

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202292Orig1s000

ENVIRONMENTAL ASSESSMENT



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmaceutical Science/Immediate Office**

Memorandum

Date: August 17, 2012

From: Raanan A. Bloom, Ph.D.
OPS/IO/PARS

To: Kevin Bugin, RPM
ODEIII/DGIEP

Through: Nakissa Sadrieh, Ph.D.
OPS/IO/PARS

Subject: **NDA 202292:** Crofelemer, 125 mg tablets.

Sponsor: Salix Pharmaceuticals, Inc.

Review of Environmental Assessment

A. Background

Salix Pharmaceuticals, Inc. requests approval of Crofelemer, 125 mg tablets. The applicant states that the drug is indicated for, “the symptomatic relief of diarrhea in patients with HIV/AIDS on anti-retroviral therapy” (NDA 202292, dated November 4th, 2012, section 41, p. 7). An Environmental Assessment (EA; dated 11/04/2011; EDR Sequence #0000) was submitted pursuant to 21 CFR part 25. An RI letter was sent to the firm (dated 06/12/2012; Reference ID: 3144042) and responses submitted in a 7/11/2012 Quality Information amendment (EDR Sequence # 0017) under section 1.11.1 and 1.12.14

B. Discussion

Executive Summary

The Environmental Assessment, dated November 4th, 2011 and responses to the IR letter, support the NDA for Crofelemer, 125 mg tablets. The EA was prepared in accordance with 21 CFR Part 25 by Salix Pharmaceuticals, Inc.

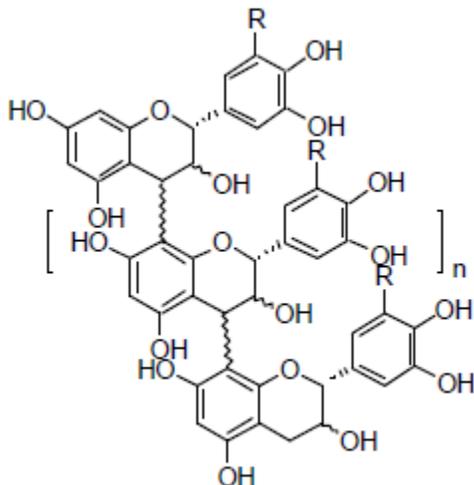
Crofelemer is a heterogeneous proanthocyanidin oligomer from *Croton lechleri* or the Croton tree, a South American species from which crude plant latex (CTL) is sourced to provide raw material for crofelemer production. The *C. lechleri* used to produce crofelemer is obtained from wildly grown sources as well as cultivated sources. Therefore, an environmental assessment was submitted and reviewed. The submitted information was as recommended in the CDER/CBER Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications (July 1998).

C. Environmental Assessment Review

1. **Date:** November 4th, 2012
2. **Applicant:** Salix Pharmaceuticals, Inc.
3. **Address:** 8510 Colonnade Center Dr. Raleigh, NC 27615
4. **Proposed Action:** Salix Pharmaceuticals, Inc. is filing an NDA pursuant to section 505(b)(1) of the Federal Food, Drug and Cosmetic Act for Crofelemer, 125 mg tablets for the symptomatic relief of diarrhea in patients with HIV/AIDS on anti-retroviral therapy.

5. Identification of Chemicals

- (i) Established Name: Crofelemer
- (ii) Brand/Proprietary Name/Tradename: To be determined
- (iii) Chemical Name: heterogeneous proanthocyanidin oligomers.
- (iv) Chemical Abstract Registration Number: 148465-45-6
- (v) Molecular Formula: $C_{15 \cdot n}H_{12 \cdot n + 2}O_{6.5 \cdot n}$ Where n = number of units
- (vi) Molecular Weight:
 - Average Molecular Weight (Mn): 1700 to 2500 Daltons
 - Polydispersity Index (Mw/Mn): 1.00 to 1.20
- (vii) Chemical Structure:



R = H (procyanidin) and/or R = OH (prodelphinidin)

n = 1–28; average n = 5

6. Environmental Characterization

The starting material used to make Crofelemer, 125 mg tablets is isolated from CTL exuded from the bark of *C. lechleri* trees following laceration. Wild grown trees used to source the starting material (b) (4)

The CTL from these trees is first tested to determine whether the tree is an acceptable source and then the tree is felled and scored to isolate CTL. Three trees are planted for every tree felled as a source of CTL. In addition to the use of wild trees, cultivated trees are used to source starting material for the production of Crofelemer.

According to the applicant, it is expected that (b) (4) of crofelemer or (b) (4) trees will be harvested each year to provide 250mg per patient per day. This equates to less than 0.1% of the estimated croton population which stands at approximately (b) (4) trees. Using (b) (4) planting three trees per wild tree harvested, and harvesting cultivated *C. lechleri* trees makes this method of harvesting a sustainable practice.

The applicant states that *C. lechleri* is not currently listed on either the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) or the US Wildlife Service for Endangered Species Act (ESA). A database query for the Latin name, *Croton lechleri*, yielded no results from CITES.

The applicant states (p. 6, 7/11/2012 Quality Information amendment, EDR Sequence # 0017, section 1.11.1) that "Salix has contracted with (b) (4) to assure that all required licenses, permits, approvals and authorizations by governmental authorities are secured and maintained by or on behalf of Salix in connection with the harvesting, supply and export of *C. lechleri* CPL. If Salix (or (b) (4) are required in the future to enter into an Access Agreement or obtain any other harvesting permits, (b) (4) will assist in obtaining said agreement or permit(s)." A certification statement (see 8, below) is also provided.

7. Mitigation Measures and Alternatives

Since no adverse environmental impact is expected, no mitigation methods are addressed.

