CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203551Orig1s000

ENVIRONMENTAL ASSESSMENT

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

Memorandum

Date: January 14, 2013

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

To: Debbie Mesmer
OPS/ONDQA/DNDQA1

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

Subject: **NDA 203-551**
Docetaxel Injection Concentrate 20 mg/mL (Rx Only)

Request for Categorical Exclusion

Submission Date: 9/30/12 (Letter Date), 10/01/12 (Stamp Date)

Actavis Inc.
60 Columbia Road, Building B
Morristown NJ 07960 USA

Background

Actavis Inc. has filed a new drug application, NDA 203-551, to gain approval for Docetaxel Injection Concentrate 20 mg/mL (Rx Only). The applicant has submitted a claim of categorical exclusion under 21 CFR 25.31(a), on two dates: 2/1/2012 and 03/2/2012 (EDR m1/1.12.14). The applicant states that the drug product is not expected to increase the use of the active moiety. Since the active moiety is derived from plant sources, the agency required additional information on the source of the plant material to determine if an EA is required under "extraordinary circumstances." An EA is required for non-cultivated plant sources.

In a June 14, 2012, Information Request, the agency requested the applicant to provide information on the source of the raw material and to indicate whether the plants are grown wild or as cultivated plants.

In a September 30, 2012, amendment to a pending NDA submission - Serial 0007 (EDR 3.2.S.2.1.6, 3.2.S.2.1.7, 3.2.S.2.1.8, 3.2.S.2.1.9), the applicant provided the following response:

" Regarding the source of the raw material, please be informed that the sources of raw material from all suppliers are grown as private/cultivated plants. Enclosed in this amendment are the Environmental Assessments (EA) from the four suppliers of plants to [redacted]):

3.2.S.2.1.6 [redacted] – Environmental Assessment
3.2.S.2.1.7 [redacted] – Environmental Assessment
3.2.S.2.1.8 [redacted] – Environmental Assessment
3.2.S.2.1.9 [redacted] – Environmental Assessment "

Review of the Current Submission

I have reviewed the submitted environmental information and determined that the applicant provides sufficient information to demonstrate that raw material is sourced from cultivated plants (Taxus baccata).

In addition, Taxus baccata is not (a) determined to be endangered or threatened under the Endangered Species Act or the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES), (b) entitled to special protection under any Federal law or international treaty to which the United States is a party, or (c) the critical habitat of a species that has been determined to be endangered or threatened under the Endangered Species Act or the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) or (d) is entitled to special protection under some other Federal law or international treaty to which the United States is a party.

Conclusion

The sponsor has provided information indicating that the raw material is derived from cultivated plant sources. The provided information indicates that no "extraordinary Circumstances" exist for this application.

Based on an evaluation of the provided information, FDA regulations at 21 CFR 25 and FDA guidance (GFI: Environmental Assessment), this application qualifies for a categorical exclusion under 21 CFR 25.31(a).

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

/s/

RAANAN A BLOOM
01/14/2013

NAKISSA SADRIEH
01/14/2013

FDA/CENTER FOR DRUG EVALUATION AND RESEARCH

ENVIRONMENTAL ASSESSMENTS / USE OF FLORA

Source: Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications (7/1998) http://www.fda.gov/cder/guidance/index.htm#chemistry

I. NDA and ANDA APPLICATIONS

a. Cultivated Plants

Actions involving drug or biologic products derived from cultivated plants (e.g., grown in plantations, nursery stock ...) are normally categorically excluded under 21 CFR 25.31(a) and/or 21 CFR 25.31(c).

i. Claims of Categorical Exclusion

To claim a categorical exclusion, the applicant must state 1) that the action requested qualifies for a categorical exclusion, citing the particular categorical exclusion that is claimed, and 2) that to the applicant's knowledge, no extraordinary circumstances exist (see 21 CFR 25.15(d)).

Typically, the following statement is provided:

> *Applicant's name* claims that approval of this (A)NDA qualifies for a categorical exclusion in accordance with 21 CFR 25.31(x) and that, to the best of the applicant's knowledge, no extraordinary circumstances exist which may significantly affect the quality of the human environment.

To facilitate Center review, when submitting a claim of categorical exclusion for actions where the drug or biologic product is derived from cultivated plants, CDER requests that the applicant provide the following information with the claim, or specifically identify where the information can be located (e.g., DMF, page number of application):

(1) biological identification (i.e., common names, synonyms, variety, species, genus and family);
(2) a statement as to whether wild or cultivated specimens are used;
(3) the geographic region (e.g., country, state, province) where the biomass is obtained; and
(4) a statement indicating:

(a) whether the species is determined under the Endangered Species Act (ESA) or the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) to be endangered or threatened,
(b) whether the species is entitled to special protection under some other Federal law or international treaty to which the United States is a party

(c) whether the species is the critical habitat of another species that has been determined to be endangered or threatened under ESA or CITES
(d) whether the species is the critical habitat of another species entitled to special protection under some other Federal law or international treaty to which the United States is a party.

