CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76268

CHEMISTRY REVIEW(S)

OFFICE OF GENERIC DRUGS
ANDA APPROVAL SUMMARY

ANDA# 76-268

DRUG PRODUCT: Digoxin Tablets USP

FIRM: Jerome Stevens Pharmaceuticals

DOSAGE FORM: Tablets

STRENGTH: 0.125 mg & 0.25 mg

cGMP STATEMENT/EIR UPDATE STATUS: cGMP certificate is satisfactory page 4482

EIR update: Recommend approval on 7-24-02 by Dr. Robert Horan.

BIO STUDY: Satisfactory
Bio was reviewed by J. Chaney and found acceptable on 04-30-02.

VALIDATION: DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S)

Both the API and drug product have USP monographs.

STABILITY- Are containers used in study identical to those in container section?: Yes

A. Data: The firm included accelerated and room temperature stability data (3, 6, 9 and 12 months) in the smallest and largest marketed packages (100s & 1000s count HDPE). The data was found to be acceptable.
B. Protocol: Stability determined in smallest and largest HDPE Containers; pilot lot placed on accelerated stability (40°C±2°C/75%% ± 5% RH 3 months); long term studies (25°C± 2°C; 60%±5%RH 0,3,6,9,12,18, and 24 months).
C. Expiration Date: 24 months based on accelerated stability data.
D. Container: Containers used in the stability testing are the same as described in the container section.

The firm proposed the following configuration for the packaging of Digoxine Tablets 0.125 mg and 0.250 mg.

1. HDPE bottles 60 cc white with 33 mm White plastic screw cap; Desiccant, 1 g; and Cotton, 12 g for 100s count of both strengths .
2. HDPE bottles 100 cc and 200 cc white with 38 mm White plastic screw cap; Desiccant, 1 g; and Cotton, 12 g for

1000s count of Digoxine Tablets 0.125 mg and 0.250 mg respectively.

LABELING: Acceptable by A.Vezza on 5-23-02.

STERILIZATION VALIDATION: N/A

SIZE OF BIOBATCH:

Jerome Stevens has been manufacturing and marketing this product under the batch certification program (CFR 310.500) using The firm produced the following batches as exhibit batches using in support of this ANDA.

i. Batch No. 004001 produced Digoxin 0.125 mg tablets. The average unit weight was mg.
ii. Batch No. 003501 produced Digoxin 0.250 mg tablets. The average unit weight was mg.

The size of this Bio-batch complies with the 10% of the proposed full production size.

FIRM'S SOURCE OF NDS OK?: Yes

DMF #

DMF Review:
Update of DMF was reviewed by N.Samaan on 03-01-02 and found to be adequate.

SIZE OF STABILITY BATCH: Same as Bio batch.

PROPOSED PRODUCTION BATCH:

Proposed production batch is tablets for the 0.125 mg strength and tablets for the 0.250 mg strength of Digoxin Tablets USP.

MANUFACTURING PROCESS: Same as Bio/ Stability.

Chemist: N. Samaan Ph.D. /S/ 7.24.02 Date: 7-24-02

Team Leader: U. Venkataram Ph.D. Date: 7/24/02

/S/

OFFICE OF GENERIC DRUGS
ABBREVIATED NEW DRUG APPLICATION REVIEW
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. **CHEMIST'S REVIEW NO.** 1

2. **ANDA#** 76-268

3. **NAME AND ADDRESS OF APPLICANT**

Jerome Stevens Pharmaceuticals
Attention: Ronald Steinlauf
60 DaVinci Drive
Bohemia, NY 11716

4. **LEGAL BASIS FOR ANDA SUBMISSION**

The application is based on the reference listed drug Lanoxin® Tablets manufactured by Glaxo Wellcome (NDA 20-405). Jerome Stevens had been marketing this product under the batch certification program (CFR 310.500).