8. Certification

"Salix Pharmaceuticals, Inc. confirms that it and all other parties with which it contacts for the harvest of *Croton lechleri* Crude Plant Latex (CTL) will comply with all requirements in the region(s) in which the CPL is harvested for Salix. Salix commits that it will comply with all requirements in the region(s) in which the CPL is sourced relating to such harvesting, including any additional requirements that may be imposed in the future, and will take appropriate measures to ensure that all such other parties continue to comply as well" (EDR Sequence # 0017 Section 1.12.14).

9. Literature Reviewed

1. Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) database.
2. US Wildlife Service for Endangered Species Act (ESA) database.

10. Comments and Conclusions

Based on an evaluation of the information provided in this EA, in FDA guidance, no significant adverse environmental impacts are expected from the harvest of wild *Croton lechleri* to produce Crofelemer, 125 mg tablets. The species is not listed on the CITES or ESA databases, and the applicant certifies compliance with requirements for the harvesting of *Croton lechleri*.

A Finding of No Significant Impact (FONSI) is recommended.

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/s/

RAANAN A BLOOM
08/17/2012

NAKISSA SADRIEH
08/17/2012

**Environmental Assessment
Finding of No Significant Impact**

**NDA 202-292
Crofelemer, 125 mg tablets**

**Food and Drug Administration
Center for Drug Evaluation and Research**

August 17, 2012

FINDING OF NO SIGNIFICANT IMPACT

NDA 202-292

Crofelemer, 125 mg tablets

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. The Food and Drug Administration (FDA) is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of the regulatory process.

NDA 202292 requests approval for Crofelemer, 125 mg tablets. This NDA is indicated for the symptomatic relief of diarrhea in patients with HIV/AIDS on anti-retroviral therapy. In support of its application, Salix Pharmaceuticals, Inc., prepared an environmental assessment (attached) in accordance with 21 CFR Part 25, which evaluates the potential environmental impact of the approval of this application for Crofelemer.

The Food and Drug Administration, Center for Drug Evaluation and Research, has carefully considered the potential environmental impact due to approval of this application and has concluded that this action is not expected to have a significant impact on the environment. Therefore, an environmental impact statement will not be prepared.

Attachment: November 4, 2011, Environmental Assessment

ENVIRONMENTAL ASSESSMENT FOR CROFELEMER TABLETS (125 MG)

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(b) (4)

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(b) (4)



(b) (4)

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LIST OF ABBREVIATIONS

ABBREVIATION	DESCRIPTION
AIDS	Acquired Immunodeficiency Syndrome
APG	Angiosperm Phylogeny Group
BID	"bis in die" (Latin = "twice daily")
CAS	Chemical Abstract Service
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CFSAN	Center for Food Safety and Applied Nutrition
CFTR	cystic fibrosis transmembrane regulator
CITES	Convention on International Trade in Endangered Species of Wild Fauna and Flora
CPL	crude plant latex
DBH	diameter at breast height
EA	Environmental Assessment
EGR	ecogeographic region
EIC	expected introduction concentration
FDA	Food and Drug Administration
GACPs	good agricultural and collection practices
GI	gastrointestinal
GRAS	Generally Recognized as Safe
ha	hectare
HIV	Human Immunodeficiency Virus
Mn	average molecular weight
Mw/Mn	polydisperity index (molecular weight/ average molecular weight)
NDA	New Drug Application
NEPA	National Environmental Protection Act
NGO	non-government organization
NTFP	non-timber forest product
OPC	oligomeric proanthocyanidin
POTW	publically owned treatment works
ppb	parts per billion
US	United States
USAN	United States adopted name

SUMMARY

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. The Food and Drug Administration (FDA) is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of the regulatory process.

NDA 202292 requests approval for Crofelemer Tablets 125 mg. The proposed indication is for the control and symptomatic relief of diarrhea in patients with HIV/AIDS on anti-retroviral therapy. In support of this application, Salix Pharmaceuticals, Inc. is submitting this environmental assessment (EA), in accordance with 21 CFR Part 25, and in consideration of applicable FDA guidance for submitting an EA.

Crofelemer is a heterogeneous proanthocyanidin oligomer of botanical origin. As such, crofelemer is subject to the FDA Guidance for Industry – Botanical Drug Products (June 2004). The crofelemer drug substance is extracted from the crude plant latex (CPL) of the croton tree, *Croton lechleri* Muell. Arg. *C. lechleri* is a tropical South American species. The CPL used as botanical raw material for crofelemer production is harvested from both wild and cultivated trees.

Pursuant to 21 CFR §25.31, the crofelemer drug substance meets the threshold criteria for categorical exclusion based on the fact that crofelemer is a natural substance comprised of ubiquitous constituents already present in the environment and the food supply, and whose environmental exposure is not altered. In addition, the estimated concentration of crofelemer drug substance introduced into the aquatic environment (EIC-aquatic, estimated introduction concentration) is < 1 parts per billion (ppb).

However, the FDA guidance for the submission of an EA specifies that:

NDA's..... for marketing approval of a biologic product where the drug or biologic product is derived from plants or animals taken from the wild, would be considered an extraordinary circumstance, and an EA should be submitted.

(US FDA Guidance for Industry: Environmental Assessment of Human Drug and Biologics. July 1998).

Therefore, Salix Pharmaceuticals, Inc. is submitting an EA for the botanical raw material used in the production of crofelemer, pursuant to 21 CFR § 25.21, and in consideration of the FDA EA guidance.

Salix Pharmaceuticals, Inc. anticipates no adverse effects to the environment as a result of the sourcing, manufacturing, or use or subsequent release or disposal of crofelemer.

1.0 DATE

November 4, 2011

2.0 NAME OF APPLICANT/PETITIONER

Salix Pharmaceuticals, Inc.

3.0 ADDRESS

8510 Colonnade Center Dr.
Raleigh, NC 27615

4.0 DESCRIPTION OF PROPOSED ACTION

4.1 Requested Approval

Approval of Crofelemer Tablets 125 mg, under NDA 202292 is being requested for the control and symptomatic relief of diarrhea in patients with HIV/AIDS on anti-retroviral therapy. Diarrhea remains an important problem for HIV-infected subjects. It can be caused by the antiviral treatment, direct effects of HIV, and the secondary infections as a result of the immunodeficiency state caused by the aforementioned. NDA 202292 has been granted “Fast Track” designation for this clinical indication.

