CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-297

ADMINISTRATIVE DOCUMENTS

This is an update for the Approval Summary written for the final approval of the ANDA.

APPROVAL SUMMARY PACKAGE

ANDA NUMBER: 75-297

FIRM: Zenith Goldline Pharmaceuticals
140 Legrand Avenue
Northvale, NJ 07647

DOSAGE FORM: Injection

STRENGTHS: 30 mg/5 mL, 100 mg/16.7 mL and 150 mg/25 mL

DRUG: Paclitaxel Injection

CGMP STATEMENT/EIR UPDATED STATUS:
EER for all facilities listed in section # 33 of this ANDA (CR # 4) is acceptable as of 9/30/99.

An update is being requested.

BIO STUDY:
Bio status: Acceptable for all three strengths.

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
MV: Acceptable as of 12-8-00. This MVP is completed in Northeast Regional laboratories, New York.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?
Containers used in the stability studies are identical to those listed in container section.

LABELING:
Acceptable for tentative approval dated 10-10-00.

FPL for final approval is acceptable per A. Payne review.

STERILIZATION VALIDATION (IF APPLICABLE):
Micro review: Acceptable as of 5/99(Hughes).

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.?):
Bio waiver is requested.

Source of NDS:
DMF : Adequate per review completed on 5-16-00 by this reviewer.

DMF : Adequate per review completed on 6-5-00 by Liang-Lii Haung.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED VIA SAME PROCESS?)
Exhibit batches:

Lot 701-6858 (30 mg/5 mL): Batch size is manufactured from active.

Lot # 701-6859 (150 mg/25 mL): Batch size is and is manufactured from active.

Lot # 801-6858 (30 mg/5 mL): Batch size is vials and is manufactured from

Lot 701-6860 (100 mg/16.7 mL): Batch size is vials and is manufactured from ctive.

All exhibit/stability batches are manufactured via same manufacturing process. active will only be used in 5 mL size post-approval.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?
Intended production batch size vials for 30 mg/5 mL and for 100 mg/16.7 mL, and ials batch size for 150 mg/25 mL.

Manufacturing process for the intended production size is identical to that used for the exhibit/bio/stability batch.

Environmental Assessment: Acceptable for per N. Sager on 4/98. Acceptable for per N. Sager on 7/00.

3/26/01

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el

M. Sola 3/26/01

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-297** Date of Submission: **December 14, 1999**
Applicant's Name: **Zenith Goldline Pharmaceuticals, Inc.**
Established Name: **Paclitaxel Injection, 6 mg/mL, 5 mL, 16.7 mL, and 25 mL vials**
Labeling Deficiencies:

1. CONTAINER (5 mL, 16.7 mL and 25 mL) – Satisfactory in final.

2. CARTON (1 x 5 mL, 1 x 16.7 mL, and 1 x 25 mL) – Satisfactory in final.

3. INSERT
   a. BOXED WARNINGS – Revise the first sentence of the last paragraph in this section to read as follows:

      ...less than 1500 cell/mm^3 and should not be given to patients with AIDS-related Kaposi's sarcoma if the baseline neutrophil count is less than 1000 cell/mm^3.

      [We note that you are not seeking approval for the Kaposi's sarcoma indication, however, it is possible that paclitaxel may not be utilized specifically to treat AIDS-related Kaposi's sarcoma, but the patient may have a concurrent disease state for which Paclitaxel Injection is indicated. Therefore, as a matter of safety, include this in your Boxed Warnings.]

   b. CONTRAINDICATIONS (last sentence) – See comment under BOXED WARNINGS.

   c. WARNINGS (second paragraph, last sentence) – Revise to read as follows:

      ...>1500 cells/mm^3 (>1000 cells/mm^3 for patients with KS) and platelets...

4. PATIENT INFORMATION LEAFLET

   The reference listed drug, TAXOL® (Bristol-Myers Squibb), received approval for a Patient Information leaflet on December 10, 1999. Since it is part of the reference listed drug's approved labeling, you are required to submit a similar leaflet for review and comment. We have enclosed a copy of this labeling for your convenience.

Please revise your insert labeling, as instructed above, and submit 12 copies of final printed insert labeling and 12 copies of final printed patient information leaflets or 4 copies of draft labeling if you prefer.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that your routinely monitor the following website for any approved changes: http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the enclosed TAXOL® labeling with all differences annotated and explained.

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-297** Date of Submission: **August 13, 1999**
Applicant's Name: **Zenith Goldline Pharmaceuticals, Inc.**
Established Name: **Paclitaxel Injection, 6 mg/mL, 5 mL, 16.7 mL, and 25 mL vials**

Labeling Deficiencies:

1. CONTAINER (5 mL, 16.7 mL and 25 mL)

   a. Add the following in conjunction with "PROTECT FROM LIGHT":

      Retain in carton until contents are used.

   b. Enhance the prominence and conspicuousness of required statements, in particular, the strength.

