

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

76268

CORRESPONDENCE

Should you have questions concerning this application, contact:

Stanley Shepperson
Project Manager
(301) 827-5849

Sincerely yours,

h
ST *ST* *ST*

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 76-268
cc: DUP/Jacket
Division File
Field Copy
HFD-610/R.West
HFD-610/P.Rickman
HFD-92
HFD-615/M.Bennett
HFD-600/
Endorsement:

HFD-615/GDavis, Chief, RSB
HFD-615/ETHomas, CSO

1
ST *ST*
ST 07-JAN-2002 date
1/7/02 date

ANDA Acknowledgment Letter!



*Labeling Review
Drafted 5-22-02
A. Vezina*

Jerome Stevens Pharmaceuticals, Inc.

May 6, 2002

ORIG AMENDMENT

N/AM

Office of Generic Drugs, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 76-268; Digoxin 0.125 & 0.250mg Tablet USP

'MINOR AMENDMENT'

Dear Sir/Madam:

This is in response to your letter dated March 27, 2002, to the referenced ANDA.

A) Chemistry Deficiencies:

1. We propose to keep the formulation with a % excess.
 - a. the manufacturer of the API typically produces batches with a potency between % . Please see exhibit (A).
 - b. The USP monograph for Digoxin has a lower assay limit of 95.0%. We could see future batches with a lower potency than what has been typically seen.
 - c. There can be a loss of API during the manufacturing process.
 - d. The exhibit batches had a final tablet potency of using the % excess.
 - e. Our in-process testing will assure no super-potent batches are produced.
2. Our commercial production batch size will be tablets for the 0.125mg strength and tablets for the 0.250mg strength.
3. We have added Identification tests (B) & (C) to our COA. Please refer to exhibit (B).
- 4a. has provided their test method for OVI/ residual solvents. The limits are as follows:

NMT %;	NMT %;
NMT % . Please refer to exhibit (C).	
- 4b. Please refer to exhibit (C) for the test method and limits. We have updated our COA to include limits for
The limit for % as per USP 2731.

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MAY 07 2002

OGD / CDER

5/7/02



Jerome Stevens Pharmaceuticals, Inc.

From the data collected it is clear that the only related substance that might be increasing is the one with a relative retention time of . The other major related substance has a relative retention of . These are . We

propose to monitor these two in our release and stability testing. The API manufacturer has a limit of % for and % for in the drug substance. Based on the data collected and the limits for the API, we propose a limit of % for

Please refer to exhibit (J) for our test method to monitor known related substances, the revised release specifications and stability specifications.

10. We lowered the limit for an individual unknown degradant at release and stability to %.
Please refer to exhibit (J) for this information.
- 11a. The data submitted comparing the exhibit batches to the RLD show that our product has a comparable related substance/impurity profile to the RLD. Our drug product shows lower total related substances under both accelerated and long term storage to the RLD under ambient storage conditions. Based on the data submitted, we believe that a limit of % for total known and unknown degradants is appropriate for this drug product at the time of release. We have lowered this limit in our stability specification to % from %. Please refer to exhibit (J) for this information.
- 11b. We tested the 90 days accelerated stability samples and found that their might be one related substance impurity that could be considered a degradant. We have incorporated it into our testing as discussed above. Our drug products' related substances and impurity profile is comparable to the RLD ;
Please refer to exhibit (J) for this information.
- B1. The primary function of the excipients are:
 - Lactose: diluent
 - Microcrystalline cellulose: binder
 - Croscarmellose sodium: disintegrant
 - Stearic acid: lubricant
 - Magnesium stearate: lubricant
 - Colloidal silicon dioxide: glidant
 - D&C Yellow aluminum lake #10: color
- B2. Our facilities involved in the production, packaging, labeling, testing, and/or release of this product do comply with cGMP requirements.



Jerome Stevens Pharmaceuticals, Inc.

B3. We have provided updated room temperature stability data. Please refer to exhibit (K) for this information.

Labeling Deficiencies:

We have made the requested revisions to the container labels and inserts. We have enclosed 12 copies each of the container labels and insert. Please refer to exhibit (M).

We have the following comments:

- 1c. We will market the 100's container sizes with a child-resistant closure. Please see exhibit (L) for the revised packaging specification form. The cap is manufactured by _____ We have included the engineers' drawing and a representative manufacturer's COA for the closure.
- 1d. The "USP, Inc." that you refer to is our company logo, "JSP, Inc." It remains on the labels as "JSP".
- 2f. The exhibit batches were manufactured with imprints "DP 914" (0.125mg) and "DP 915" (0.250mg). The "JSP 545" and "JSP 544" tablet imprint are on the insert too match the Jerome Stevens Pharmaceuticals Inc. (JSP) container labeling, which was submitted. We might manufacture this product with a different tablet identification and container labels, depending on our customer requests. All appropriate labeling changes will be made and submitted by a supplement to the ANDA.