4.2 Need for Action

Crofelemer will be delivered orally at 125 mg twice daily (BID) for the control and symptomatic relief of diarrhea in patients with HIV/AIDS on anti-retroviral therapy.

Currently, there is no FDA-approved product available to address diarrhea in HIV/AIDS patients. The consequences of this unmet medical need can include a negative impact on subject compliance with antiviral treatment regimens and a negative impact on patient quality of life. Many HIV patients fail to adhere to an antiviral drug treatment regimen due to debilitating gastrointestinal (GI) side effects that may lead to development of resistant HIV strains, resurgence in viral replication and progression of disease with increasing mortality ([Haubrich 1999](#); [Paterson 2000](#); [Sherman 2000](#); [Tinnmouth 2007](#)).

Crofelemer produces an anti-diarrheal effect through a novel mechanism of action, most likely due to the inhibition of cystic fibrosis transmembrane regulator (CFTR) channel and calcium-activated chloride channel in the GI lumen. The inhibition blocks chloride secretion and accompanying high volume water loss in secretory diarrhea, normalizing the flow of chloride ions and water in the GI tract ([Fischer 2004](#); [Tradtrantip 2010](#)).

4.3 Locations of Use

Crofelemer will be used as a prescription agent in home and in hospital environments throughout the United States (US).

4.4 Disposal Sites

End-user disposal at US hospitals, pharmacies or clinics of empty or partially empty packages will follow hospital, pharmacy or clinic procedures. Empty or partially empty containers in residences will typically be disposed of by a community's solid waste management system, which may include landfills, incineration and/or recycling. Minimal quantities of unused drug may be disposed of in sewer or septic systems.

5.0 CHEMICAL SUBSTANCES SUBJECT OF THE PROPOSED ACTION

Crofelemer is a heterogeneous oligomeric proanthocyanidin (OPC) of botanical origin. As such, crofelemer is subject to the FDA Guidance for Industry on Botanical Drug Development (June 2004). The botanical raw material is the sap, a CPL, of the South American croton tree, *Croton lechleri* Muell. Arg. The CPL is obtained by cutting through the bark of a harvested tree. It is collected as a sticky, reddish-colored liquid resembling blood, hence its common name, "dragon's blood croton" or "sangre de drago," in Spanish.

Once processed, the resulting crofelemer drug substance is a heterogeneous mixture of polymeric chains ranging from 3 to 30 units, with an average length of 7 units. The polymeric chains are comprised of four monomers which appear in random order: catechin, epicatechin, galocatechin, and epigallocatechin. These components are members of a class of compounds collectively referred to as proanthocyanidins. Proanthocyanidins and proanthocyanidin polymers are ubiquitous, naturally occurring substances, occurring in fruits, nuts, and vegetables, as well as other common foods, as discussed further in [Section 6.8.2.4](#) (Carando 1999; Gu 2004).

The finished drug product, Crofelemer Tablets, 125 mg, is an enteric-coated, compressed tablet produced using a conventional manufacturing process. In addition to the drug substance, the tablet contains standard pharmaceutical excipients.

5.1 Nomenclature

5.1.1 Established Name (USAN)

Crofelemer

5.1.2 Tradename

To be determined

5.2 Chemical Abstracts Service (CAS) Registration Number:

148465-45-6

5.3 Molecular Formula:

$C_{15 \cdot n} H_{12 \cdot n + 2} O_{6.5 \cdot n}$ where n = number of units

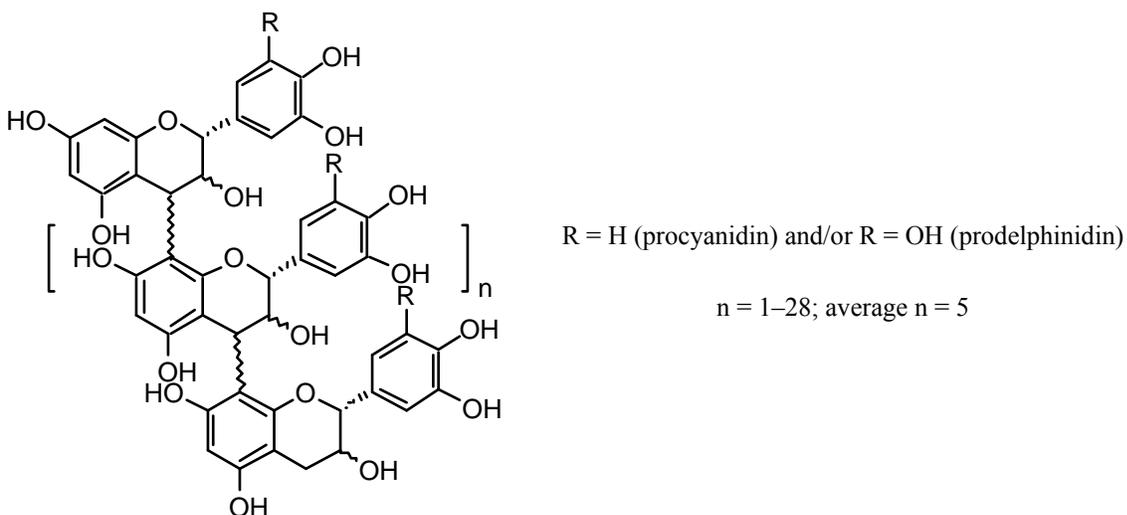
5.4 Molecular Weight:

- **Average Molecular Weight (Mn):** 1700 to 2500 Daltons
- **Polydispersity Index (Mw/Mn):** 1.00 to 1.20