5. **SUPPLEMENT(s)**: N/A

6. **PROPRIETARY NAME:** N/A

7. **NONPROPRIETARY NAME:** Digoxin Tablets USP

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

9. **AMENDMENTS AND OTHER DATES**

Firm:

10-29-01	Original Submission
12-17-01	Firm response to telephone conversation
03-11-02	Bioequivalence amendment

FDA:

11-07-01	Acceptance to File
12-10-01	Telephone conversation
01-07-02	Acknowledgement letter.
02-21-02	Bioequivalence deficiency letter

10. **PHARMACOLOGICAL CATEGORY:** Cardiotonic glycoside

11. **HOW DISPENSED**: **Rx**

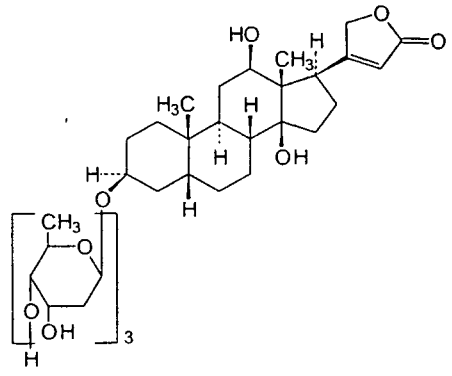
12. **RELATED IND/NDA/DMFs:**

NDA 20-405 Glaxo Wellcome (RLD-Lanoxin®), also See item # 37

13. **DOSAGE FORM/ROUTE OF ADMINISTRATION**: Tablets/Oral

14. **STRENGTH(s)**: 0.125 mg & 0.25 mg

15. **CHEMICAL NAME AND STRUCTURE**



3ß-[(*O*-2,6-Dideoxy-ß-*D*-*ribo*-hexopyranosyl-(1→4)-*O*-2,6-dideoxy-ß-*D*-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-ß-*D*-*ribo*-hexopyranosyl)oxy]-12ß,14-dihydroxy-5ß-card-20(22)-enolide.

CAS [20830-75-5]

$C_{41}H_{64}O_{14}$ 780.96

16. **RECORDS AND REPORTS**: N/A

17. **COMMENTS**

A draft federal register notice declared digoxin tablets to be a new drug and on 9/30/97 FDA approved Glaxo Wellcome's NDA for Lanoxin Tablets. Prior to this, digoxin tablets were considered a "grandfather drug" by the Agency and had been legally marketed without an approved application since 1936. Although Jerome Stevens and other firms are presently marketing the product under the batch certification program. When the federal register notice is finalized, all firms will have to have an approved application in order to market this product.

a. Chemistry review: Deficient (MINOR)

b. Bio-review: Deficient by J. Chaney on 1-31-02
c. Micro-review: N/A
d. Labeling review: Deficient by A.Vezza on 2-01-02.
e. Method validation: Both the API and drug product have USP monographs.
f. EERs: Inspection scheduled on 1-8-02. No action until 3-19-02

18. **CONCLUSIONS/RECOMMENDATIONS**

Not Approvable **(MINOR)**

19. **REVIEWER**	**DATE COMPLETED**
Nashed I. Samaan, Ph.D.	03-11 & 3-19-02

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Chem Review #1

Applicant's Responses to Review #1

ANDA: 76-268

APPLICANT: Jerome Stevens Pharmaceuticals

DRUG PRODUCT: Digoxin Tablets USP 0.125 mg and 0.250 mg.

The following deficiencies were sent to the applicant per review #1 and represent MINOR deficiencies. Each response made by the applicant follows the reviewer's comment.

A. Chemistry Deficiencies

FDA comment # 1:

The exhibit batches of Digoxin Tablets USP, 0.125 mg and 0.250 mg used in support of this ANDA and the proposed commercial batches are formulated with a % overage of Digoxin. Please eliminate this overage or justify.

Firm Response on 5-6-02: Not satisfactory

The firm proposed to keep the formulation with a % Overage due to the following facts:

a. The API potency is between %.
b. The USP monograph established 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 firm's in-process testing will assure no super-potent batches are produced.

