CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-297

CORRESPONDENCE

Zenith Goldline
PHARMACEUTICALS

March 14, 2001

Mr. Gary Buehler
Acting Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

NEW CORRESP NC

AMENDMENT: Request to withdraw ONXOL™ name

Re: ANDA 75-297 Paclitaxel Injection, 6 mg/mL

Dear Mr. Buehler:

Reference is made to our tentatively approved ANDA #75-297 for Paclitaxel Injection 6 mg/mL. Reference is also made to the minor amendment of March 5, 2001 and conversations with Angela Payne of the labeling review group on March 13 and March 14, 2000.

Ms. Payne indicated that approval of the proposed trade name ™ (paclitaxel) Injection by the Office of Pharmaceutical Drug Product Risk Assessment could delay the drug product's approval. With this in mind, Zenith Goldline Pharmaceuticals, Inc. wishes to withdraw, without prejudice, the trade name (paclitaxel) Injection as shown on the labeling contained in Appendix 6 of the March 5, 2000 submission. Therefore, the proposed labeling reverts to that submitted on December 14, 1999 and June 21, 2000 that contains the generic name **Paclitaxel Injection.**

If you have any questions or require further information, please do not hesitate to contact me at (201) 767 1700 ext. 330/331.

Sincerely,

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
MAR 16 2001
OGD

Karen M. Rocco for K.R.
Karen Rocco, RAC
Director, Global Regulatory Affairs

3/21/01

140 Legrand Avenue, Northvale, New Jersey 07647 ▪ (201) 767-1700 (800) 631-1583

Miami • Ft. Lauderdale • Cidra, P.R. • St. Croix, U.S. V.I. • Shreveport • Mason • Syosset

1. CHEMISTRY REVIEW NO. 5

2. ANDA # **75-297**

3. NAME AND ADDRESS OF APPLICANT
Zenith Goldline Pharmaceuticals (ZGP)
140 Legrand Ave.
Northvale, NJ 07647

4. LEGAL BASIS FOR SUBMISSION
Reference listed drug for the 30 mg/5mL: Taxol (paclitaxel) Injection, 30mg/5mL (6 mg/mL) manufactured by Bristol-Myers Squibb Co., approved in NDA number 20-262.

Paclitaxel for Injection Concentrate, 150mg/25mL (6mg/mL), submitted by Fujisawa USA, Inc., which was approved in ANDA suitability Petition for a new strength (Docket No. 97P-0058/CP1- approved June 10, 1997).

The RLD for all vials (5 mL, 16.7 mL and 25 mL) belong to BMS. The petition only allows the 25 mL to be submitted as an ANDA.

This ANDA was tentatively approved on 10-10-00. This amendment is submitted to get final approval.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None used.

7. NONPROPRIETARY NAME
Paclitaxel Injection

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
FIRM:
Original submission: 12-30-97
NC: 2-4-98
NC: 2-6-98
NC: 3-30-98
NC: 6-29-98
Major Amendment: 3-23-99 (Response to NA letter dated 8-4-98)
Amendment: 6-25-99
Amendment: 8-13-99
Major Amendment: 12-6-99 (Response to NA letter dated 10-14-99)
Labeling amendment: 12-14-99
Gratuitous Amendment: 5-9-00
Amendment: 5-17-00
Fax Amendment: 6-9-00
Telephone amendment: 8-15-00
Telephone amendment: 9-19-00

* Amendment: 3-5-01 (Submitted to get final approval)

FDA:
Accepted for filing letter: 2-11-98 (Acceptable for filing date: 12-31-97
NA (Major) amendment letter: 8-4-98
NA (Major) amendment letter: 10-14-99
NA (FAX) amendment letter: 6-1-00
Tentatively approved on: 10-10-00

10. PHARMACOLOGICAL CATEGORY
Treatment of breast cancer

11. Rx or OTC
RX

12. RELATED IND/NDA/DMF(s)
Reference listed drug Taxol (paclitaxel injection, 30mg/5mL)
NDA 20-262 for Bristol-Myers Squibb Company (BMS) approved on 12-29-92.
ANDA 75-184----Under review for Immunex.
ANDA 75-278 Under review for Mylan
DMF II)----Paclitaxel drug substance----
BioTherapeutics, Inc.
DMF)---Paclitaxel drug substance---

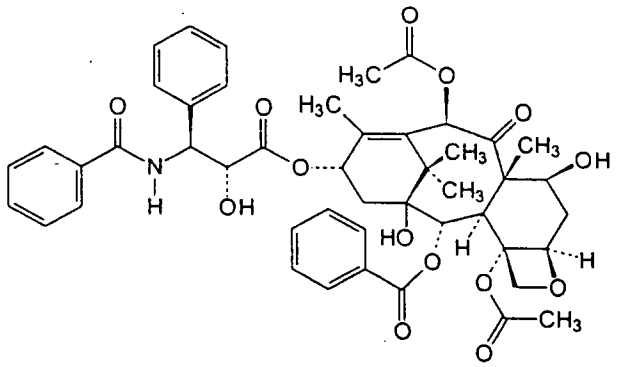
13. DOSAGE FORM
Injection

14. POTENCY
6 mg/mL

[Vial fill sizes: 30 mg/5mL, 100 mg/16.7 mL and 150 mg/25 mL]

15. CHEMICAL NAME AND STRUCTURE

Paclitaxel. Benzenepropanoic acid, □-(benzoylamino)-□-hydroxy-, 6,12b-bis(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1*H*-cyclodeca[3,4]benz[1,2-b]oxet-9-yl ester, [2a*R*-[2a□,4□,4a□,6□,9□(□*R**,□*S**),11□,12□,12a□,12b□]]-. $C_{47}H_{51}NO_{14}$. 853.93. 33069-62-4. Antineoplastic. USAN 1995, page 499.



16. RECORDS AND REPORTS
None

17. COMMENTS:
No major changes are made since tentative approval of this ANDA.

Following minor revisions are made in amendment dated 3-5-01:

1. Zenith Goldline clarified that their tentatively approved ANDA # 75-297 and also tentatively approved ANDA for Baker Norton ANDA # 75-184 not only use the identical regulatory test methods and laboratories for their drug product, but the manufacturing facility is also the same.

2. A correction of a critical ten-fold step in the analytical procedure STP- is made. Revised method is submitted. Acceptable.

3. s is a contract manufacturer for the drug product. Zenith would like to add g as an alternate laboratory to perform the testing of Sterility, Bacterial Endotoxins and testing of Particulate Matter in the finished drug product. Zenith Goldline clarified that the test methods approved in the application will be used by enith Goldline has indicated that has the capability of performing the intended testing and has a satisfactory cGMP inspection held on April 11-19, 2000.

MVP was satisfactorily completed after the tentative approval of the ANDA.

18. CONCLUSIONS AND RECOMMENDATIONS
Approve.

19. REVIEWER: Mujahid L. Shaikh
DATE COMPLETED: 3-12-01

Revised on 3-19-01.