5.5 Structural Formula

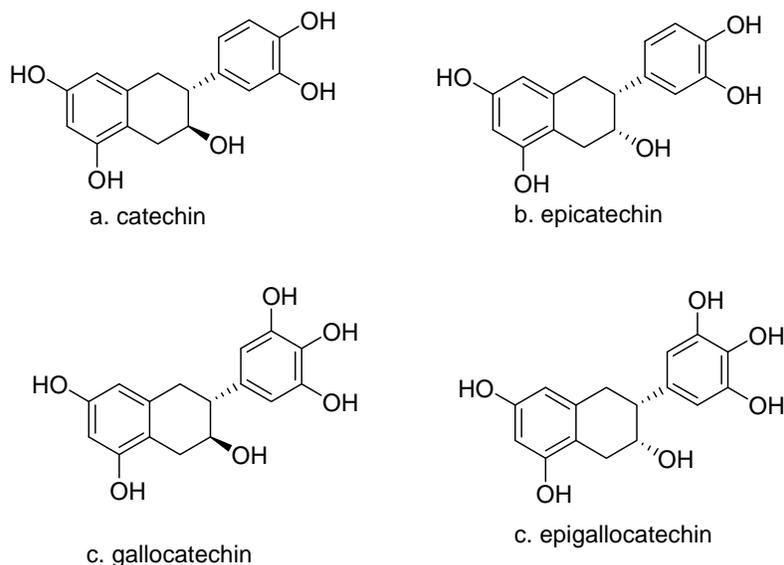
A representation of crofelemer's polymeric structure is shown in [Figure 1](#).

Figure 1: General Structure of Crofelemer



Crofelemer is comprised of four randomly assorted monomers whose structures are shown in [Figure 2](#).

Figure 2: Monomers of Proanthocyanidin Polymers in Crofelemer.



The polymer consists of linear chains of 5,7,3',4'-tetrahydroxy (catechin or epicatechin) or 5,7,3',4',5'-pentahydroxy flavan-3-ol (gallo catechin or epigallo catechin) units linked together through either C-4 to C-6 and/or C-4 to C-8, with the latter shown in [Figure 1](#). The monomer unit of the polymer chain may be based on either of two stereochemistries of C2 and C3 in the C ring, designated *cis* and termed epicatechin or *trans* and named catechin, and on either of two B ring oxidation patterns, 3',4'-dihydroxyphenyl (designated as a procyanidin unit) or 3',4',5'-trihydroxyphenyl (designated as a prodelfphinidin unit). The polymer chains create a wide variety of polymeric proanthocyanidins and a large number of possible isomers.

5.6 FDA-Approved Drug(s) Containing Catechins

Crofelemer is not the first drug comprised of catechins. In 2006, FDA approved NDA 21-902 for the botanical drug kunecatechins (VeregenTM), a topical cream for the treatment of genital warts. Kunecatechins is comprised of a mixture of catechins and other components from the leaves of cultivars of green tea, *Camellia sinensis* (L.) O Kuntze. Catechins constitute 85% to 95% (by weight) of the total drug substance, which includes more than 55% of epigallo catechin gallate, other catechin derivatives such as epicatechin, epigallo catechin, epicatechin gallate, and some additional minor catechin derivatives (i.e., gallo catechin gallate, gallo catechin, catechin gallate, and catechin) ([VeregenTM Package Insert](#)).

6.0 ENVIRONMENTAL ISSUES

The CPL used for manufacturing crofelemer drug substance is collected from cuts in the bark of harvested trees that are grown in specific EcoGeographic Regions (EGRs) of South America, as described in [Appendix A](#).

C. lechleri is a member of the genus *Croton*, a large one with over 1200 species of trees and shrubs distributed across the tropical and subtropical regions of both hemispheres. The *Croton* species are well-known medicinal plants. Four species, *C. draco*, *C. gossypifolius*, *C. lechleri* and *C. urucurana*, of section *Cyclostigma* are recognized for their red latex. *C. lechleri* is the most widely used of these species and is extensively planted and commercially exploited for its latex and also for its bark ([Borges 2000](#)).

6.1 Description of Harvest

For several decades, there has been an increase in the commercial product of *C. lechleri* CPL. The tree needs to be felled to harvest the latex for commercial purposes. In preliminary studies performed on *C. lechleri*, the tapping method of latex harvest was found to be less sustainable to the traditionally-used felling method for large-scale production. In addition, the average volume of latex obtained differs significantly for the two methods of harvesting; the amount of latex harvested is significantly greater from the felling method than from tapping. Additionally, trees suffered a high mortality rate after tapping because the type of *C. lechleri* cell that makes up the latex (non-articulated laticifers) does not regenerate to allow continual tapping and latex production. The felling method of maximum CPL collection was therefore chosen to mitigate the impact of over-harvesting of *C. lechleri* for its latex ([Ubillas 1994](#)).

6.2 Sustainable Cultivation

C. lechleri has become a viable non-timber forest product (NTFP) in the western local and international levels. *C. lechleri*'s botanical and ecological characteristics are quite favorable for agroforestry cultivation and reforestation purposes. Its medicinal and traditional use by numerous indigenous cultures has contributed to this tree's adaptation in sustainable management systems. The economic incentive of sustainably managing *C. lechleri* is already assisting many forest communities to shift from logging timber to harvesting latex. Because of these considerations, *C. lechleri* is being incorporated into conservation initiatives in the Amazon basin. The *C. lechleri* species has been produced in both agroforestry systems and in natural forests. As the trees planted in agroforestry systems mature, latex harvest will gradually shift to agroforestry cultivation. The reliance of partial supply from forests provides NTFP incentives and income generation which contribute to the valuation of secondary and primary forest management as well as maintains the management of native germplasm of *C. lechleri* ([King 1997](#); [Borges 2000](#)).