Comment on rev. # 2:

Your response to our comment # 1 is not satisfactory. In this regard:

a. You have cited the variable potency of digoxin lots as the rationale for using a % overage in the manufacture of this drug product. The lot to lot

variation in assay potency of the active is not a good reason for including the overage in the manufacturing formula. An equation that calculates actual amounts to be used in the manufacture of the drug product (DP), based on the active "as is potency", will provide the assurance that the product is always formulated to 100% potency as required in the regulations. Please revise your formula cards (p. 4486 and p. 4496) and resubmit.

b. You cited the possibility of a loss of API during the manufacturing process as another reason for including an overage for the drug substance digoxin. Please provide data, identifying the production/process step(s), to support your claim that loss of API occurs during the manufacturing process.

FDA comment # 2 on rev 1:

In your original submission (p. 4485 and p. 4496), you provided Blank Manufacturing records batch sizes of tablets for Digoxin Tablets USP, 0.125 mg and 0.250 mg strength, respectively. However, in your submission dated 12-17-01, you provided Blank Manufacturing records batch sizes of tablets for Digoxin Tablets USP, 0.125 mg and 0.250 mg strength, respectively. Please clarify your commercial production batch size.

Firm Response on 5-6-02: *Satisfactory*

The firm's commercial batches will be tablets for the 0.125 mg strength and tablets for the 0.250 mg strength of Digoxin Tablets USP.

FDA comment # 3 on rev 1:

The USP monograph includes Identification tests B and C by for the drug substance. Please add these identification tests to your specifications for Digoxin drug substance.

Firm Response on 5-6-02: *Satisfactory*

The firm added identification tests (B) & (C) to its

specifications (exhibit B).

FDA comment # 4 on rev 1:

The manufacturer of the drug substance, has provided results for residual solvents by in their certificate of analysis (COA) (p. 4429 on first submission). In this regard:

a. The COA does not include limits for the test. Please request revised COA from that includes limits for each test and submit.

Firm Response on 5-6-02: *Satisfactory*

i. The firm submitted a statement from the manufacturer of API, in which the firm confirmed that they are using one of the solvents mentioned as "OVI" in the USP 25. is tested by and limited to NMT %. Beside this the firm does not use any other of the four remaining solvents mentioned in USP <467>.

ii. Jerome Stevens, proposed the following limits for OVI/ residual solvents in API:

Solvent	Proposed limits	USP 25 limits
	NMT ppm	NMT 2000 ppm
	NMT ppm	NMT 2000 ppm
	NMT ppm	NMT 3000 ppm ICH
	NMT ppm	N/A

iii. The firm provided a copy of method for the detection and quantitation of the solvents in the API product exhibit (C). The RSD % is NMT % and the limits of quantitation is

ppm
ppm
ppm

b. Please include a test method and limits for the Organic Volatile Impurities and residual solvents to your drug substance specifications. In this regard we note that

the manufacturer's certificate of analysis for the drug substance, Digoxin (p. 4428), reported test results of % (1000 ppm) for . Please note that the ICH limit for is NMT ppm. Please comment.

Firm Response on 5-6-02: ***Satisfactory***

The firm updated its API specifications to include limits for OVI and residual solvents. The firm adopted test method and specifications as shown in a above. In addition, the USP25/NF20 monograph of digoxin established limit of NMT 2000 ppm (0.2%) for both

FDA comment # 5 on rev 1:

In addition, has identified the related substance impurities in its certificate of analysis (p.4429). Please identify and establish a limit for each known related substance impurity in the drug substance.

Firm Response on 5-6-02: ***Satisfactory***

the API manufacturer, has provided its impurity limits and test method for identity and purity of digoxin (exhibit D). Jerom Stevens has updated its drug substance specifications to incorporate these related substances and their limits as follow:

Test	Impurity	Limit
Related substance		NMT %
		NMT %
		NMT %
		NMT %
		NMT %
		NMT %
		NMT %
		NMT %

FDA comment # 6:

You have proposed a re-test schedule of 18 months (p.4442 & 4478 on the original submission). Please justify with data.