Page(s) 11

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

Chem Rev 5

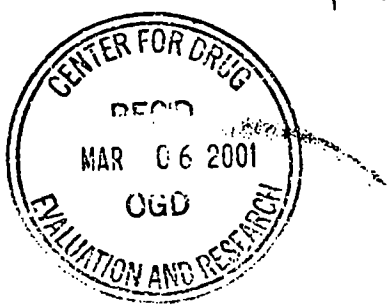
3/12/01

Zenith Goldline
PHARMACEUTICALS

March 5, 2001

ORIG AMENDMENT
N/Am

Fax: (301) 594-0183



Mr. Gary Buehler
Director, Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation & Research
Metro Park North II - HFD 600
7500 Standish Place
Rockville, Maryland 20855

RE: ANDA 75-297, Paclitaxel Injection, 6 mg/mL

Minor Amendment

Dear Mr. Buehler:

In a letter dated March 5, 2001, copy attached as appendix 1, Baker Norton Pharmaceuticals (BNP) waived its 180-day exclusivity for Paclitaxel Injection selectively to Zenith Goldline Pharmaceuticals (ZGP). Zenith Goldline ANDA #75-297 for paclitaxel injection was tentatively approved on October 10, 2000. Based on this correspondence, ZGP respectively requests immediate final approval of its ANDA #75-297.

Zenith Goldline has submitted a Paragraph IV patent certification under Section 505(j)(2)(A)(vii)(IV) of the Act and has notified FDA that on August 17, 2000, the 30-month Hatch-Waxman stay of approval period has expired. As stated in our correspondence to the Agency on July 5, 2000 that federal Judge William Walls entered a judgment of invalidity on April 7, 2000. Bristol-Myers Squibb filed a notice of appeal to the Court of Appeals for the Third Circuit on April 17, 2000 and the appellate proceeding on patent infringement litigation remains pending. ZGP intends to market Paclitaxel Injection immediately upon approval of its ANDA.

Since the tentative approval of this ANDA, there are minor changes to the chemistry, manufacturing and controls section of the application as described below. Both ZGP and BNP not only use the identical regulatory testing methods and laboratories for their drug products, but the manufacturing facility is also the same. BNP has the following supplemental changes to its ANDA #75-184 and the changes as approved are deemed relevant to the ZGP ANDA #75-297. Authorization to cross-reference the supplements listed below is provided in the attached letter (appendix 2).

NW 3/7/01

4400 Biscayne Blvd., Miami, Florida 33137 • (305) 575-4100

A Subsidiary of IVAX Corporation

ANDA 75-297

Zenith Goldline Pharmaceuticals, Inc.
Attention: Patricia Jaworski
140 Legrand Avenue
Northvale, NJ 07647

OCT 10 2000

Dear Madam:

This is in reference to your abbreviated new drug application dated December 30, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Paclitaxel Injection, 6 mg/mL (packaged in 5 mL, 16.7 mL and 25 mL multiple dose vials).

Reference is also made to your amendments dated December 6 and December 14, 1999; May 9, June 9, June 21, August 15 and September 19, 2000.

We have completed the review of this abbreviated application and have concluded that, based upon the information you have presented to date, the drug is safe and effective for use as recommended in the submitted labeling. Therefore, the application is **tentatively approved.** This determination is based upon information available to the Agency at this time (i.e., information in your application and the status of current good manufacturing practices of the facilities used in the manufacturing and testing of the drug product) and is therefore subject to change on the basis of new information that may come to our attention.

The listed drug product referenced in your application is subject to periods of patent protection which expire on August 3, 2012, (U.S. Patents No. 5,641,803 [the '803 patent], 5,670,537 [the '537 patent]) and March 9, 2013 (U.S. Patent No. 5,496,804 [the '804 patent]). Your application contains a patent certification under Section 505(j)(2)(A)(vii)(IV) of the Act stating that your manufacture, use, or sale of this drug product will not infringe on these patents. Section 505(j)(5)(B)(iii) of the Act provides that approval of an abbreviated application shall be made effective immediately unless an action is brought before the expiration of forty-five days from the date the notice provided under paragraph (2)(B)(I) is received by the owner of the new drug application (NDA) for the referenced listed drug product and the patent holder. You have notified FDA that Zenith Goldline Pharmaceuticals, Inc. has complied with the requirements of Section 505(j)(2)(B) of the Act

and that Bristol-Myers Squibb initiated a suit against Zenith Goldline Pharmaceuticals, Inc. and Ivax Corporation in the United States District Court for the District of New Jersey (Bristol-Myers Squibb Company v. Zenith Goldline Pharmaceuticals, Inc. and Ivax Corporation, Civil Action No. 97-6050). You have notified the Agency that on August 17, 2000, the 30 month period has expired precluding the Agency from approving this product and the court has not extended this period.

Please note that an abbreviated application for Paclitaxel Injection, 6 mg/mL, containing a Paragraph IV Patent Certification was accepted for filing by this Office prior to the filing of your application. This application, submitted by Baker Norton Pharmaceuticals, Inc., received final approval on September 15, 2000. Consequently, Baker Norton Pharmaceuticals is eligible for 180-days of generic drug market exclusivity. Your application will be eligible for final approval beginning one hundred and eighty (180) days after the first commercial marketing of the drug by Baker Norton Pharmaceuticals, Inc. We refer you to the Agency's guidance document entitled "180-Day Generic Drug Exclusivity Under the Hatch-Waxman Amendments" (June 1998), for additional information.

Because the Agency is granting a tentative approval for this application, please submit an amendment at least 60-days but not more that 90-days prior to the date you believe your application will be eligible for final approval. This amendment should identify changes, if any, in the conditions under which the drug product was tentatively approved, and should include updated information such as final printed labeling, chemistry, manufacturing and controls data as appropriate. Alternatively, an amendment should be submitted stating that no changes have been made to the terms of the application since the date of tentative approval. This submission should be designated clearly in your cover letter as a MINOR amendment. In addition to, or instead of, the amendment requested above, the Agency may, at any time prior to the final date of approval, request that you submit an amendment containing the information described above.

Any changes in the conditions outlined in this abbreviated application and the status of the manufacturing and testing facilities' compliance with current good manufacturing procedures are subject to Agency review before final approval of the application will be made.

In addition to, or instead of, the amendments referred to above, the Agency may, at any time prior to the final date of approval, request that you submit amendments containing the information requested above.

Failure to submit either or both amendments may result in rescission of this tentative approval determination, or delay in issuance of the final approval letter.

The drug product that is the subject of this abbreviated application may not be marketed without final Agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug before the effective final approval date is prohibited under section 501 of the Act. Also, until the Agency issues the final approval letter, this drug product will not be listed in the Agency's "Approved Drug Products with Therapeutic Equivalence Evaluations" list.

The amendment should be designated as a MINOR AMENDMENT in your cover letter. Before you submit the amendment, please contact Michelle Dillahunt, Project Manager, at (301) 827-5848, for further instructions.

The introduction or delivery for introduction into interstate commerce of the drug before the effective approval date is prohibited under 21 U.S.C. 331(d).

Sincerely yours,

Gary Buehler 10/10/00

Gary Buehler
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

Zenith Goldline
PHARMACEUTICALS

September 19, 2000

Mr. Gary Buehler
Acting Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

NDA ORIG AMENDMENT
N/FA

TELEPHONE AMENDMENT

RE: ANDA 75-297: Paclitaxel Injection, 6 mg/mL packaged in 30 mg/5 mL, 100 mg/16.7 mL and 150 mg/25 mL container sizes.

Dear Mr. Buehler:

Reference is made to Zenith Goldline Pharmaceuticals pending abbreviated new drug application for Paclitaxel Injection, 6mg/mL packaged in 30 mg/5 mL, 100 mg/16.7 mL and 150 mg/25 mL containers sizes. Zenith Goldline Pharmaceuticals, Inc. (ZG) hereby amends its certification in the above ANDA pursuant to 21 C.F.R. § 314.94(a)(12)(viii)(B) to withdraw the paragraph IV certification to Patent No. 6,096,331 ('331). That certification was submitted on August 14, 2000. ZG certifies under 21 C.F.R. § 314.94(a)(12)(ii) that no relevant patents as described in 21 C.F.R. § 314.94(a)(12)(i) claim the listed drug other than those identified in the certification prior to August 14, 2000. The reason for this change in certification is that Bristol-Myers Squibb has withdrawn from the Orange Book the '331 patent listing submitted on August 11, 2000, and pursuant to 21 C.F.R. § 314.94(a)(12)(vi), ZG is not required to certify to any subsequent listing of the '331 patent that was made more than 30 days after August 1, 2000.