6.3 Good Agricultural and Cultivation Practices

Good Agricultural and Collection Practices (GACPs), as recommended by the World Health Organization guidelines for medicinal plants; Annex 2 ([WHO 2003](#)), have guided the original and current control of the growing and collection processes for the botanical raw material used to manufacture crofelemer drug substance. Considerable controls are in place regarding the CPL used to produce the crofelemer drug substance. A manual on the sustainable harvesting and collection of *C. lechleri* in Spanish has been produced and distributed widely to all collaborating

CPL suppliers. This manual is part of the GACP process followed by Salix Pharmaceuticals and previous sponsors. Additional controls include:

- Identification and qualification of the geographic regions from which the botanical raw material may be grown and collected
- Training of those who grow and collect the botanical raw material using Spanish language standard operating procedures developed specifically for CPL collection
- Recording and maintaining botanical documentation, including Voucher Specimens and Certificate(s) of Authenticity.
- Consistent and sustainable growing, harvesting and collection practices

Salix Pharmaceuticals is committed to assuring that the CPL suppliers conduct the growing, cultivation and collection of CPL, in accordance with GACP ([WHO 2003](#)).

6.4 Biological Identification

C. lechleri Muell. Arg. is the species from which the CPL is collected for the manufacturing of crofelemer drug substance. The following represent the scientific and common names and taxonomic classification. The American Herbal Products Association assigns the common names “dragon’s blood croton” and “sangre-de-drago” as acceptable names for use in US commerce ([McGuffin 2000](#)).

SCIENTIFIC NAME: *Croton lechleri* Muell. Arg.

COMMON NAMES: “Dragon’s blood”croton (Spanish: Sangre de grado, Sangre de drago)

Table 1: Taxonomic Classification of *Croton lechleri*

Division:	Streptophyta
Class:	Equisetopsida
Subclass:	Magnoliidae
Order:	Malpighiales
Family:	Euphorbiaceae
Genus:	Croton
Subgenus	Adenophylli
Section:	Cyclostigma
Subsection:	Cyclostigma
Species:	<i>Croton lechleri</i> Muell.Arg.

Source: based on [APG \(2009\)](#)

As a genus, *Croton* is one of the largest members of the *Euphorbiaceae*, or spurge family, a family of plants that have a characteristic specialized latex-forming tissue that produces clear or colored latex. The genus *Croton* has been the subject of a molecular systematic revision that allowed proposing an updated genus circumscription and more clear affinities in its evolutionary history (Berry 2005). Currently, the genus is recognized with 4 subgenera, 31 sections and 10 subsections (van Ee 2011). *C. lechleri* is recognized as a member of subgenus *Adenophylli* (Griseb.) Riina, section *Cyclostigma* Griseb. The section *Cyclostigma* is characterized by all 41 members being woody (either shrubs or trees), with leaves palmately veined, glands at the base of the lamina or apex of the petiole, and producers of high amount of latex from laticifers in the secondary xylem (van Ee 2011). This section includes fast growing trees and shrubs typical of secondary forest vegetation (Webster 1993; Riina 2009).

A botanical description of *C. lechleri* is provided in Table 2.

Table 2: Growth Habit, Foliar and Reproductive Characteristics of *Croton lechleri*

CHARACTERISTICS	<i>C. LECHLERI</i>
Growth Habit	Tall tree usually > 8 m – 20 m in height
Bark	Smooth, mottled white or gray
Foliage	Large, heart-shaped, bright-green leaves
Size (cm)	5–25 × 3–19
Leaf position	alternate
Stipules	Present, sublanceolate, 2 mm long
Individual leaf area (cm ²)	60±280
Shape	ovate to widely ovate
Upper surface	Glabrescent with scattered stellate hairs
Color (young leaf)	Brownish
Vestiture on lower surface	Lamina sparsely silvery pubescent to glabrous with age
Margin	entire
Apex	Acuminate to long acuminate
Base posture	Broadly lobate to cordate
Inflorescence	Monoecious inflorescences (flowers female, or male, or bisexual)
Type of inflorescence	Racemose with spread cymules
Flowers	Different in size
Sepals	Five, valvate
Petals	Present only in male flowers
Ovary	Globular, densely stellate pubescent
Style	Bifid
Stamens	15 with pilose filament
Fruit	capsule 3–4 mm long, with numerous seeds
Shape	Globose, trilobite
Size (cm)	0.6–0.8
Number of seeds	Mostly 3/fruit

From: [Meza 1999](#); [van Ee 2011](#)

6.5 Statement: Use of Wild or Cultivated Specimens

Both wild and cultivated Peruvian croton trees are currently used to supply the CPL for crofelemer drug substance.

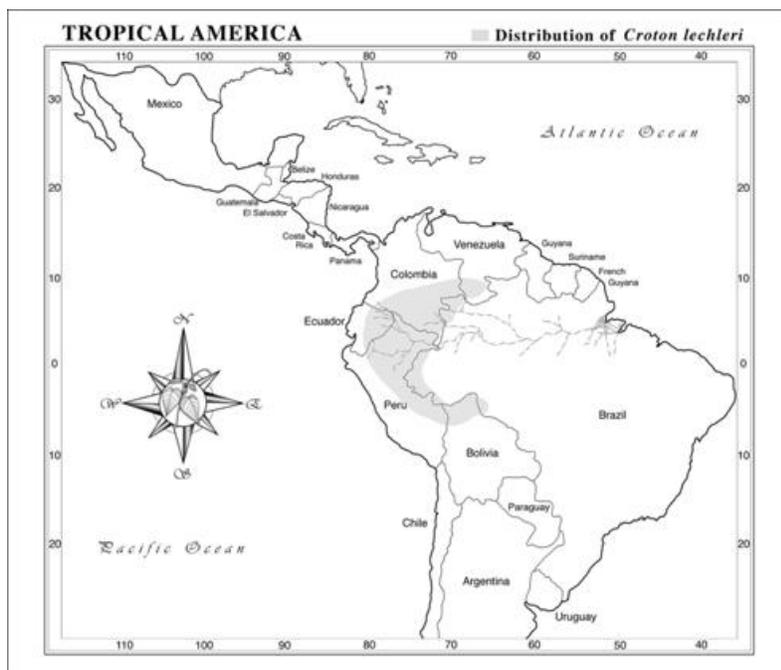
6.6 Geographic Region Where the Biomass is Obtained

Countries producing the CPL for both domestic and international markets include Colombia, Ecuador, and Peru ([Borges 2000](#)). The collection sites and procedures for CPL collection for crofelemer drug substance are described in [Appendix A](#).