Firm Response on 5-6-02: ***Satisfactory***

The API manufacturer has submitted to Jerom Stevens firm stability data which demonstrates that the API maintain its' specifications up to 60 months. The firm believes that these data justifies their proposed re-test schedule of 18 months. Copies of these data are provided in exhibit (E).

FDA comment # 7 on rev 1:

Please clarify the notations C and M in your packaging records. Additionally, please submit packaging and labeling reconciliation data. Submit your acceptance criteria.

Firm Response on 5-6-02: *Satisfactory*

In the firm's Packaging records "C" represents a package size of 100 tablets and "M" represents a package size of 1000 tablets. The exhibit batches were bottled but not labeled. The firm submitted copies for its labeling reconciliation. The acceptance criterion is 97.0 % to 103.0% (exhibit F).

FDA comment # 8 on rev 1:

The USP monograph for digoxin tablets includes two identification tests, ID(A) which is based on retention times and ID(B) which relies on Rf values. Please add the second ID test to your finished product specifications.

Firm Response on 5-6-02: *Satisfactory*

The firm updated its finished product specifications to include identification test B as per USP (exhibit G).

FDA comment # 9 on rev 1:

Please identify the known related substance impurities in your drug product at release and stability study. Establish test method and a limit for each and incorporate it in your release and stability specifications.

Firm Response on 5-6-02: *Satisfactory*

a. The firm identified six related substance impurities in the drug product digoxin tablets. These six impurities are find in the digoxin raw material, digoxin tablets

(exhibit batches) as well as in the RLD product, Lanoxin Tablets and in competitor's Digitek Tablets manufactured by Amide Pharmaceuticals (exhibit H).

b. The API, 90 day accelerated stability samples and controlled room temperature storage samples show similar quantities of each related substance.
c. The exhibit batches show a similar profile to the RLD.
d. The Guidance for industry states that "Impurities present in the drug substance need not be monitored in the drug product unless they are also degradation products" (exhibit I). Hence, from the data collected, the only related substance that might be increasing is the one with relative . The other major related substance has a relative These two impurities are respectively. The firm proposed to monitor these two impurities at release and stability testing. The firm's proposed limits are:

Impurity	Limit in DS	Proposed limit in DP
	%	%
	%	%

FDA comment # 10:

The limit for any unknown impurity in your drug product at release and stability specifications is high. At the proposed levels they may need to be identified. Please tighten the limits.

Firm Response on 5-6-02: *Not Satisfactory*

The firm lowered the limit for an individual unknown degradant at stability to % (exhibit J)

FDA comment on rev. # 2

Your response to our comments # 10 is not satisfactory. Your proposed limit for an individual unknown degradant at stability of NMT % is not acceptable. The current office practice is to require identification of impurities/ degradants obaserved at %. In this regard, please also note the General Notices of the USP 25/NF 20 under title "Foreign Substances and Impurities". Please revise and resubmit.

FDA comment # 11:

Your proposed limits for total related substance impurities at release and stability are high. In this regard:

a. Your long-term stability data of the exhibited batches do not support the proposed high limits of the related substance impurities. Please tighten these limits. Alternatively, you can provide data including chromatograms comparing your drug product impurity profile with that of the RLD.

Firm Response on 5-6-02: *Not Satisfactory*

The data submitted comparing the exhibit batches to the RLD show that our product has a comparable related substance/impurity profile to the RLD. Based on the data submitted, the firm proposed a limit of NMT % for total known and unknown degradant at release and stability study.

b. Your accelerated stability data do not include results for the related substance impurities. Please reanyalyze and submit the data. Data including chromatograms comparing your drug product impurity profile with that of the RLD.