Reference is also made to the telephone calls between Dr. Allen Rudman and Dr. Jane Hsiao regarding the final specifications for the drug substance and drug product.

This amendment reflects the recommendation by the Agency to establish two specifications for the active drug substance (ADS) for each of the two approvable ADS suppliers. These specifications are attached as Appendices 1 and 2.

Furthermore, the finished product specification has been modified to reflect the use of STP-463 as the regulatory method, to include reference to "Meets USP <1> Injections" where [illegible] and to tighten the release and/or stability limits for seven impurities. Therefore, included in Appendix 3, is the revised regulatory specification for Paclitaxel Injection, 6 mg/mL.

140 Legrand Avenue, Northvale, New Jersey 07647 • (201) 767-1700 (800) [illegible]

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The post-approval stability protocol has also been revised to incorporate the revised finished product specification. This revised stability protocol is included in Appendix 4.

Should any questions arise, please do not hesitate to contact our office at (201) 767-1700 ext. 330/331, via fax at (201) 767-3804, or via e-mail to karen_rocco@ivax.com.

Sincerely,

ZENITH GOLDLINE PHARMACEUTICALS, INC.

Karen M. Utt for K.A.R.

Karen A. Rocco, RAC
Director, Global Regulatory Affairs

LACHMAN CONSULTANT SERVICES, INC.
CONSULTANTS TO THE PHARMACEUTICAL AND ALLIED INDUSTRIES

1600 STEWART AVENUE
WESTBURY, NY 11590
(516) 222-6222 • FAX (516) 683-1887

August 16, 2000

(FAX DOCUMENT 8/16/00)

Mr. Gary Buehler
Acting Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

NEW CORRESP
NC

RE: ANDA 75-297, Paclitaxel Injection, 6mg / mL in
30 mg / 5 mL, 100 mg / 16.7 mL and 150 mg / 25 mL Container Sizes

Paragraph IV Patent Certification

Dear Mr. Buehler:

As agent for Zenith-Goldline Pharmaceuticals (ZGP), we wish to correct a typographical error contained in the amendment to their pending application for Paclitaxel Injection submitted on August 14, 2000. The amendment revised Section III, Patent Certification and Exclusivity Statement, to add reference to Patent No. 6,096,331, which has just been added to the Approved Drug Products with Therapeutic Equivalence Evaluations, 20th Edition (Orange Book). The date in the parenthetical in the first line of the first paragraph regarding the expiration date of the patent should read February 22, 2014.

If you have any questions regarding this information, please contact Karen Rocco of ZGP at (201) 767-1700, ext. 330-331.

Sincerely,

Robert W. Pollock
Vice President

RP/sf

cc: L. Lachman

36p0229a

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REC'D
AUG 17 2000
OGD

Zenith Goldline
PHARMACEUTICALS
Regulatory Affairs

August 15, 2000

NDA ORIG AMENDMENT
N/FA

Mr. Gary Buehler
Acting Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

TELEPHONE AMENDMENT

RE: ANDA 75-297: Paclitaxel Injection, 6mg/mL in 30 mg/5 mL, 100 mg/16.7 mL and 150 mg/25 mL containers

Dear Mr. Buehler:

Reference is made to Zenith Goldline Pharmaceuticals' (ZGP) pending ANDA # 75-297 for Paclitaxel Injection, 6 mg/mL in 30 mg/5 mL, 100 mg/16.7 mL and 150 mg/25 mL container sizes. Reference is also made to a telephone call from Mike Smela, Chemistry Team Leader, Office of Generic Drugs, to Karen Rocco on August 11, 2000 requesting three changes to our application.

Included in Exhibit 1 is a revised product specification modified to include:

1. A change in release and stability assay range from ; and
2. Addition to the release specification of the requirement of USP<1> Foreign Matter. (Please note we have also removed from the specification the Part B list of tests needed for re-release of clinical supplies. This section is not necessary for a commercial product.)

Included in Exhibit 2 is a revised stability protocol that includes the new stability assay range of

ZGP commits to tighten its specification back to if justified, after evaluation of full term data from the first three commercial batches.

In addition, ZGP commits to use the qualified source of excipient, .nanufactured by on. Should it be necessary to change the source or technical grade of this substance, a prior approval supplement will be submitted.

Should any questions arise, please do not hesitate to contact our office at (201) 767-1700 ext. 330/331, via fax at (201) 767-3804, or via email to karen_rocco@ivax.com.

Sincerely,

ZENITH GOLDLINE PHARMACEUTICALS, INC.

Karen A. Rocco, RAC
Director, Global Regulatory Affairs

cc: District Office

140 Legrand Avenue, Northvale, New Jersey 07647 • (201) 767-1700 (800)387-0133 Fax (201)767-3804

Miami, Fl • Walton, KY • Cidra, PR • St. Croix, U.S.V.I.

Zenith Goldline
PHARMACEUTICALS

August 14, 2000

Mr. Gary Buehler
Acting Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

NEW CORRESP
NC

RE: ANDA 75-297, Paclitaxel Injection, 6mg/mL in
30 mg/5 mL, 100 mg/16.7 ml and 150 mg/25 mL container sizes

Paragraph IV Patent Certification

Dear Mr. Buehler:

We wish to amend our pending application for Paclitaxel Injection to revise Section III, Patent Certification and Exclusivity Statement, to add reference to Patent No. 6,096,331, which has just been added to the Approved Drug Products with Therapeutic Equivalence Evaluations, 20th Edition (Orange Book).

If you have any questions regarding this information, please contact me at (201) 767-1700 ext. 330-331.

Sincerely,

Karen M. Lit for KAR
Karen A. Rocco, RAC
Director, Global Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
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AUG 14 2000
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Zenith Goldline
PHARMACEUTICALS

VIA FAX (301) 827-4337
VIA FEDERAL EXPRESS

ORIG AMENDMENT

June 9, 2000

NCTOFAX

FPL

Mr. Gary Buehler
Acting Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

FAX AMENDMENT - CHEMISTRY, LABELING AND ENVIRONMENTAL DEFICIENCY RESPONSE

RE: ANDA 75-297: Paclitaxel Injection, 30 mg/5 mL, 100 mg/16.7 mL and 150 mg/25 mL

Dear Mr. Buehler:

Reference is made to Zenith Goldline Pharmaceuticals pending abbreviated new drug application for Paclitaxel Injection, 30 mg/5 mL, 100 mg/16.7 mL and 150 mg/25 mL. This submission is the response to the deficiencies noted in the Agency's facsimile correspondence dated ~~June 1,~~ 2000 (copy attached in the Reference section).

The responses to the Chemistry, Environmental Assessment (EA), and Labeling comments are provided in the Appendix to this letter. FDA comments are presented in **bold** print followed by Zenith Goldline's response in regular print.

Revised and updated Chemistry documents are provided in Attachments 1 - 3.