6.6.1 Ecological Habits, Distribution and Density of *Croton*

The ecological habitat and distribution of *Croton* species varies greatly. *C. lechleri* is found in the Amazon regions of Bolivia, Brazil, Colombia, Ecuador, and Peru, and most commonly in the lowland northwestern Amazonian forest region from 100–800 meters and at higher elevation from 800 to 2500 meters (Figure 3). Numerous studies of the ecology, distribution, density, growth habits, marketing, agroforestry, management and collection methods have been conducted in four countries (Castillo-Quiliano 2010). *C. lechleri* grows in a variety of soils and habitats. Frequently, it is found in secondary forests, rarely along rivers and streams but it does not do well in areas with repetitive flooding. Because *C. lechleri* behaves as a pioneer species, it can grow in disturbed sites, including cultivated fields and abandoned orchards. The croton tree grows at an exceedingly rapid rate (~1 foot per month), which is influenced by soil type and precipitation (Forero-Pinto 2000; King 1997; Borges 2000).

Figure 3: Natural Distribution of *Croton lechleri*



The density of *C. lechleri* trees has been assessed in central Peru (Department of Ucayali). (Phillips 1991). A density of 3–10 trees > 10 cm diameter at breast height (DBH) per hectare was common, especially in riparian habitat, as shown in Figure 4 and Figure 5. Other studies have shown that density per area varies among natural populations. For example, in central Peru, densities for trees > 25 cm DBH were 5–149 trees/hectare (ha), while in disturbed sites these densities varied from 42–57 trees/ha.

Figure 4: Sample *C. lechleri* Densities from Trees with > 10 cm Diameter at Breast Height (DBH) in 4 Lowland Peruvian Forest Sites, at 140 meters

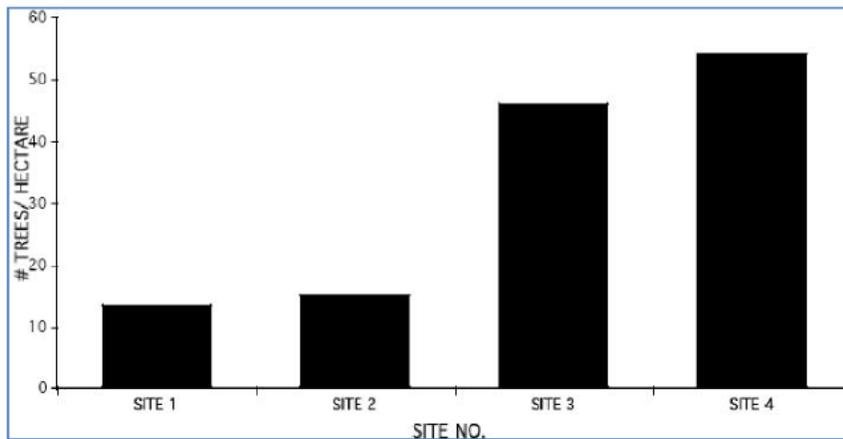
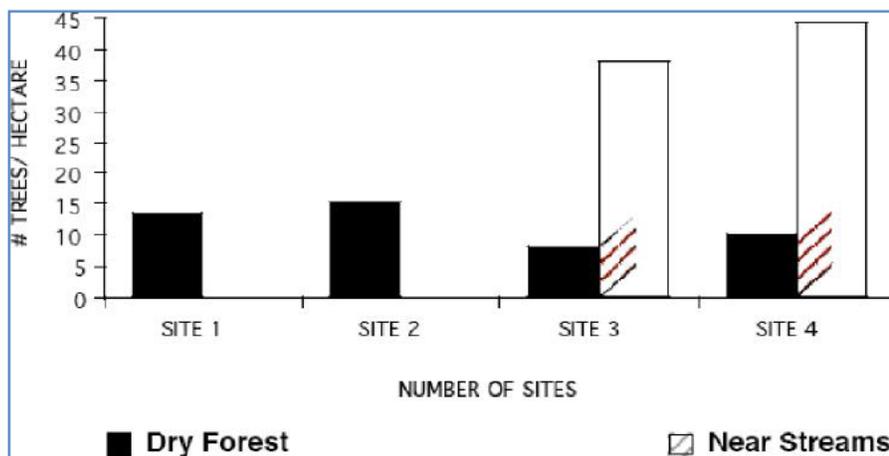


Figure 5: Sample *C. lechleri* densities from Trees with > 10 cm Diameter at Breast Height DBH in 4 Lowland Dry and Riparian Peruvian Forest Sites, at 140 meters



6.7 Endangered Species Status

- *C. lechleri* is not listed as endangered or threatened under the Endangered Species Act or the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES).
- *C. lechleri* is not entitled to special protection under some other Federal law or international treaty to which the US is a party.
- *C. lechleri* harvesting does not endanger the critical habitat of a species that has been determined to be endangered or threatened under the Endangered Species Act or CITES

or is entitled to special protection under some other Federal law or international treaty to which the US is a party.

C. lechleri wild and planted individuals occupy lowland and mid-elevation tropical forests. These forests are generally considered threatened mostly by deforestation from several economic and social causes. However, *C. lechleri*'s botanical and ecological characteristics are quite favorable for agroforestry cultivation and reforestation purposes. Its medicinal and traditional use by numerous indigenous cultures has contributed to this tree's adaptation in sustainable management systems. The economic incentive to sustainably manage *C. lechleri* is already assisting many forest communities to shift from logging timber to harvesting latex. Because of these considerations, *C. lechleri* is being incorporated into conservation initiatives in the Amazon basin (Borges 2000).

