anti-retroviral therapy (ART).

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 125 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

SPOTS product – Form Completed

Not a SPOTS product

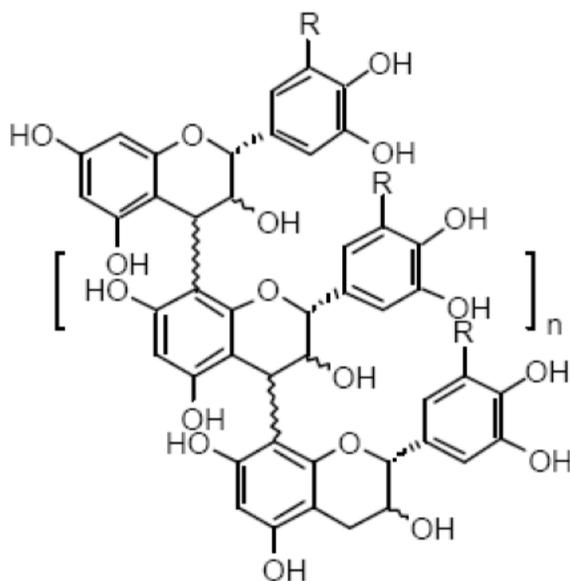
1. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

NAME: Crofelemer

CHEMICAL NAME: Oligomeric proanthocyanidin from the latex of *croton lechleri* with average molecular weight of approximately 2300 daltons (adopted from USAN).

STRUCTURAL FORMULA:

CMC Review Data Sheet



R = H (procyanidin) and/or R = OH (prodelphinidin)  
 N = 3 – 30; average n = 5

MOLECULAR FORMULA:  $C_{15 \cdot n}H_{12 \cdot n + 2}O_{6.5 \cdot n}$ , where n = 3 to 30 monomer units, with an average length of 7 units, the monomer units are (+)-catechin, (-)-epicatechin, (+)-gallocatechin, and (-)-epigallocatechin.

MOLECULAR WEIGHT: an average molecular weight of approximately 2300 daltons

CAS NUMBER: [148465-45-6]

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)		Pending	07/02/2012	IR letter was sent on 07/03/2012
	III			1	Adequate	03/21/2012	By G. Holbert, Ph. D.
	IV			4	Adequate		

CMC Review Data Sheet

<sup>1</sup> 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")

<sup>2</sup> 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	51,818	

18. STATUS:

**ONDQA:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Acceptable	03/26/2012	
Pharm/Tox	NA		
Biopharm	Pending		Mark Seggel, Ph. D.
LNC	NA		
Methods Validation	Submitted		
DMEPA	NA		
EA	Pending		Raanan A. Bloom, Ph. D.
Microbiology	NA		

# The CMC Review for NDA 202-292

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The applicant of this NDA has not provided sufficient information to assure the identity, strength, purity, and quality of the drug product.

The Office of Compliance has made a final acceptable recommendation for the facilities involved in this NDA.

Issues on label/labeling also have not been resolved.

Therefore, from the ONDQA perspective, this NDA is not recommended for approval per 21 CFR 314.125 (b)(1)&(6) in its present form until the issues delineated in the List of Deficiencies (see p. 196 ) are satisfactorily resolved.

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

NA

### II. Summary of CMC Assessments

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

##### (1) Drug Substance

Crofelemer is an NME botanical drug substance, which is extracted and purified from the crude plant latex (CPL) of *croton lechleri*. Crofelemer is a member of a class of compounds collectively referred to as proanthocyanidins, which are found as naturally occurring phenolic substances in a wide variety of plants. Crofelemer is an oligomeric/polymeric mixture made up of linked monomer units of varying chain lengths with an average molecular weight of approximately 2300 daltons (Da). The monomer units are (+)-catechin, (-)-epicatechin, (+)-gallocatechin, and (-)-epigallocatechin (b) (4)

The manufacturing process for crofelemer consists of three steps (b) (4)

## CMC Assessment Section

(b) (4)

. During the drug substance manufacturing, adequate in-process and controls are in place for each intermediate steps to reasonably maintain the batch to batch consistency.