A revised EA report incorporating the changes listed in this response is provided in Attachment 4. This report incorporates all the responses to the EA deficiencies listed in this amendment and further requests to clarify Section 6.2.a/Endangered Species and Yew, and Section 8, Alternatives to the Proposed Action from Ms. Nancy Sager, Associate Director for Chemistry Quality Implementation, on May 25, 2000 by telephone. The EA report appendices are not being

re-submitted at this time because there are no changes in them. Therefore, the current EA report Table of Contents references the page numbers for the text sections 1-11 from the current EA (revised June 2000), and references the pages for all appendices from the original EA report (May 1999).

Revised final printed labeling is provided in Attachments 5 and 6. Please note that, based on the innovator's labeling, an additional change not requested in the labeling deficiencies was made to the Warnings section of the package insert. The change is the addition of "...than 1,500 cells/mm^3 (<1000 cells/mm^3 for patients with KS)". This appears in the second paragraph, third sentence of the Warnings section.

As required by 21 CFR 314.96(b), provided is a Field Copy Certification of this Amendment. Zenith Goldline requests that all information in this file be treated as confidential within the meaning of 21 CFR 314.430, and that no information from the file be submitted to an application without our written consent to an authorized member of your Office. Zenith Goldline is confident that the information provided is complete and approvable.

Should any questions arise, please do not hesitate to contact our office at (201) 767-1700 ext. 330/331, via fax at (201) 767-3804, or via email to karen_rocco@ivax.com.

Sincerely,

ZENITH GOLDLINE PHARMACEUTICALS, INC.

Steven M. Utz for

Karen A. Rocco, RAC
Director, Global Regulatory Affairs

cc: District Office

FJUN 1 2000]

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-297 APPLICANT: Zenith Goldline Pharmaceuticals

DRUG PRODUCT: Paclitaxel Injection, 30 mg/5mL, 100 mg/16.7 mL and 150 mg/25mL

The deficiencies presented below represent FAX deficiencies.

A. Chemistry Deficiencies:

1. Please revise your acceptance specifications for the Paclitaxel drug substance by lowering the limit for the impurity or justify the current limit.

2. Please revise your impurity specifications for release of the drug product by setting the limits the same as your limits for the impurities in the drug substance.

3. Your proposed limits for the known impurities of and for monitoring the stability of the drug product appear excessive. Please lower the limits significantly. Alternatively, you can justify with test data from the Reference Listed Drug or confirm that they are approved limits in NDA 20-826 for Paxene.

4. Environmental Assessment Deficiencies:

a. Section 6.2.a/Use of Resources: Please provide the last date of harvesting from state lands.

b. Section 6.2.a/Permitting Authorities:

1) In the discussion under permitting authorities for private and state lands, harvesting from state land in Washington and Montana is discussed. Appendix A implies that these are the only two states where harvesting occurred from state lands but it is identified as a partial list. Please specifically identify the states where harvesting from state lands occurred. If harvesting from state land occurred in other states, provide additional information similar to what is provided for Washington and Montana.

2) Confirmation should be included that harvesting from private, state and federal land was conducted in accordance with all applicable federal, state, and local laws, regulations, and guidances.

c. Section 6.2.a/Endangered Species and Yew: Information on any federal, state or local regulations and guidances that were intended to provide protection to endangered or threatened species under circumstances that would have included harvesting of Pacific Yew Trees should be provided. Also, information on whether these regulations or guidances were followed should be provided.

d. In section 6.2.c. it is stated that no future harvesting of Pacific Yew trees will occur and that alternative renewable biomass sources will be used in the future. However, the alternative renewable biomass sources are not identified. You need to identify by name the alternative renewable biomass sources you intend to use to substitute for the Pacific Yew tree derived material.

e. Section 7: Please confirm that you accomplished the mitigation measures required by the federal, state, and local governmental authorities.

f. Section 8:

1) In section 6.2.c. you state that alternative biomass sources will be used in the future and cross reference section 8 for more information. However, a discussion of these alternative biomass sources (including identification by biological name(s) and viability of the options) is not included in section 8.

2) You should indicate whether any of the alternatives, even though not currently used, are those you plan to use in the future.

3) For each alternative, a discussion should be included of any environmental factors that were considered in deciding whether or not to use the alternative.

4) The EA indicates that you will be switching to a cultivated biomass source and will continue to investigate alternative sources. This should be clarified to state that when you switch biomass sources, FDA will be notified in accordance with 21 CFR 314.96 or 314.70 and additional EA information will be provided to FDA if required.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Labeling deficiencies will also need to be addressed in your reply.

2. Please be advised that DMF is pending review. Deficiencies, if any, will be communicated to the holder.

3. Please be advised that samples for methods validation will be requested at a later date once the testing issues have been resolved.

4. Please provide any additional stability data that is available.

Sincerely yours,

f.c. Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

Zenith Goldline
PHARMACEUTICALS

Regulatory Affairs

May 17, 2000

NDA ORIG AMENDMENT
N/A A

Mr. Gary Buehler
Acting Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

AMENDMENT – ENVIRONMENTAL ASSESSMENT
DEFICIENCY RESPONSE

Re: ANDA 75-297: Paclitaxel Injection, 30 mg/5 mL, 100 mg/16.7 mL, and 150 mg/25 mL

Dear Mr. Buehler:

Reference is made to Zenith Goldline Pharmaceuticals pending abbreviated new drug application for Paclitaxel Injection, 30 mg/5 mL, 100 mg/16.7 mL and 150 mg/25 mL. This submission is the response to the deficiencies noted in the Agency's facsimile correspondence dated April 11, 2000 (copy attached).

The responses to the Environmental Assessment (EA) comments are provided in the Appendix to this letter. FDA comments are presented in **bold** print followed by Zenith Goldline's response in regular print. A revised EA incorporating the changes listed in this response is provided. The appendices are not being resubmitted because there are no changes in them. Therefore, the Table of Contents lists the page numbers of this Amendment for EA sections 1 – 11 and the page numbers of the June 25, 1999 submission for the Appendices.

As required by 21 CFR 314.96(b), provided is a Field Copy Certification of this Amendment. Zenith Goldline requests that all information in this file be treated as confidential within the meaning of 21 CFR 314.430, and that no information from the file be submitted to an application without our written consent to an authorized member of your Office. Zenith Goldline is confident that the information provided is complete and approvable.

Should any questions arise, please do not hesitate to contact our office at (201) 767-1700 ext. 330/331, via fax at (201) 767-3804, or via e-mail to karen_rocco@ivax.com.

Sincerely,

ZENITH GOLDLINE PHARMACEUTICALS, INC.

Karen A. Rocco, RAC
Director, Global Regulatory Affairs

cc: District Office

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAY 19 2000
OGD

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Zenith Goldline
PHARMACEUTICALS
Regulatory Affairs

May 9, 2000

Mr. Gary Buehler
Acting Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

NDA DRUG AMENDMENT
AA

GRATUITOUS AMENDMENT
ADDITIONAL INFORMATION

Re: ANDA 75-297: Paclitaxel Injection, 30 mg/5 mL, 100 mg/16.7 mL and 150 mg/25 mL

Dear Mr. Buehler:

Reference is made to our pending abbreviated new drug application (ANDA 75-297) for Paclitaxel Injection 6 mg/mL concentration in 30 mg/5 mL, 100 mg/16.7 mL and 150 mg/25 mL vial sizes. Reference is also made to our original submission of December 30, 1997, our Major Amendment of March 23, 1998, our Gratuitous Amendments of June 25, 1999 and August 13, 1999, the Agency's correspondence of October 14, 1999 (copy attached), and our Major Amendment dated December 6, 1999.