As a pioneer species, *C. lechleri* grows quite well among cultivated lands and is often grown alongside crops such as banana, orange, coffee, yucca, and cacao. Many of these crops grow well in the shade produced by the *C. lechleri* tree. *C. lechleri* reproduces early and profusely. Seed dispersal occurs by wind, birds and other animals, and it has no specialized pollinators. Mature mother trees produce up to 600,000 seeds per tree per season, which at times can occur twice in a year. On average, 1 kg of dry weight of seeds will contain about 70,000 seeds. Seed germination is quite successful, especially under the disturbed conditions of a forest clearing. As a result, natural regeneration is widespread and dozens of seedlings compete for light and nutrients at the base of mother trees (Borges 2000).

The use of *C. lechleri* from plantations is considered a viable and sustainable alternative to avoid additional pressure to its wild populations, as well as being a potential economic source for rural families. (See Appendix A).

Management plans for the commercial production of the CPL were initiated in South America in the early 1970s. Today, CPL is sustainably harvested by local peoples who have been trained over the past decade with the aim of ensuring a high degree of quality and ecological integrity.

6.8 Environmental Fate and Effect Issues

6.8.1 Environmental Concentrations: Expected Introduction Concentration (EIC)

Crofelemer has high solubility in both water and alcohol but exhibits extremely poor permeability *in vitro* and *in vivo*. *In vivo*, crofelemer is considered a gut-targeted, topically acting GI agent. Crofelemer has low oral bioavailability; fewer than 5% of healthy and HIV-associated diarrhea subjects have any detectable plasma concentration of crofelemer following oral dosing. Consequently, after human consumption, it is anticipated that the majority of the drug product enters the sewer or septic systems. As a water soluble material, crofelemer is expected to partition into the aqueous environmental compartment.

The expected introduction of an active moiety into the aquatic environment was calculated as follows.

EIC-aquatic (ppb) = $A \times B \times C \times D$ where:

A = kg/yr produced for direct use (Confidential Appendix 1)

B = 1/ liters per day entering POTWs*

C = years/ 365 days

D = 1×10^9 $\mu\text{g}/\text{kg}$ (conversion factor)

* 1.224×10^{11} liters per day entering publically owned treatment works (POTWs)

(Source: *Clean Watersheds Needs Survey, 2008 Report to Congress*)

The EIC of the crofelemer active moiety (the botanical drug substance) entering into the external aquatic environment (EIC-aquatic) has been calculated and is presented in [Appendix B](#). The EIC-aquatic is < 1 ppb. No adjustments have been made to account for metabolism, other environmental depletion mechanisms, or for the dilution of wastewater effluents into the receiving waters. No seasonal patterns of use are expected.

6.8.2 Prior and Current Human Intake and Use

6.8.2.1 Traditional Use (Ethnobotany)

Latex from croton species has been widely used in traditional medical practice since ancient times by many cultures ([Bussmann 2006](#); [Gupta 2008](#)). *C. lechleri* sap (CPL) and bark are used in traditional medicine in South America. Even today, the CPL from *C. lechleri* is a common household remedy in Peru, Ecuador, and other Latin American countries, and among the Latin American population of the US ([Jones 2003](#); [Lindner 2009](#)). The earliest written reference dates its use to the 1600s, when Spanish naturalist and explorer P. Bernabé Cobo documented the wide-reaching acceptance of the botanical material's therapeutic powers among the indigenous tribes of Mexico, Peru, and Ecuador.

For medicinal use, the CPL is administered both topically and orally. It is used externally by indigenous tribes and local people in Peru as a "liquid bandage" for wounds, insect bites, contact dermatitis, and other skin maladies. Applied to mucosal surfaces, it is used to treat oral and dental conditions, rectal hemorrhoids, and as a vaginal douche for gynecologic hemorrhaging, and before and following childbirth. Taken orally, CPL is used to treat throat, gastrointestinal conditions, including gastric ulcers and diarrhea, including severe diarrhea associated with cholera. Traditionally, 5–10 drops of CPL are diluted in hot or warm water, juice, milk, or alcohol and ingested 1 to 3 times a day for up to 3 weeks ([Ubillas 1994](#); [Duke 1994](#); [Castner 1998](#); [Gupta 2008](#)).

6.8.2.2 Dietary Intake as Food Components

Proanthocyanidins, a class of compounds that includes the four monomeric substances that make up crofelemer, are found in a wide range of fruits, cereals, beans, nuts, and beverages, including red and white wines (Table 3). Data from the US Department of Agriculture indicate that the mean intake of proanthocyanidins in the US population (≥ 2 years old) is approximately 57.7 mg per person. Monomers, dimers, trimers, and larger polymers contribute 7.1%, 11.2%, 7.8%, and 73.9% of total proanthocyanidins, respectively. The major sources in the US diet are apples (32.0%), chocolate (17.9%) and grapes (17.8%) (Gu 2004; Carando 1999).

Table 3: Examples of Common Foods Consumed in the United States that Contain Proanthocyanidins

FOOD CATEGORY	FOOD	ESTIMATED PROANTHOCYANIDIN CONCENTRATION ¹ (MG/100 G FRESH FOOD WEIGHT; MG/L BEVERAGE)
Fruits	Blueberries	180 ± 51
	Strawberries	145 ± 25
	Cherries	8 ± 3
	Green Grapes	82 ± 15
	Red Grapes	61 ± 12
	Apples (Granny Smith)	141 ± 26
	Peaches	67 ± 21
	Bananas	4 ± 0.6
Cereals and Beans	Sorghum, Sumac Bran	3965 ± 402
	Pinto Beans, Raw	796 ± 59
	Red Kidney Beans	564 ± 10
	Barley	74 ± 3
	Black Eye Peas	33 ± 4
Nuts	Hazelnuts	501±152
	Pecans	494 ± 86
	Almonds	184 ± 48
	Walnuts	67 ± 15
	Peanuts, Roasted	16 ± 2
	Cashews	9 ± 3
Beverages and Snack	Baking Chocolate, Unsweetened	1636 ± 335
	Milk Chocolate	192 ± 29
	Chocolate Milk	26 ± 2
	Red Wine	313 ± 5
	Beer	23 ± 2
	Cranberry Juice Cocktail	231 ± 2
	Grape Juice	524 ± 2
Spices	Cinnamon, Ground	8108 ± 424
	Curry Powder	74 ± 2

¹ Values are mean ± standard deviation; n = 4–8

Source: Gu 2004.