Firm Response on 5-6-02: *Satisfactory*

The firm tested the 90 days accelerated stability samples and submitted the data (exhibit H). The firm incorporated its proposed specifications in long term stability study data sheets (exhibit J)

Comments in rev. # 2:

In addition to you have proposed a limit of NMT % for Individual known impurity/degradant. Please identify this known impurity/degradant. Your long term room temperature data, for up to 12 months, showed % for individual known and unknown impurity/ degradant. Please tighten the limit.

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

your response:

FDA comment # 1 in section B:

Please include the primary function of each excipient in your components and composition statement.

Firm Response on 5-6-02: *Satisfactory*

The firm submitted the following information:

Excipent	Function
Lactose Anhydrous NF	Diluent
Microcrystalline Cellulose NF	Binder
Stearic Acid NF	Lubricant
Croscarmellose Sodium NF	Disintegrant
Magnesium Stearate NF	Lubricant
Colloidal Silicon Dioxide NF	Glidant
D&C Yellow Aluminum Lake # 10	Color

FDA comment # 2 in section B:

Please be informed that all facilities involved in the production, packaging, labeling, testing, and/or release of this product should comply with cGMP requirements at the time of approval of this ANDA.

Firm Response on 5-6-02: *Satisfactory*

The firm's facilities involved in the production of this product do comply with cGMP requirements.

FDA comment # 3 in section B:

Please submit available updated room temperature stability data.

Firm Response on 5-6-02: *Satisfactory*

The firm submitted updated room temperature stability data up to 12 months. The test results are within the proposed specifications (exhibit K)

38. Chemistry Comments to be provided to the applicant

ANDA: 76-268

APPLICANT: Jerome Stevens Pharmaceuticals

DRUG PRODUCT: Digoxin Tablets USP 0.125 mg and 0.250 mg.

The deficiencies presented below represent MINOR deficiencies:

A. Chemistry Deficiencies

1. Your response to our comment # 1 is not satisfactory. In this regard:

   a. You have cited the variable potency of digoxin lots as the rationale for using a % overage in the manufacture of this drug product. The lot to lot variation in assay potency of the active is not a good reason for including the overage in the manufacturing formula. An equation that calculates actual amounts to be used in the manufacture of the drug product (DP), based on the active "as is potency", will provide the assurance that the product is always formulated to 100% potency as required in the regulations. Please revise your formula cards (p. 4486 and p. 4496) and resubmit.

   b. You cited the possibility of a loss of API during the manufacturing process as another reason for including an overage for the drug substance digoxin. Please provide data, identifying the production/process step(s), to support your claim that loss of API occurs during the manufacturing process.

2. Your response to our comments # 10 is not satisfactory. Your proposed limit for an individual unknown degradant at stability of NMT % is not acceptable. The current office practice is to require identification of impurities/degradants observed at >0.2%. In this regard, please also note the General Notices of the USP 25/NF 20 under title "Foreign Substances and Impurities". Please revise and resubmit.

3. In addition to you have proposed a limit of NMT % for Individual known impurity/degradant. Please identify this known impurity/degradant. Your long term room temperature data, for up to 12 months, showed % for individual known and unknown impurity/ degradant. Please tighten the limit.

Sincerely yours,

/S/ 6/24/02

for

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

OFFICE OF GENERIC DRUGS
ABBREVIATED NEW DRUG APPLICATION REVIEW
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. CHEMIST'S REVIEW NO. 2

2. ANDA# 76-268

3. NAME AND ADDRESS OF APPLICANT

Jerome Stevens Pharmaceuticals
Attention: Ronald Steinlauf
60 DaVinci Drive
Bohemia, NY 11716

4. LEGAL BASIS FOR ANDA SUBMISSION

The application is based on the reference listed drug Lanoxin® Tablets manufactured by Glaxo Wellcome (NDA 20-405). Jerome Stevens had been marketing this product under the batch certification program (CFR 310.500).