We hereby submit a Gratuitous Amendment to our December 6, 1999 Amendment. The purpose of this Gratuitous Amendment is to present updated documentation on the use of predetermined weights of excipients recommended by the Agency as described in Comment # 3 of the Agency's letter dated October 14, 1999. This documentation was received subsequent to our December 6, 1999 response. We also wish to revise our response of December 6, 1999 to Comment # 4a and to clarify our response to Comment # 5b. Regarding Comment # 4a, a new specification for the residual solvent of the drug substance is proposed based on actual test results obtained for 65 lots of drug substance. Regarding Comment # 5b, we wish to clarify our intentions as to when STP 463 may be used.

In a section noted as "Additional Information," this Amendment also includes the updated specifications for drug substance and drug product. Also included is a table that summarizes the product fill sizes and drug substance sources currently filed with this application as well as a complete copy of the final master batch record for the production of the product.

In order to simplify the reviewer's process and alleviate any confusion that may arise in reviewing both Amendments simultaneously, we are attaching to this letter, as Addendum A, a table that lists the question numbers in the Agency's correspondence of October 14, 1999. The table indicates which response should be reviewed: that of the December 6, 1999 Amendment, that of the attached Amendment,

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EVALUATION AND RESEARCH

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Zenith Goldline
PHARMACEUTICALS
Regulatory Affairs

DEC 14 1999

Center for Drug Evaluation and Research
Food and Drug Administration
ATTN: Mr. Douglas L. Sporn
Director, Office of Generic Drugs
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

NDA ORIG AMENDMENT

GRATUITOUS AMENDMENT- LABELING AND EXCLUSIVITY

Re: ANDA 75-297
Paclitaxel Injection, 30 mg/5 mL, 100 mg/16.7 mL and 150 mg/25 mL

Dear Mr. Sporn:

Reference is made to our pending abbreviated new drug application for Paclitaxel Injection 30 mg/5 mL, 100 mg/16.7 mL and 150 mg/25 mL. Reference is also made to the Major Amendment deficiencies communicated to Zenith Goldline Pharmaceuticals on October 14, 1999 (copy attached) by the Office of Generic Drugs. This submission amends our December 6, 1999 amendment with relative labeling and exclusivity information.

We have updated the Zenith labeling as requested to the most current Taxol labeling approved on October 25, 1999. This labeling includes approval for adjuvant treatment of node-positive breast cancer for which Bristol-Myers has received exclusivity. Therefore, in addition to second line treatment of AIDS-related Kaposi's Sarcoma and Orphan Drug Exclusivity, which we have previously acknowledged, we have updated our exclusivity statement to include node-positive breast cancer and two other indications for which we are not seeking marketing approval:

- For the adjuvant treatment of node-positive breast cancer administered sequentially to standard doxorubicin-containing combination chemotherapy;
- *First-line* therapy for the treatment of advanced carcinoma of the ovary in combination with cisplatin. We are, however, seeking approval for *subsequent* therapy for the treatment of advanced carcinoma of the ovary in combination with cisplatin; and
- Paclitaxel Injection in combination with cisplatin for first line treatment of non-small cell lung cancer.

Certification for the Kaposi Sarcoma and Orphan Drug Exclusivity was previously provided in the original ANDA submission of December 30, 1997. All four indications are deleted from our proposed labeling and the revised final draft labeling is provided.

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Zenith Goldline Pharmaceuticals has made a concerted effort to ensure that this gratuitous amendment contains all of the information that the Office of Generic Drugs may require. Should you have any questions, please contact our office at (201) 767-1700 ext. 239/331.

With best regards,

ZENITH GOLDLINE PHARMACEUTICALS, INC.

Jason A. Gross, Pharm.D.
Director, Global Regulatory Affairs

Zenith Goldline
PHARMACEUTICALS
Regulatory Affairs

November 9, 1999

VIA FACSIMILE: (301) 594-0181

Office of Generic Drugs
Center for Drug Evaluation and Research
ATTN: Ms. Michelle Dillahunt
Project Manager, Chemistry Review Branch I
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

NEW CORRESP
NC

Re: ANDA 75-297 - Paclitaxel Injection 30 mg/5 mL, 100 mg/16.7 mL, and 150 mg/25 mL
Facsimile Question - Request for Clarification

Dear Ms Dillahunt:

Reference is made to the Office of Generic Drugs' Major Amendment letter dated October 14, 1999, specifically question "A.7". Thank you for returning Zenith Goldline Pharmaceuticals' telephone call regarding our question. As requested, we are reducing our question to writing for your review and consideration. For your convenience, we have reiterated your comment followed by our question.

OGD: A batch record, in process and release data and accelerated stability for all three fill sizes are needed to support the proposed new source of paclitaxel.

ZGP: Zenith Goldline Pharmaceuticals has reviewed this comment and is perplexed, as we have interpreted this request to mean that a batch of product is required for each vial size. Zenith Goldline Pharmaceuticals has always tried to ensure that our applications are in compliance with all applicable Office of Generic Drugs' policies and procedures. Specifically, we reviewed Policy and Procedure Guide 22-90, which addresses the information required when an application seeks approval of more than one source of active drug substance in an application. This guidance document stipulates:

That, in the event more than one source of the NDS is proposed for use in making the product, the applicant should demonstrate that all sources are chemically and physically equivalent by manufacturing at least one batch of the drug product for each additional source of the NDS. The applicant is expected to submit a supplemental application and receive prior approval if proposal of a new source of the NDS is made after approval of an ANDA unless such a change is in accordance with 21 CFR 314.70(c)(3). The supplement should contain supportive information including three (3) months of accelerated stability data and full comparative dissolution profile data (comparing data derived from the alternative NDS source against data derived from the approved original NDS source bioequivalency batch).

RECEIVED
NOV 15 1999

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Zenith Goldline Pharmaceuticals manufactured all three fill sizes using the original source. The data to support the use of was submitted on 12/30/97 (30 mg/5 mL and 150 mg/25 mL fill sizes) and on 8/13/99 (100 mg/16.7 mL). This completed the requirements of submitting each fill size of the original source. When we requested approval of an alternative source , one batch was manufactured, and the data to support the use of the alternative source was submitted to the Agency on 6/15/99, as stipulated in P&P 22-90.

We believe this fulfills our regulatory requirements for one supportive batch on an alternate source of NDS and that further batches, as requested in the Agency's letter of 10/14/99, should not be required.

Zenith Goldline Pharmaceuticals would like to submit our response to your correspondence within the next few days; however, your comments regarding this question has the potential to affect the timing of this response.

To expedite this request, Zenith Goldline Pharmaceuticals would find it acceptable to resolve this issue through telephone communication.

With best regards,

ZENITH GOLDLINE PHARMACEUTICALS, INC.

Jason A. Gross, Pharm.D.
Director, Global Regulatory Affairs

JAG:dj

38. Chemistry Comments to be Provided to the Applicant
ANDA: 75-297 APPLICANT: Zenith Goldline Pharmaceuticals

DRUG PRODUCT: Paclitaxel Injection, 30 mg/5mL, 100 mg/16.7 mL and 150 mg/25mL

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

1. DMF r Inc, is inadequate. Please request them to respond to the recent FDA letter.

2. Please submit a composition statement per mL for the proposed container size of 100 mg/16.7 mL.

3. In your amendment dated March 23, 1999, you have submitted changes in your mixing instructions for the manufacturing process. We recommend that you use predetermined weights of the excipients for the manufacturing of the drug product and not to vary the composition on a batch to batch basis. Please submit revised master manufacturing records for all three vial sizes.