6.8.2.3 FDA GRAS Status

Grape seed extract, a food substance composed primarily of proanthocyanidins, includes the same compounds as found in the crofelemer drug substance. Grape seed extract is Generally Recognized As Safe (GRAS) by the FDA for use in beverages, beverage bases, breakfast cereals, fats and oils, frozen dairy desserts and mixes, grain products, milk (whole and skim), milk products, and processed fruits and fruit juices at levels ranging from 0.01% to 0.08% (FDA GRN 000124 2003; www.fda.gov).

6.8.2.4 Food Uses

Products containing CPL and certain extracts of CPL have been generally considered as dietary ingredients in the US. In 2005, the Utah Natural Products Alliance, in comments submitted in response to the FDA’s Premarket Notification Program for New Dietary Ingredient Request for Comments, *C. lechleri* was included on the list of “old” dietary ingredients, i.e., ingredients marketed in the US prior to the October 15, 1994 cut-off date set by the Dietary Supplement Health and Education Act. Dietary supplements containing CPL and CPL-derived ingredients are currently being marketed in powder and liquid formulations. Between 1999 and 2003, a CPL extract containing crofelemer (~ 70.6% ± 7.2% by weight) was marketed as a dietary supplement in the US. Examples of dietary supplements containing CPL currently being marketed in the US are listed in Table 4.

Table 4: Examples of Dietary Supplements Currently Marketed in the United States that Contain *C. lechleri* as the Principal Ingredient

BRAND NAME	INGREDIENTS	MANUFACTURER / DISTRIBUTOR
Sangre de Grado Wildcrafted Dragon’s Blood (liquid)	Sangre de Grado	Amazon Therapeutic Laboratories PO Box 446 Murphy, OR 97533
Sangre de Grado Resin (Croton lechleri) (liquid)	Sangre de Grado Resin	Raintree Nutrition, Inc. 3579 Highway 50 East, Suite 222 Carson City NV 89701
Ashaninka Sangre de Drago 100% Pure Sap (liquid)	Sangre de Drago Sap 100% Pure Sap	Rainforest Pharmacy PO Box 771686 Miami, FL 33177
Ashaninka Sangre de Drago 200 and 500 mg capsules	Sangre de Drago Concentrated Powder Extract	
Ulcerex with Sangre de Drago (capsules)	Cat’s Claw (<i>Uncaria tomentosa</i>), Calahuala (<i>Polypodium leucotomos</i>) and Sangre de Drago (<i>Croton lechleri</i>)	

6.8.3 Criteria for Inclusion of Environmental Fate and Effects Data

Crofelemer does not meet the three FDA criteria for inclusion of environmental fate and effects data, for the following reasons:

- The estimated concentration of the active moiety at the point of entry into the aquatic environment is < 1 ppb ([US FDA Guidance for Industry: Environmental Assessment of Human Drug and Biologics. July 1998. Section III.A](#));
- The substance occurs naturally in the environment; however FDA's approval of the NDA will not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment ([US FDA Guidance for Industry: Environmental Assessment of Human Drug and Biologics. July 1998. Section III.B](#)); or
- There are no data to show that, at the expected level of exposure, there is the potential for serious harm to the environment ([US FDA Guidance for Industry: Environmental Assessment of Human Drug and Biologics. July 1998. Section III.C.1](#)).

Therefore, the evaluation of crofelemer environmental fate and effects is unnecessary because none of the three threshold criteria have been met.

6.8.4 Summary

Crofelemer drug substance qualifies for a claim of categorical exclusion based on the fact that crofelemer is a natural substance comprised of constituents already present in the environment and the food supply, and whose environmental exposure is not altered. There is a significant history of prior and current human use of *C. lechleri* CPL, as well as certain extracts of CPL, both of which are recognized in the US as dietary ingredients. The constituents of CPL and crofelemer drug substance are ubiquitous in the US diet. The estimated concentrations of crofelemer drug substance introduced into the aquatic environment (EIC-aquatic) is < 1 ppb, pursuant to 21 CFR § 25.31. Therefore, no environmental fate and effects data for the drug substance crofelemer are being submitted.

The fact that the CPL is collected from wild growing *C. lechleri* trees is considered an **extraordinary circumstance** for which this EA is being submitted, pursuant to 21 CFR § 25.21 and in consideration of the [US FDA Guidance for Industry: Environmental Assessment of Human Drug and Biologics. July 1998. Section III](#).

Based on the above, Salix Pharmaceuticals, Inc. anticipates no adverse effects to the environment as a result of the sourcing, manufacturing, or use or subsequent release or disposal of crofelemer.

7.0 MITIGATION MEASURES

No adverse environmental effects have been identified. No mitigation measures are required.

8.0 ALTERNATIVES TO THE PROPOSED ACTION

No potential effects have been identified for this proposed action. No alternatives to the proposed action are required.

9.0 LIST OF PREPARERS

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Consulting to the botanical drug industry, with expertise in Chemistry, GMPs, Toxicology, Botany, and Regulatory Affairs

A full list of preparers with credentials is provided in [Appendix C](#) (confidential).

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11.0 APPENDICES [CONFIDENTIAL]

APPENDIX A: [REDACTED] (b) (4) [CONFIDENTIAL]

APPENDIX B: [REDACTED] (b) (4) (EIC)
[CONFIDENTIAL]

APPENDIX C: [REDACTED] (b) (4) [CONFIDENTIAL]

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