CDER will use this information to evaluate whether the claim of categorical exclusion is appropriate.

b. Non-Cultivated Plants

An Environmental Assessment (EA) is ordinarily required for NDAs, abbreviated applications and applications for marketing approval of a biologic product where the drug or biologic product is *derived from plants taken from the wild.* EAs are also ordinarily required for supplements to such applications that relate to changes in the source of the wild biomass (e.g., species, geographic region where biomass is obtained), or supplements to such applications that are considered to increase the use of an active moiety or biologic substance and which will cause more harvesting than what was described in the original EA. The content and format follows.

i. EA Content and Format

This section describes the basic information that should be submitted in an EA for a drug or biologic product derived from plants taken from the wild. Alternative formats may be used, but the applicant should recognize that use of a standard format, such as described in this guidance, promotes efficiency in the review process.

1. Date

The EA should include the date the EA was originally prepared and the date(s) of any subsequent amendments.

2. Name of Applicant or Petitioner

The EA should identify the applicant who is submitting the application.

3. Address

The EA should contain the address where all correspondence is to be directed.

4. Description of Proposed Action

a. Requested Approval

The description of the requested approval should include the drug or biologic application number (if available), the drug or biologic product name, the dosage form and strength, and a brief description of the product packaging. For example, "XYZ Pharmaceuticals has filed an NDA pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for TRADE NAME (established name), 250 mg and 500 mg, packaged in OHDPE bottles. An EA has been submitted pursuant to 21 CFR part 25."

b. Need for Action

The EA should briefly describe the drug's or biologic's intended uses in the diagnosis, cure, mitigation, treatment, or prevention of disease.

c. Locations of Use

The EA should identify the location(s) where the product will be used. Depending on the type of product and its use, the locations of use are typically identified as hospitals, clinics and/or patients in their homes. If use is expected to be concentrated in a particular geographic region, this fact should be included.

d. Disposal Sites

Unless other disposal methods by the end user are anticipated, it is sufficient to state that at U.S. hospitals, pharmacies, or clinics, empty or partially empty packages will be disposed of according to hospital, pharmacy, or clinic procedures and/or that in the home, empty or partially empty containers will typically be disposed of by a community's solid waste management system, which may include landfills, incineration, and recycling, although minimal quantities of the unused drug could be disposed of in the sewer system.

5. Identification of Substances that are the Subject the Proposed Action

a. Nomenclature
   i. Established Name (U.S. Adopted Name-USAN)
   ii. Brand/Proprietary Name/Tradename
   iii. Chemical Names or Genus/Species of Biologic Product
      Chemical Abstracts (CA) Index Name (inverted form)
      Systematic Chemical Name (uninverted form)
b. Chemical Abstracts Service (CAS) registration number
c. Molecular Formula
d. Molecular Weight
e. Structural (graphic) Formula/Amino Acid Sequence

6. Environmental Issues

a. Use of Resources

Information relating to the source of the plant, such as biological identification, government oversight of harvesting, geographic region where biomass is obtained, and harvesting methods

and techniques should be included in the EA. The EA should include, but not be limited to, the following types of information:

- Biological identification (i.e., common names, synonyms, variety, species, genus, and family).
- A statement as to whether wild or cultivated specimens are used.
- The geographic region (e.g., country, state, province) where biomass is obtained and whether harvesting occurred on public or private land.
- A brief description of government oversight of the harvesting including, if applicable, the identity of the authority permitting harvesting and identity of authorities consulted regarding the harvesting. Submission of copies of permits or harvesting regulations relating to the specific species is helpful. For species covered under CITES, CDER or CBER could request copies of relevant permits.
- A brief description of the applicant's oversight of the harvesting.
- A statement indicating:
  (a) whether the species is determined under the Endangered Species Act (ESA) or the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) to be endangered or threatened,
  (b) whether the species is entitled to special protection under some other Federal law or international treaty to which the United States is a party
  (c) whether the species is the critical habitat of another species that has been determined to be endangered or threatened under ESA or CITES
  (d) whether the species is the critical habitat of another species entitled to special protection under some other Federal law or international treaty to which the United States is a party.
- A statement describing the part of the plant used and whether it is a renewable resource.
- A detailed description of the method of harvest including such information as the type of harvesting (e.g., clear cut, gleaning from timber stands destined for clear cutting, salvaging, pruning), frequency of harvest, whether the harvesting technique will affect the ecosystem (and if so, how), and whether the harvesting is conducted in accordance with government regulations or guidance (include citations to applicable regulations or guidance).
- Bulk weight or other appropriate measure of biomass needed to yield one kilogram of active moiety or biologic substance, the amount that has been harvested to date to support the proposed Agency action for the product, and the amount expected to be harvested in the future.
- The amount of biomass needed to produce the active moiety or biological substance used to treat the average patient. This should be provided in terms easy to understand (e.g., 2-3 trees per patient). The expected patient population and number of kilograms of active moiety or biologic substance needed per year should be provided. *(This information may be provided in confidential appendix).*
- An estimate of the total number of plants in the geographic region where the biomass is obtained.
- Any uses of the plant other then for the proposed use (humans, food source, habitat for fauna).