The Field Copy of the CMC section is being sent under separate cover to the New York District Office:

New York District Office
New York (NYK-DO)
158-15 Liberty Ave.
Jamaica, NY 11433

Please contact the undersigned if there are any questions regarding this application.

Yours sincerely,

Ronald Steinlauf
Vice President
Jerome Stevens Pharmaceuticals Inc.



Jerome Stevens Pharmaceuticals, Inc.

December 17, 2001

NEW CORRESP
NC.

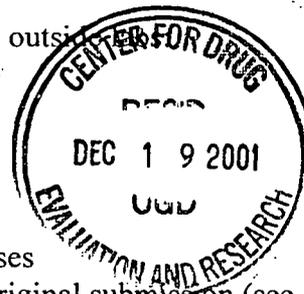
Office of Generic Drugs
~~CDER, FDA~~
Metro Park North II
7500 Standish Place, Room 150
Rockville, Md. 20855
Attn: Ms. Emily Thomas, CSO

Re: ANDA: - 76-268
Drug Name: Digoxin Tablets, USP
Company: Jerome Stevens Pharmaceuticals, Inc.

Dear Ms. Thomas:

Enclosed please find our response to your request as per our telephone conversation on December 10, 2001:

- | | |
|--|---|
| Item #1 – Original Signatures: | Field Copy Certification
Disbarment Certification
List of Convictions
Patent Certification |
| Item #2 – Labeling: | Side by side bottle label of Digoxin / Lanoxin with differences annotated and explained. |
| Item #3 – CGMP or CGLP Certification for the following four (4) outside: | |
| Item #4 – Container Closure: | Supplier Names and Addresses
DMF Letters sent with the original submission (see Vol. 11 pg. 4829 – 4837) |





Jerome Stevens Pharmaceuticals, Inc.

Item #5 – Batch Records:

Executed Batch Record sent with original submission (see Vol. 11 pg. 4507 – 4542).
Blank Batch for proposed Commercial Batch (enclosed).

Item #6 – Packaging Records:

Finish packaging records enclosed for two executed batches.
Blank packaging records sent with original submission (see Vol. 11 pg. 4574 – 4582).

As always, if you have any questions with regard to the information provided, please do not hesitate to contact me.

Sincerely,

Ronald J. Steinlauf
Vice President



*Labeling review
drafted 1/31/02
A. Vezina*

*505(b)(2)(A) OK
07-JAN-2001
Muganyizi S. Dand*

October 29, 2001

Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

Re: ANDA - Drug Name: Digoxin Tablets, USP
Company: Jerome Stevens Pharmaceuticals Inc.

Dear:

Jerome Stevens Pharmaceuticals Inc. is hereby submitting an original Abbreviated New Drug Application (ANDA) for Digoxin Tablets, USP.

This ANDA is compiled in accordance with 21 Code of Federal Regulations Part 314.0, and contains 11 volumes (archival copy) of documentation to support the proposed bioequivalence of the drug with the reference product, Lanoxin® Tablets.

The proposed drug is indicated for the treatment of heart failure and atrial fibrillation.

Please note that this application includes a CMC and bioequivalence ESD electronic submission. The corresponding CD is enclosed.

The Field Copy of the Chemistry and Manufacturing and Controls section is being sent under separate cover to the New York District Office:

New York District Office
New York (NYK-DO),
158-15 Liberty Ave.,
Jamaica, NY 11433



The correspondent for the ANDA is:

Ronald Steinlauf
Jerome Stevens Pharmaceuticals
60 DaVinci Drive
Bohemia NY
USA 11716

Yours sincerely,
Jerome Stevens Pharmaceuticals Inc.

Ronald Steinlauf

Ronald Steinlauf
Vice President



Jerome Stevens Pharmaceuticals, Inc.

meB

March 11, 2002

Krista M. Scardina
Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, Md. 20855

ORIG AMENDMENT

N/AB

Re: ANDA – Digoxin Tablets, USP
ANDA No. 76-268
Company: Jerome Stevens Pharmaceuticals, Inc.
BIOEQUIVALENCY AMENDMENT

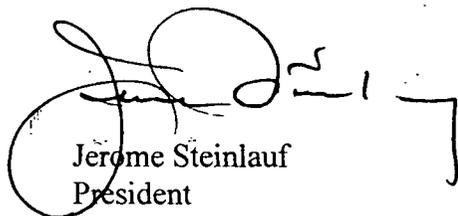
Dear Doctor Scardina:

Jerome Stevens Pharmaceuticals, Inc. is hereby submitting a bioequivalency amendment to an original Abbreviated New Drug Application (ANDA) for Digoxin Tablets, USP (ANDA Number 76-268). This is in response to your correspondence of February 21, 2002. A copy of this correspondence and a completed Form 356h is provided.