2. CARTON (1 x 5 mL, 1 x 16.7 mL, and 1 x 25 mL)

   Delete the storage temperature recommendation from the principle display panel.

3. INSERT

   Please revise your insert labeling to be in accord with the most recent labeling for the reference listed drug, TAXOL® (Bristol-Myers Squibb; approved January 8, 1999). In addition, please update your Patent Certification and Exclusivity statement.

Please revise your container labels, carton and insert labeling, as instructed above, and submit 12 copies of final printed container labels, along with 12 copies of final printed carton labeling and 4 copies of draft insert labeling.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that your routinely monitor the following website for any approved changes: http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

John D. Grace for

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-297 Date of Submission: **March 23, 1999**
Applicant's Name: **Zenith Goldline Pharmaceuticals, Inc.**
Established Name: **Paclitaxel Injection, 6 mg/mL, 5 mL and 25 mL vials**

Labeling Deficiencies:

1. CONTAINER (5 mL and 25 mL)

   Add the following in conjunction with "PROTECT FROM LIGHT":

   Retain in carton until contents are used.

2. CARTON (1 x 5 mL and 1 x 25 mL)

   Delete the storage temperature recommendation from the principle display panel.

3. INSERT

   Please revise your insert labeling to be in accord with the enclosed copy of the most recent labeling for the reference listed drug, TAXOL® (Bristol-Myers Squibb; approved January 8, 1999). In addition, please update your Patent Certification and Exclusivity statement.

Please revise your container labels, carton and insert labeling, as instructed above, and submit 12 copies of final printed container labels, along with 12 copies of final printed carton labeling and 4 copies of draft insert labeling.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that your routinely monitor the following website for any approved changes: http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-297** Date of Submission: **December 30, 1997**

Applicant's Name: **Zenith Goldline Pharmaceuticals, Inc.**

Established Name: **Paclitaxel Injection, 6 mg/mL, 5 mL and 25 mL vials**

Labeling Deficiencies:

1. CONTAINER (5 mL and 25 mL)

   a. We encourage you to differentiate your product strengths with the use of boxing, contrasting colors or some other means.

   b. Include "MUST BE DILUTED PRIOR TO IV USE" rather than "Caution: Dilution required" on the main panel. This statement should appear in red, consistent with Taxol.

   c. Relocate the storage temperature recommendations to the side panel.

   d. Add the following in conjunction with "PROTECT FROM LIGHT":

      Retain in carton until contents are used.

   e. We note that the storage recommendations of the RLD is 20° to 25°C. Is there any reason why your product cannot be stored at a lower temperature, in particular, in a refrigerator at 2° to 8°C?

   f. Replace the "CAUTION: Federal law..." statement with the symbol "Rx only" or "℞ only". We refer you to the Guidance For Industry, "Implementation of Section 126, Elimination of Certain Labeling Requirements...", at the internet site, **http://www.fda.gov/cder/guidance/index.htm** for guidance.

2. CARTON (1 x 5 mL and 1 x 25 mL)

See comments under CONTAINER.

3. INSERT

a. TITLE

See comment f under CONTAINER.

b. DESCRIPTION

List the process from which paclitaxel is obtained from "*Taxus X media* Hicksii".

c. CLINICAL PHARMACOLOGY

i. Paragraph six - Revise to read "50 mcg/mL" rather than "50 g/mL".

ii. Paragraph seven - Insert a comma following "6∝,-3'-*p*-dihydroxypaclitaxel".

d. PRECAUTIONS

i. Nervous System, paragraph two - Insert "injection" following ""Paclitaxel".

ii. Carcinogenesis, Mutagenesis, Impairment of Fertility, last paragraph - Revise to read "increased" rather than "increase" in the last sentence.

e. ADVERSE REACTIONS

i. Table

A) Revise the title to read as follows:

...812 PATIENTS RECEIVING PACLITAXEL

B) Cardiovascular - Do not indent "Vital Sign Changes" or "Significant Cardiovascular Events

C) Abnormal ECG - Revise to read "ECG" rather than "Ecg".

D) Peripheral Neuropathy and Myalgia/Arthralgia - Delete "symptoms"

from both subsections.

ii. Hypersensitivity Reactions - Insert the following text as the last paragraph:

Rare reports of chills and reports of back pain in association with hypersensitivity reactions have been received as part of the continuing surveillance of paclitaxel safety.

f. DOSAGE AND ADMINISTRATION

i. Preparation for Intravenous Administration - Insert "injection" following "Paclitaxel" in the second sentence.

ii. Stability - Revise the first sentence to read as follows:

...vials of paclitaxel injection are stable...store between 2° to 25°C (36° to 77°F) in the original....

g. HOW SUPPLIED

i. Storage - Revise to read as follows:

Store the vials in original cartons between 2° to 25°C (36° to 77°F). Retain in the original carton until contents are used to protect from light.

ii. See comment f under CONTAINER.

Please revise your container labels, carton and insert labeling, as instructed above, and submit final printed labels and carton labeling and draft insert labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research