4. We have the following comments regarding the drug substance:

   a. Your test results for residual solvents for material do not justify your proposed specifications. Please set your limits based on your results for the lots used in the exhibit batches.

   b. Please provide a single regulatory specification for the drug substance regardless of source. You may have tighter in-house limits for one source or the other if desired.

5. We have following comments regarding the drug product controls:

   a. Please provide a single release specification for the drug product regardless of source of drug substance. The assay limits proposed for Hauser material should be used. You may have tighter in-house limits for one source or the other if desired.

b. Please be advise that you cannot use Alternate Method (STP for stability as it has not been validated as stability indicating. Please confirm that your alternate method is used for release of the drug product and the validated method previously submitted is being used for stability.

c. Please state your target fill volume for each vial size and include as an in-process control.

6. We have the following comments regarding the stability of the drug product:

a. Please provide a single stability specification for the drug product regardless of source of drug substance. The assay limits proposed for material should be used. You may have tighter in-house limits for one source or the other if desired.

b. Please revise your stability protocol for all fill sizes to include stability monitoring in upright position annually. The first three batches and one batch annually of each fill size should be included in the stability program.

7. A batch record, in-process and release data, and accelerated stability data for all three fill sizes are needed to support the proposed new source of paclitaxel

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Labeling deficiencies will also need to be addressed in your reply.

2. An acceptable compliance evaluation is needed for approval. We have requested an evaluation from the Office of Compliance.

3. Please provide any additional stability data that is available for the exhibit batches.

4. Please be advised that samples for methods validation will be requested at a later date once the testing issues have been resolved. Please include a copy of all current regulatory (not alternate) methods used for release in a separate section of the amendment to facilitate Methods Validation.

5. If you do not intend to use as a source of Paclitaxel drug substance in the future, we recommend that you withdraw it from the ANDA.

6. Your environmental information for al is pending review.

Sincerely yours,

Paul S Shweng for

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

Zenith Goldline
PHARMACEUTICALS

Regulatory Affairs

AUG 13 1999

ORIG AMENDMENT

AA

Center for Drug Evaluation and Research
Food and Drug Administration
ATTN: Mr. Douglas L. Sporn
Director, Office of Generic Drugs
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

GRATUITOUS AMENDMENT – CHEMISTRY, BIOEQUIVALENCE & LABELING

Re: ANDA-75-297 Paclitaxel Injection 6 mg/mL [30 mg/5 mL vial] and [150 mg/25 mL vial]
Addition of New Container Size: Paclitaxel Injection 6 mg/mL [100 mg/16.7 mL vial]

Dear Mr. Sporn:

Reference is made to our pending Abbreviated New Drug Application for Paclitaxel Injection 6 mg/mL [30 mg/5 mL vial] and [150 mg/25 mL vial]. Reference is also made to our March 23, 1999 response to the Office of Generic Drugs' chemistry letter dated August 04, 1998. The 100 mg vial has the same concentration and total drug content as that of the reference listed drug.

Zenith Goldline Pharmaceuticals had intended to include the 100 mg vial size in the bracket between the 30 mg and 150 mg vial as part of our original December 30, 1997 submission. However, upon the quality assurance review, the test result for the 100 mg vial was found to be outside of the upper specification limit for potency. The data was not submitted pending a quality compliance review. Upon subsequent review it was concluded that the batch as manufactured could be used as an exhibit batch, not for human use, and we are now retroactively using this batch to support the 100 mg vial size. This submission, accordingly, should be considered retroactively as part of our original December 30, 1997 submission; and the application deemed amended as of December 30, 1997. Since the reference listed drug is defined by its concentration (i.e., 6 mg/mL) and not by vial size, our original application applied, in effect, to all approved vial sizes.

The manufacturing process of the 100 mg vial size was identical to that for the 30 mg and 150 mg vials except the container sizes, which are already contained within this application, as filed in our March 23, 1999 amendment.

The container closure integrity testing of the 100 mg vial has been bracketed by the testing conducted on the 30 mg and 150 mg vials. The 150 mg vial uses the same closure components as the 100 mg vial. Zenith Goldline Pharmaceuticals has included eighteen months of controlled room temperature and six months of accelerated stability testing for the 100 mg fill for your review.

Revised final draft labeling which references the 100 mg vial in the HOW SUPPLIED section, and a request for a waiver of in vivo bioequivalence has been included in this submission.

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
AUG 16 1999
OGD

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A Subsidiary of IVAX Corporation

Zenith Goldline Pharmaceuticals has made a concerted effort to ensure that this application contains all of the information that the Office of Generic Drugs may require. Should you have any questions or require some additional information please contact our office at your convenience (201) 767-1700 ext. 239/331.

With best regards,

ZENITH GOLDLINE PHARMACEUTICALS, INC.

Jason A. Gross, Pharm.D.
Director, Global Regulatory Affairs

Zenith Goldline
PHARMACEUTICALS

Regulatory Affairs

JUN 25 1999

NDA ORIG AMENDMENT
N/AA

Mr. Douglas Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

GRATUITOUS AMENDMENT
NEW MANUFACTURER OF ACTIVE DRUG SUBSTANCE

RE: ANDA 75-297 - Paclitaxel Injection, 30 mg/5 mL and 150 mg/25 mL

Dear Mr. Sporn:

Reference is made to our Original Abbreviated New Drug Application dated December 30, 1997 and our Major Amendment dated March 23, 1999 for the above referenced pending application. Pursuant to 21 CFR 314.96, we hereby amend our application to provide for an additional source of active drug substance manufactured by

In support of this alternate source of active drug substance an exhibit batch of Paclitaxel Injection, 30 mg/5 mL, Lot # 8016858, was manufactured. In addition, the following documents are provided:

- Field Copy Certification as required under 21 CFR 314.94(d)(5).
- Table of Contents.
- A Drug Master File Authorization Letter from
- Certificate of Analysis, Specifications and Test Results from the Drug Substance Manufacturer.
- Zenith Goldline's Specifications, Test Data and Certificate of Analysis for the Active Drug Substance.
- Comparative Active Drug Substance Specifications and Test Data: Lot 1492-27397-A the proposed source and Lot A-3120-97-0001 - , the previously submitted source.
- Certificates of Analysis for each lot of excipient used in the Exhibit Lot No. 8016858.
- Executed Batch Record for Paclitaxel Injection, 30 mg/5 mL, Lot No. 8016858, the exhibit lot made from raw material.
- Comparative Finished Dosage Specifications and Test Data for Lot No. 8016858, exhibit batch raw material) and Lot No. 7016858, previously submitted batch raw material)
- Zenith Goldline's Specifications, Test Data and Certificates of Analysis for the Finished Dosage Form.
- Stability Protocols and Test Data for Lot No. 8016858.
- Environmental Assessment.

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A Subsidiary of IVAX Corporation

The active drug substance manufactured by c. is derived from the Pacific Yew (*Taxus brevifolia*). Based on the requirements of 21 CFR, Section 25.24(c)(1) for Human Drugs and Biologic Products, we are including an Environmental Assessment package in this amendment. (Please note that Appendices 1-3 of the Environmental Assessment package are Confidential documents.) Our original application filed December 30, 1997 contained an Environmental Assessment Exclusion Request (page 1836 or our original application).

Zenith Goldline and Baker Norton Pharmaceuticals are wholly owned subsidiaries of the IVAX Corporation. Paclitaxel Injection is being manufactured for both Zenith Goldline Pharmaceuticals and Baker Norton Pharmaceuticals by

Zenith Goldline Pharmaceuticals requests that all information in this file be treated as confidential within the meaning of 21 CFR 314.430, and that no information from the file be submitted to an applicant without our written consent to an authorized member of your Office. We are confident that the information provided is complete and approvable. Should any questions arise, please do not hesitate to contact the undersigned at (201) 767-1700, or via fax at (201) 784-1719.