Crofelemer, a reddish powder, was subjected to structural elucidation using elemental analysis (EA), a combination of various spectroscopic techniques including circular dichroism (CD), infrared (IR), ultraviolet (UV), nuclear magnetic resonance (NMR), mass (MS), and x-ray powder diffraction (XRPD). However, these spectroscopic structural data did not concretely define the identity of this reddish powder at the molecular level.

To further establish the identity, additional chemical tests were carried out by digesting this complex mixture of oligomeric drug substance to yield: 1) the average monomer ratio of catechin/epicatechin to galocatechin/epigallocatechin in the oligomers; 2) average molecular weight based on the number of monomers; 3) the extent of digestion (depolymerization) of the oligomers, conversion yield. Data obtained from 11 batches of drug substance have shown characteristic values on these parameters with certain ranges serving as useful surrogate markers for the identity of the drug substance.

Therefore, these chemical tests are added to the specification as part of the identification tests together with the physical tests based on IR, (b) (4), and HPLC retention time. Although all the physical and chemical identity tests are placed in the specification, they, as a whole, are still deemed far from fulfilling the statutory requirement for the identity of a drug.

The specification also needs further revision with: 1) the tightened acceptance criterion for heavy metals, 2) test for quantitative distribution for oligomers of 3 to 30 units per (b) (4) 3) validation for the newly added test methods for (b) (4) determination of monomer ratio, conversion yield, mean degree of polymerization, and oligomer composition and distribution.

The analytical methods for assay and related substance have not been demonstrated to be stability indicating, especially for those degradants formed under extreme oxidation and heat condition.

The available release and stability data for batches used for toxicological studies, phase 2 and phase 3 clinical trials, and registration show that they complied with the originally proposed drug substance specification. However, it is not certain whether these batches will meet the revised specification including the tests for (b) (4) monomer ratio, conversion yield, mean degree of polymerization, as well as the oligomer composition and distribution.

The applicant recommended storage condition for the drug substance is (b) (4), which is too wide compared to that for stability study. The storage

## CMC Assessment Section

condition was recommended to be changed from (b) (4) with excursions permitted to (b) (4). The proposed retest period of (b) (4) can be granted if on the submitted stability data conform the revised specification.

**(2) Drug Product**

The proposed drug product, crofelemer delayed-release tablets, 125 mg, is a white, oval, plain, film-coated tablet for oral administration and will be manufactured by Patheon Pharmaceutical Inc. Commercial tablets will be printed with "125SLXP" in black ink on 1 side. The drug products will be packaged in 60-count, white, high-density polyethylene bottles with (b) (4). Each bottle will contain 60 tablets. Citation for CFR compliance for direct food contact for an (b) (4) is yet submitted.

The to-be-marketed formulation is the same as those used in the clinical trials and registration batches. The formulation consists of microcrystalline cellulose (b) (4), croscarmellos sodium, colloidal silicon dioxide, magnesium stearate, (b) (4) white dispersion (b) (4) talc- (b) (4) triethyl citrate, and (b) (4). All excipients are compendial (USP/NF) and sufficient controls are in place.

The manufacturing process for crofelemer tablets, 125 mg, involves (b) (4). The proposed commercial manufacturing scale is (b) (4). Adequate in-process controls are in place.

The originally proposed drug product specification includes appearance, identification (b) (4) HPLC retention time), crofelemer assay (HPLC), related substances (HPLC), uniformity of dosage units (HPLC), (b) (4) dissolution, acid resistance, molecular weight (GPC), and microbial limits (USP <1111>). The analytical methods for assay and related substance are not stability indicating, especially for degradants formed under extreme oxidation and heat condition. Given the botanical nature of the drug product, and that most of the degradants are non toxic and naturally coexisted with the drug substance, it has been agreed (*Memorandum prepared by M. Kowblansky, Ph. D. dated 05/18/2012*) that these two methods can be developed within one year of the approval of this NDA.