The amendment is composed of an updated analytical validation report for the determination of Digoxin in human serum. Data demonstrating the stability of Digoxin in serum stored frozen _____ days has been added in order to justify the storage time from the first day of collection to the last day of analysis.

Please note that this application includes a bioequivalence ESD electronic submission amendment. The corresponding CD is enclosed.

Yours Sincerely,
Jerome Stevens Pharmaceuticals, Inc.


Jerome Steinlauf
President

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MAR 13 2002

OGD / CDER



Jerome Stevens Pharmaceuticals, Inc.

January 7, 2002

NEW SERIES

Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, Md. 20855
Attn: Ms. Emily Thomas, CSO

NC

Re: ANDA: 76-268
Drug Name: Digoxin Tablets, USP
Company: Jerome Stevens Pharmaceuticals, Inc.

Dear Ms. Thomas:

Enclosed please find FDA Form 356h as per your request. If you have any further questions regarding this matter, please do not hesitate to contact me.

Sincerely,

Ronald J. Stein
Vice President





Jerome Stevens Pharmaceuticals, Inc.

2.1

July 22, 2002

ORIG AMENDMENT

N/AM

Office of Generic Drugs, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 76-268; Digoxin 0.125 & 0.250mg Tablet USP

~~MINOR AMENDMENT~~

Dear Sir/Madam:

This is in response to comments made Dr. Nashed Samann during the PAI of our facility from 7/15 - 7/18/02.

A) Chemistry Deficiencies:

1. We have eliminated the % overage of digoxin in the manufacture of the drug product. Please see the revised proposed production batch master formula. To assure that the product is manufactured to a potency of 100%, we will adjust

Please refer to the revised batch production records.

2. We have increased the limit for individual unknown degradant at release and stability to %. Please refer to the attached forms.
3. We have added a specification for Total known & unknown degradant including . The limit proposed is NMT %. Please refer to the attached forms.
4. We have revised the Accelerated and Long Term Stability Data tables. Please refer to the attached forms. We have also included the revised "Digoxin Tablets Related Substances & Impurities" table.
5. We have revised our SOP: Storage and Retesting of Raw Materials to include a provision to retest inactive ingredients 18 months after the release date. Please refer to the enclosed SOP.

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JUL 23 2002

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Handwritten signature/initials



Jerome Stevens Pharmaceuticals, Inc.

Please contact the undersigned if there are any questions regarding this application.

Yours sincerely,

A handwritten signature in black ink, appearing to read 'Ronald Steinlauf'. The signature is written in a cursive, flowing style.

Ronald Steinlauf
Vice President

Jerome Stevens Pharmaceuticals Inc.



Jerome Stevens Pharmaceuticals, Inc.

July 1, 2002

Office of Generic Drugs, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT

N/AM

RE: ANDA 76-268; Digoxin 0.125 & 0.250mg Tablet USP

'MINOR AMENDMENT'

Dear Sir/Madam:

This is in response to your letter dated June 24, 2002, to the referenced ANDA.

A) Chemistry Deficiencies:

1a,b. We have eliminated the 2% overage of digoxin in the manufacture of the drug product. Please see the revised proposed production batch master formula. To assure that the product is manufactured to a potency of 100%, we will

to 100% potency based on assay that is conducted on each batch. Please refer to the revised blend COAs.

2. We have reduced the limit for individual unknown degradant at release and stability to %. Please refer to the attached forms.

3. We have eliminated the limit for individual known degradant. Please refer to the revised forms.

Please contact the undersigned if there are any questions regarding this application.

Yours sincerely,

Ronald Steinlauf
Vice President
Jerome Stevens Pharmaceuticals Inc.

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JUL 02 2002

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Jerome Stevens Pharmaceuticals, Inc.

January 28, 2002

~~NEW CORRESP~~
BIOAVAILABILITY

NC

Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, Md. 20855
Attn: Ms. Christa Scardina

Re: ANDA: 76-268
Drug Name: Digoxin Tablets, USP
Company: Jerome Stevens Pharmaceuticals, Inc.

Dear Ms. Scardina:

Enclosed please find stability data for Digoxin Serum at _____ as per your request. If you have any questions regarding this information, please do not hesitate to contact me.

Sincerely,

Ronald J. Steinlauf
Vice President