Sincerely,
ZENITH GOLDLINE PHARMACEUTICALS, INC.

Jason Gross, Pharm.D.
Director of Global Regulatory Affairs

cc: District Office

Zenith Goldline
PHARMACEUTICALS
Regulatory Affairs

March 23, 1999

Mr. Douglas L. Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, Maryland 20855

NDA ORIG AMENDMENT
N|AC

MAJOR AMENDMENT

Re: Paclitaxel Injection
30 mg/5 mL vial and 150 mg/25 mL vial
ANDA 75-297

Dear Mr. Sporn:

Reference is made to our pending abbreviated new drug application for Paclitaxel Injection, 30 mg/5mL and 150 mg/25mL (ANDA 75-297). At this time we are responding to the deficiencies noted in the Agency's facsimile correspondence dated August 4, 1998 (copy attached). We understand that our response will be considered a Major Amendment.

The deficiencies are restated below in bold print, followed by our responses.

A. Deficiencies:
1.

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GENERIC DRUGS

Page(s) 14

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

3/23/99

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. **The firms referenced in your ANDA application relative to the manufacturing and testing of the product must be in compliance with cGMP's at the time of approval.**

   We acknowledge that the firms referenced in our ANDA application relative to the manufacturing and testing of the product must be in compliance with cGMP's at the time of approval.

2. **The FDA district office will be performing method validation on the drug substance, the finished drug product, Paclitaxel Injection concentrate and dilute.**

   We acknowledge that the FDA district office will be performing method validation on the drug substance, the finished drug product, Paclitaxel Injection concentrate and dilute.

3. **Our microbiology review has not been completed. After this review is completed, any deficiencies found will be communicated to you under separate cover.**

   We acknowledge that the microbiology review has not been completed, and that any deficiencies found will be communicated to us under separate cover.

LABELING DEFICIENCIES:

1. **Container:** With regard to Point a. , we have differentiated our product strengths with the use of contrasting colors. Concerning Point e., we intend to maintain our proposed storage recommendations at 20 to 25° C., based on our stability data, and in accord with the current TAXOL ® labeling. All other points have been addressed, and 12 copies of final printed labels and cartons are included with this amendment (6 copies in each the archival and review copies). (Appendix 17.)

2. **Carton:** See above – Container.

3. **Insert:** We have revised our package insert in accord with agency recommendations. Appendix 17 includes 4 copies of our revised draft insert (4 copies in the archival copy and 4 copies in the review copy.)

ADDITIONAL INFORMATION: (Appendices 18, 19, and 20)

In addition to the responses provided, we propose to include two new features to the container closure system, and other updates regarding the mixing process and test methods:

1) Multi-dose extraction capability of the stopper
2)) Sheathing for the glass vials
3) Modification of Method of Mixing
4) Updated Analytical Methods

The stopper is the same as that submitted in the original submission. However, data to support the multi-dose capability of the stopper was not previously submitted and is included in this submission. The multi-dose capability allows for multiple extractions of drug product with complete resealability and no coring tendency in the stopper. Multi-dose use is also provided for in the labeling section of the original submission (Volume 1, Section V, pages 040-209).

The (Sheathing system is a protective plastic covering shrink wrapped onto the glass vial as protection against breakage and product containment upon breakage. The plastic covering does not touch the drug product and is considered secondary packaging. These two features present an improvement over existing packaging. Supporting information is provided in Appendix 18 (Multidose) and 19 athing).

Since the original submission, formal process validation studies were performed and completed on 3 lots of drug product. During these studies, improvements were made to the manufacturing process that included a slight change in the method of mixing of the raw material to assure that all active drug substance is used, and the use of larger filters (10" vs 4") to reduce aseptic filtration time. These changes were initiated with lot 7036858 (30 mg/5 mL) and is intended for all commercial production batches of both sizes of drug product. A Process Validation Summary Report has been prepared in this regard and is available for FDA District review. Please refer to Appendix 2 for a summary of these modifications, as well as a copy of the new blank batch record.

Additionally, in Appendix 20, we are providing copies of certain analytical methods which have been revised to generalize their applicability without regard to drug product size.

We acknowledge that the Division of Bioequivalence has completed its review and has no questions at this time. We note that these results are preliminary and subject to revision.

We trust this major amendment responds to the deficiencies identified, as well as adequately addresses the additional issues noted, i.e. multi-dosing, sheathing, method of mixing modifications, and updated analytical methods. If you have any questions or require further information, please do not hesitate to contact the undersigned at (201) 767-1700 x 239, or via fax at (201) 784-1719.

Sincerely,
ZENITH GOLDLINE PHARMACEUTICALS, INC.

Jason Gross, Pharm.D.
Director, State, Federal
and International Regulatory Affairs

Zenith Goldline
PHARMACEUTICALS

NOTED
8/7/98

Regulatory Affairs

June 29, 1998

Fax to: (301) 594-0180

Mr. Joe Buccine
Project Manager, Division of Chemistry I
CDER, FDA
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

NEW CORRESP

Subject: Telephone Amendment
ANDA 75-297 Paclitaxel Injection

Dear Mr. Buccine:

Reference is made to our telephone conversation today regarding our referenced Abbreviated New Drug Application which is pending FDA approval. Reference is also made to our telephone conversations of June 26 and June 29, 1998. Specifically you inquired about Lot #'s 701-6858 and 701-6859 and if they were used as an exhibit batch for NDA 20-826.

Lot #'s 701-6858 and 701-6859 were not submitted as an exhibit batch to NDA 20-826, as they were not used to support efficacy, toxicology, or safety, rather they were submitted by Baker Norton for ancillary stability and was not required as a condition of approval. Based on your request, Zenith Goldline reviewed NDA 20-826 and has assembled a list of all lot numbers (n=28) that were mentioned in NDA 20-826 and for what reason they were submitted.

Should you have any questions, please contact my office at your convenience.

With best regards,
ZENITH GOLDLINE PHARMACEUTICALS, INC.

Jason A. Gross, Pharm.D.
Director, State, Federal and
International Regulatory Affairs

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Attachment

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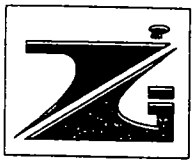

Zenith Goldline
PHARMACEUTICALS

NC

March 30, 1998

Mr. Douglas Sporn
Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Telephone Amendment

noted NCAI Sarkute 4/6/98

RE: **Paclitaxel Injection 30 mg/5mL and 150 mg/25mL**
ANDA #: 75-297

Dear Mr.Sporn:

Reference is made to our telephone conversation of March 30, 1998, with Ms. Nancy Sager in which we were requested to provide the Agency with a modified "Environmental Assessment Exclusion Request" for our above application.

We are enclosing the amended "Environmental Assessment Exclusion Request", citing the updated regulations as per 21 CRF 25.31(a). A copy of the facsimile message sent to Ms. Sager is also attached to this correspondence.

Should you have any additional questions or require further information, please feel free to contact me.

Sincerely,

ZENITH GOLDLINE PHARMACEUTICALS, INC.