All registration batches met the proposed drug product specification.

Stability data (accelerated and long term) are provided for a total of 3 primary stability batches as well as 11 supporting clinical batches. Apparently, the stability data indicate that the drug product is physically and chemically stable. However, in order for the proposed expiration dating period of 24 months to be granted, further updated stability data are needed as well as satisfactory evaluation of dissolution data by Biopharmaceutical Reviewer.

## CMC Assessment Section

The final recommendation for environmental assessment (EA) has not been issued by EA Reviewer, R. Bloom, Ph. D.

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

One crofelemer, 125 mg tablet dosed twice daily (BID) for a total daily dose of 250 mg for the control and symptomatic relief of diarrhea in patients with human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) on anti-retroviral therapy (ART).

**C. Basis for Not-Approval Recommendation**

21 CFR 314.125(b)(1)

- The characterization of the drug substance has not been satisfactorily carried out to establish its structural identity of the drug substance.
- The specifications of the drug substance and drug product are not adequate to assure the identity, strength, purity, and quality

(see the List of Deficiencies on p. 196).

21 CFR 314.125(b)(6)

- Issues on labels and labeling have *not* been resolved yet

(see the List of Deficiencies on p. 196).

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

*(See appended electronic signature page)*

Nina Ni, Ph. D., CMC Reviewer, Branch IV, ONDQA

**B. Endorsement Block:**

*(See appended electronic signature page)*

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

**C. CC Block:** entered electronically in DFS

Marie Kowblansky, Ph. D., CMC Lead, Branch IV, ONDQA

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/s/  
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NINA NI  
07/13/2012

MOO JHONG RHEE  
07/13/2012  
Chief, Branch IV

Initial Quality Assessment  
Branch 3  
Pre-Marketing Assessment Division 2

**OND Division:** Division of Gastroenterology and Inborn Error Products  
**NDA:** 202-292  
**Applicant:** Salix Pharmaceuticals, Inc.  
**Stamp Date:** 12/5/2011  
**Review Date:** 1/10/2012  
**PDUFA Date:** 6/5/2012 priority review  
**Filing Meeting:** 1/18/2012  
**Proposed Trademark:** To be determined  
**Established Name:** crofelemer  
**Dosage Form:** tablet  
**Route of Administration:** oral  
**Indication:** HIV-associated diarrhea  
**CMC Lead:** Marie Kowblansky, PhD

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

### A. Summary

The proposed product is a delayed release tablet intended for twice daily administration in the control and relief of HIV-related diarrhea. This product has been developed under IND 51,818 and contains 125 mg of crofelemer drug substance, which is a highly purified polymeric botanical extract. According to the Chemical Classification Code the drug substance is a new molecular entity and consequently, this is a Type 1 application. (b) (4)  
clinical trials were conducted with enterically coated tablets, the same delayed formulation is being proposed for the commercial product.

#### Drug Substance

Crofelemer is isolated from the red latex sap of the plant species *Croton lechleri* from the Amazon regions of South America. It is a polymeric proanthocyanidin extract consisting of monomers (+)-gallocatechin, (-)-epigallocatechin, (+)-catechin, and (-)-epicatechin, linked in random sequence through (b) (4)



Oligomers/polymers composed of catechin and epicatechin are called procyanidins; those composed of gallic catechin and epigallocatechin are referred to as prodelphinidins.

Crofelemer drug substance will be manufactured and tested by (b) (4) The manufacturing process consists of (b) (4)

(b) (4)

The reported structure of crofelemer is based on investigations using a range of spectroscopic techniques, including Circular Dichroism, Ultraviolet Absorption, Infrared, Nuclear Magnetic Resonance (<sup>1</sup>H-NMR and <sup>13</sup>C-NMR), Mass Spectrometry, X-Ray Powder Diffraction, GPC, and monomer ratio [(epi)gallocatechins/(epi)catechins] determination.