- Plant growth rates and/or life span and, if applicable, the rate of reproduction/ regeneration.
- A discussion of whether harvesting provides for sustained yield (e.g., percentage of sustainable harvest needed to supply annual needs based on the proposed use and any prior approved uses).

7. Mitigation Measures

Describe measures taken to avoid or mitigate any potential adverse environmental effects associated with the proposed action. If no adverse environmental effects have been identified, it should be so stated and indicated that no mitigation measures are needed.

Discuss mitigation measures for actions involving flora such as mitigation measures taken before (e.g., developing a process that uses a renewable part of a plant), during (e.g., limiting/selecting specimens to be harvested), and after harvesting (e.g., reforestation) (see 40 CFR 1508.20).

8. Alternatives to the Proposed Action

If no potential adverse environmental effects have been identified for the proposed action, the EA should state this. If potential adverse environmental effects have been identified for the proposed action, the EA "shall discuss any reasonable alternative course of action that offers less environmental risk or that is environmentally preferable to the proposed actions" (21 CFR 25.40(a)). The discussion should include the no-action alternative and measures that FDA or another government agency could undertake as well as those the applicant or petitioner would undertake. The EA should include a description of those alternatives that will enhance the quality of the environment and avoid some or all of the adverse environmental effects of the proposed action. The environmental benefits and risks of the proposed action and the environmental benefits and risks of each alternative should be discussed.

Discuss alternatives for actions involving flora. A discussion must be provided of the reasonable alternatives that were considered when deciding which biomass source would be used to produce the active moiety or biologic substance (21 CFR 25.40(a)). All alternatives that were considered (e.g., other species, wild or cultivated sources, chemical synthesis) should be discussed. A brief discussion of the factors (e.g., environmental effects) that were considered in deciding whether or not the alternative would be used should be provided. The no-action (i.e., no approval) alternative should also be discussed. It should be indicated if any of the alternatives not currently used are planned for use in the future.

9. Certification

{Applicant Name} confirms that it and the other parties with which it contracts for this harvesting (e.g., any and all buyers and collectors) have complied with all requirements under *{Country/State where harvested}* law to date relating to the harvesting of *{plant species}* for *{Applicant Name}*. *{Applicant Name}* commits that it will continue to comply with all requirements under *{Country/State where harvested}* law 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.

10. List of Preparers

The EA should include the name, job title, and qualifications (e.g., educational degrees) of those persons preparing the assessment and should identify any persons or agencies consulted. Contract testing laboratories should be included in the list of consultants, although this may be included in a confidential appendix. Curriculum vitae can be included in lieu of a description of an individual's qualifications.

11. References

The EA should include a list of citations for all referenced material and standard test methods used in generating data in support of the EA. Copies of referenced articles that are not generally available and that are used to support specific claims in the EA document should be attached in a nonconfidential appendix.

12. Appendices

Both confidential and nonconfidential appendices can be included. A list of the appendices should be included in the EA summary document with a designation of confidential or nonconfidential following each of the listings. Typically, the nonconfidential appendices include data summary tables and copies of referenced articles that are generally unavailable or that were used to support specific claims in the EA. Proprietary or confidential information, such as use estimates and test reports, should be included in the confidential appendices.

EA FORMAT OUTLINE

1. Date
2. Name of Applicant/Petitioner
3. Address
4. Description of Proposed Action
    a. Requested Approval
    b. Need for Action
    c. Locations of Use
    d. Disposal Sites
5. Identification of Substances that are the Subject of the Proposed Action
    a. Nomenclature
        i. Established Name (U.S. Adopted Name - USAN)
        ii. Brand/Proprietary Name/Tradename
        iii. Chemical Names or Genus/Species of Biologic Product (e.g., virus)
            •Chemical Abstracts (CA) Index Name
            •Systematic Chemical Name
    b. Chemical Abstracts Service (CAS) Registration Number
    c. Molecular Formula
    d. Molecular Weight
    e. Structural (graphic) Formula/Amino Acid Sequence
6. Environmental Issues
7. Mitigation Measures
8. Alternatives to the Proposed Action
9. List of Preparers
10. References
11. Appendices
12. Certification

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/s/

DEBORAH M MESMER
06/14/2012

JANICE T BROWN
06/14/2012