Jason A. Gross, Pharm. D.
Director, Regulatory Affairs

Attachments

JAG/pj

cc: Mr. Douglas Tolen
Food and Drug Administration
Orlando District Office
555 Winderly PL Suite 200
Maitland, Fl 32751
Telephone: 407-648-6823

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Madeline 4-6-98

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Zenith Goldline
PHARMACEUTICALS

February 4, 1998

VIA FAX

Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Attention: Gregory Davis, Project Manager

Re: ANDA 75-297, Paclitaxol Injection

Dear Mr. Davis:

Reference is made to the telephone conversation with you, Karen Rocco and myself on February 3, 1998, requesting additional information to support the filing of our application. Attached is a summary of our discussion.

We would like to thank you for taking the time to discuss the status of our application. We are currently reviewing your request and expect to provide correspondence responding to your concerns shortly.

Should you have any questions or require any additional information, please feel free to contact Karen Rocco at your convenience.

Sincerely,

ZENITH GOLDLINE PHARMACEUTICALS, INC.

Jason A. Gross, Pharm.D.
Director, Regulatory Affairs

JAG:go
Attachment
24jag4.doc

cc: K. Rocco

140 Legrand Avenue, Northvale, New Jersey 07647 • (201) 767-1700 (800) 631-1583
Miami • Ft. Lauderdale • Cidra, P.R. • St. Croix, U.S. V.I. • Shreveport • Mason • Syosset

Zenith Goldline
PHARMACEUTICALS

NEW CORRESP

February 6, 1998

Gregory Davis, Project Manager
Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Correspondence to the Application

RE: Paclitaxel Injection 30 mg/5mL and 150 mg/25mL
ANDA #: 75-297

Dear Mr. Davis:

Reference is made to our telephone conversation of February 3, 1998, in which Karen Rocco also participated. You indicated that our application was being reviewed for acceptability of filing; and that additional information was required before the review could be completed. We have assembled the information you requested and are submitting it with this correspondence for your review.

Should you have any additional questions or require further information, please feel free to contact Karen Rocco at your convenience.

Sincerely,

ZENITH GOLDLINE PHARMACEUTICALS, INC.

Jason A. Gross, Pharm. D.
Director, Regulatory Affairs

Attachments

JAG/pj

cc: Mr. Douglas Tolen
Food and Drug Administration
Orlando District Office
7200 Lake Ellenor Drive, Suite 120
Orlando, Florida

RECEIVED
FEB 10 1998
GENERIC DRUGS

140 Legrand Avenue, Northvale, New Jersey 07647 • (201) 767-1700 (800) 631-1583

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ANDA 75-297

Zenith Goldline Pharmaceuticals, Inc.
Attention: Jason A. Gross, Pharm. D.
140 Legrand Avenue
Northvale, NJ 07647

FEB 11 1998

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to the telephone conversation dated February 3, 1998 and your correspondence dated February 9, 1998.

NAME OF DRUG: Paclitaxel Injection, 30 mg/5 mL vial and 150 mg/25 mL vial

DATE OF APPLICATION: December 30, 1997

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 31, 1997

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(I)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

1) Each owner of the patent or the representative designated by the owner to receive the notice;

2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet "PATENT AMENDMENT" with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

- You must submit a copy of a final order or judgement from which no appeal may be taken (which might not be the one from the District Court), or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Peter Rickman, Chief, Regulatory Support Branch, at (301)827-5862.

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Sheila O'Keefe
Project Manager
(301) 827-5848

Sincerely yours,

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

c

e

Zenith Goldline
PHARMACEUTICALS

J. Gross was asked to clarify the data that was assembled from NDA 20-826. I explained to "franchising policy" J. Gross will call back. J Bm 6/26/98

December 30, 1997

Mr. Douglas Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, Maryland 20855

RECEIVED
DEC 31 1997
GENERIC DRUGS

SUBJECT: **Original Abbreviated New Drug Application**
Paclitaxel Injection
30 mg/5 mL vial and 150 mg/25 mL vial

Dear Mr. Sporn:

Pursuant to Section 505(j) of the Food, Drug, and Cosmetic Act and in compliance with 21 CFR 314.94, Zenith Goldline Pharmaceuticals, Inc. herewith submits an Abbreviated New Drug Application (ANDA) for **Paclitaxel Injection, 30 mg/5 mL vial and 150 mg/25 mL vial.**

Zenith Goldline and Baker Norton Pharmaceuticals are wholly owned subsidiaries of the IVAX Corporation. Paclitaxel Injection is being manufactured for both Zenith Goldline Pharmaceuticals and Baker Norton Pharmaceuticals, Inc., by Limited. On December 24, 1997, Baker Norton Pharmaceuticals, Inc. received a tentative approval letter for Paxene® (paclitaxel) Injection, NDA 20-826. Marketing of Paxene (Paclitaxel) is delayed until August 4, 2004 pending the expiry of the orphan dug exclusivity of Taxol.

The data required to be included in this Abbreviated New Drug Application has been assembled from the Chemistry, Manufacturing and Controls section of the Baker Norton NDA 20-826. It is worth noting that the data contained in this ANDA have been reviewed and accepted by the Division of Oncology Drug Products, Office of Drug Evaluation I. In addition, the compliance status of the suppliers of the active drug substance, , and the drug products, were found to be satisfactory prior to the issuance of the December 24, 1997 tentative approval letter (copy of the letter follows this cover letter for your reference). Based on this fact, we are requesting the Agency's consideration for an expedited review of this application.

140 Legrand Avenue, Northvale, New Jersey 07647 ▪ (201) 767-1700 (800) 631-1583

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In support of this Application, the information outlined below is provided:

- Index.
- Application Form (FDA 356h).
- Debarment, Conviction and Field Copy Certifications.
- Basis for Submission.
- Patent Certification and Exclusivity Statement.
- Comparison between the proposed drug and the reference listed drugs, Taxol® (paclitaxel) Injection, 30 mg/5 mL manufactured by Bristol-Myers Squibb, and Paclitaxel for Injection, 150 mg/25 mL (permitted under an approved ANDA Suitability Petition - Docket No. 97P-0058/CP1 - submitted by Fujisawa USA, Inc.).
- Draft Labeling (four copies each in the archival [blue], review [red] binders and review [orange] binder).
- Bioequivalence Waiver Request (the drug product is a parenteral solution intended solely for administration by injection, and contains the same active and inactive ingredients (except as permissible under 21 CFR 314.94(a)(9)(iii)) in the same concentration as the reference listed drug).

- Chemistry, Manufacturing and Controls Information.
- Sterility Assurance Data.
- Methods Validation Package (one copy in the archival [blue] binder, one copy in the review [red] binder and three additional copies, each separately bound and identified).
- Toxicity Study Summaries (Section XXI): The active drug substance contained in the proposed drug product is derived from a natural botanical source, depending on the species or the method of isolation and purification. Since questions may arise as to the complexity of the 'impurities' and the possible toxicity of these components, Zenith Goldline has incorporated certain relevant data from the safety studies contained in the New Drug Application for

paclitaxel, NDA #20-826, sponsored by Baker Norton Pharmaceuticals, Inc. The toxicity study summaries of this application support the safe use of ZGP's generic paclitaxel injection as indicated.

The archival copy of this application consists of 6 volumes, the review copy consists of one volume containing the bioequivalence section (orange binder) and 6 volumes containing CMC data (red binders).

Zenith Goldline Pharmaceuticals requests that all information in this file be treated as confidential within the meaning of 21 CFR 314.430 and that no information from the file be submitted to an applicant without our written consent to an authorized member of your Office. We are confident that the information provided is complete and approvable. Should any questions arise, please do not hesitate to call the undersigned at (201) 767-1700.

Signed on behalf of Zenith Goldline Pharmaceuticals, Inc.

Jason A. Gross, Pharm.D.
Director, Regulatory Affairs

Enc.