Potential impurities (b) (4)

(b) (4)

Crofelemer drug substance will conform to the following specification

Tests	Specifications
appearance	Dark reddish brown powder
solubility	Soluble in water, methanol, and ethanol
Identification:	
IR (b) (4)	conforms to standard
HPLC retention time (b) (4)	conforms to standard
pH (b) (4)	conforms to standard
assay (b) (4)	(b) (4)
Residual solvents (b) (4)	(b) (4)
taspine	(b) (4)
Heavy metals	(b) (4)
Average molecular weight (M <sub>n</sub> )	
polydispersity	
Related Compounds (HPLC), % (b) (4)	

The proposed specification limits for a number of the product attributes such as assay, average molecular weight, moisture, and pH were based on statistical analysis of data from over 220 batches and represent (b) (4) standard deviations from the average. From this preliminary review, however, it is not clear whether all these batches were prepared by the current (b) (4) methods, analyzed by current analytical procedures, whether all were used in the clinical trials, or whether these were sub-batches (b) (4)

(b) (4)

(b) (4)

The method for determining molecular weight requires significant scrutiny. According to the submission, molecular weights were historically determined by (b) (4)

(b) (4)

(b) (4)

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**Drug Product**

The proposed product will be manufactured at Pantheon Pharmaceuticals as a 125 mg delayed release tablet with the following composition (as reproduced from the submission):

Ingredient	Reference to Standard	Function	Theoretical Quantity (mg/unit dose)
<b>Uncoated Tablet</b>			
Crofelemer	In-House	Active	125.00 <sup>a</sup>
Microcrystalline Cellulose (b) (4)	NF		(b) (4)
Croscarmellose Sodium	NF		
Colloidal Silicon Dioxide	NF		
Magnesium Stearate	NF		
Uncoated Tablet Weight:			
<b>Coating<sup>c</sup></b>			
Ethyl Acrylate and Methylacrylate Copolymer Dispersion - (b) (4)	NF		(b) (4)
White Dispersion (b) (4)	Supplier		
Talc (b) (4)	USP		
Triethyl Citrate (b) (4)	NF		
(b) (4)	USP		
Total Theoretical Weight:		---	550.0

(b) (4)  
Finished tablets will be packaged in 60-count, 60 mL high density polyethylene bottles.

The proposed formulation is the same as was used in Phase 3 studies. According to the applicant, crofelemer drug substance is stable for (b) (4).  
(b) (4) the commercial formulation will continue to be manufactured with an enteric coating.

The manufacturing process for Crofelemer Tablets, involves (b) (4).  
(b) (4)

A full environmental assessment has been submitted in the application and has been consulted to OPS for review.

Inspection requests for the facilities involved in the manufacture of the drug substance and drug product have been entered into EES.

Established name: crofelemer. This is the USAN name for this drug substance.

Testing methods will not be sent to the St. Lois laboratories for validation until the deficiencies in the submitted methods and the reference standards are resolved.

The full CMC review of this NDA will be done by Dr. Nina Ni; the Biopharmaceutics information will be reviewed by Dr. Mark Seggel; and cultivation, collection, and control of the raw material will be reviewed by the Botanical Review Team.

## **B. Critical issues for review**

The following issues will require particularly close scrutiny during the course of the review

-- In addition to [REDACTED] (b) (4)  
[REDACTED] The only impurities identified in the submission are [REDACTED] (b) (4)  
[REDACTED] These do not contain any [REDACTED] (b) (4) the levels of these impurities are substantial and their source should be identified.

-- The alkaloid taspine is listed as a potential impurity, with a specification limit in the [REDACTED] (b) (4) range. This impurity should be discussed with the toxicology reviewer to determine whether it is particularly toxic and whether the proposed limit is acceptable.

-- While HPLC chromatograms from forced degradation studies show some decrease in crofelemer content, there does not appear to be a discussion of what the degradation products may be and where they may appear in the chromatograms. From this preliminary review, it does not appear that this matter has received sufficient attention.

-- Specification limits for each of the tested parameters for the most part are based on actual batch data, with the limits set [REDACTED] (b) (4) standard deviations from the mean. This results in fairly broad acceptance criteria, which in this reviewer's opinion are excessive. This will have to be further evaluated to determine whether the batch specification was based on the blended final batches on the individual sub-batches before blending.

-- The certificate of analysis does not report crofelemer reference standard purity. The purity of the reference material should be established, probably in terms of catechin, epicatechin, gallicocatechin, and epigallocatechin content. Assay should then be recalculated based on the purity of the reference standard that was used.

-- The manufacturing process involves [REDACTED] (b) (4)

- [REDACTED] (b) (4)

[REDACTED] The firm should be requested to provide the following information:

-Data to establish the oligomer composition of the crofelemer batches used in clinical trials

- [REDACTED] (b) (4) For this purpose end group analysis would be acceptable. The applicant may already have data for this purpose from the [REDACTED] (b) (4) experiments that were performed to determine the procyanidin/prodelphinidin ratio.

**C. Comments for 74-Day Letter --**

The following comments should be conveyed to the applicant:

The results of your elemental analyses for crofelemer include (b) (4)  
The only impurities identified in the submission are (b) (4)  
These do not contain any (b) (4); please explain the source and identity of these (b) (4) impurities.

The certificate of analysis for crofelemer reference standard does not report the purity of this material. The purity of the reference material should be established in terms of total catechin, epicatechin, gallocatechin, and epigallocatechin content and added to the certificate of analysis. Assay values that are reported throughout the submission should then be recalculated based on the purity of the reference standard that was used.

To address our concerns, please provide the following information:

-Data to establish the oligomer composition and distribution in crofelemer batches used in clinical trials. Based on literature reports for other procyanidins, HPLC/MS methods will likely be useful for this purpose.

For this purpose end group analysis would be acceptable. You may already have the raw data for this purpose from the (b) (4) experiments that were performed to determine the procyanidin/prodelphinidin ratio.

Please add procyanidin/prodelphinidin ratio to the drug substance specification

**D. Recommendation – From the CMC perspective this application is fileable**

Marie Kowblansky, PhD  
CMC Lead

2/3/2012  
Date

Moo-Jhong Rhee, PhD  
Branch Chief

**NDA Number:** 202-292      **Supplement Number and Type:** original      **Established/Proper Name:** crofelemer  
**Applicant:** Salix Pharmaceuticals      **Letter Date:** December 5, 2012      **Stamp Date:**

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*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	√		Have been entered into EES
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? <b>This question is not applicable for synthesized API.</b>			Not applicable

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"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	√		
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"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	√		

9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	√		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	√		

\* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	√		

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

<b>E. DRUG PRODUCT (DP)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
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?		√	NA
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; not a filing issue
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		√	Not required; not a filing issue

<b>F. METHODS VALIDATION (MV)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
29.	Is there a methods validation package?	√		Not required – electronic submission (information in body of submission)

<b>G. MICROBIOLOGY</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?		√	NA

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

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

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	<b>IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?</b>	√		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.			
36.	Are there any <b>potential review</b> issues to be forwarded to the Applicant for the 74-day letter?	√		

*{See appended electronic signature page}*

Marie Kowblansky, Ph.D.  
 CMC Lead  
 Division of New Drug Assessment #2  
 Office of New Drug Quality Assessment

Date

*{See appended electronic signature page}*

Moo-Jhong Rhee, Ph.D.  
 Branch Chief  
 Division of New Drug Assessment #2  
 Office of New Drug Quality Assessment

Date

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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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MARIE KOWBLANSKY  
02/06/2012

MOO JHONG RHEE  
02/06/2012  
Chief, Branch IV