5. SUPPLEMENT(s): N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME: Digoxin Tablets USP

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

9. AMENDMENTS AND OTHER DATES

Firm:

10-29-01	Original Submission
12-17-01	Firm response to telephone conversation
03-11-02	Bioequivalence amendment
05-06-02	Minor amendment

FDA:

11-07-01	Acceptance to File
12-10-01	Telephone conversation

01-07-02	Acknowledgement letter.
02-21-02	Bioequivalence deficiency letter
03-27-02	Chemistry deficiency letter

10. **PHARMACOLOGICAL CATEGORY:** Cardiotonic glycoside

11. **HOW DISPENSED: Rx**

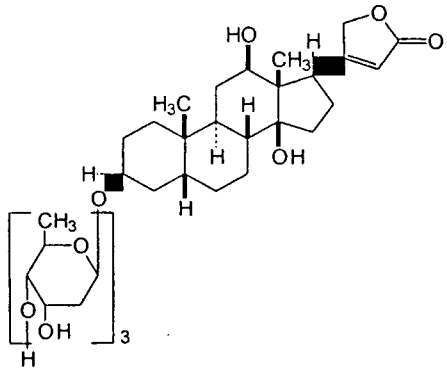
12. **RELATED IND/NDA/DMFs:**

NDA 20-405 Glaxo Wellcome (RLD-Lanoxin®), also See item # 37

13. **DOSAGE FORM/ROUTE OF ADMINISTRATION:** Tablets/Oral

14. **STRENGTH(s):** 0.125 mg & 0.25 mg

15. **CHEMICAL NAME AND STRUCTURE**



3ß-[(*O*-2,6-Dideoxy-ß-*D*-*ribo*-hexopyranosyl-(1→4)-*O*-2,6-dideoxy-ß-*D*-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-ß-*D*-*ribo*-hexopyranosyl)oxy]-12ß,14-dihydroxy-5ß-card-20(22)-enolide.

CAS [20830-75-5]

$C_{41}H_{64}O_{14}$ 780.96

16. **RECORDS AND REPORTS:** N/A

17. **COMMENTS**

A draft federal register notice declared digoxin tablets to be a new drug and on 9/30/97 FDA approved Glaxo Wellcome's

NDA for Lanoxin Tablets. Prior to this, digoxin tablets were considered a "grandfather drug" by the Agency and had been legally marketed without an approved application since 1936. Although Jerome Stevens and other firms are presently marketing the product under the batch certification program. When the federal register notice is finalized, all firms will have to have an approved application in order to market this product.

a. Chemistry review: Deficient (MINOR)
b. Bio-review: Acceptable by J. Chaney on 04-30-02
c. Micro-review: N/A
d. Labeling review: Acceptable by A.Vezza on 5-23-02.
e. Method validation: Both the API and drug product have USP monographs.
f. EERs: Inspection scheduled on 5-1-02. No action until 5-30-02

18. CONCLUSIONS/RECOMMENDATIONS

Not Approvable **(MINOR)**

19. REVIEWER	DATE COMPLETED
Nashed I. Samaan, Ph.D.	6-04-02

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Chem. Review #2

OFFICE OF GENERIC DRUGS
ABBREVIATED NEW DRUG APPLICATION REVIEW
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

✓1. **CHEMIST'S REVIEW NO.** 3

2. **ANDA# 76-268**

3. **NAME AND ADDRESS OF APPLICANT**

Jerome Stevens Pharmaceuticals
Attention: Ronald Steinlauf
60 DaVinci Drive
Bohemia, NY 11716

4. **LEGAL BASIS FOR ANDA SUBMISSION**

The application is based on the reference listed drug Lanoxin® Tablets manufactured by Glaxo Wellcome (NDA 20-405). Jerome Stevens had been marketing this product under the batch certification program (CFR 310.500).

5. **SUPPLEMENT(s)**: N/A

6. **PROPRIETARY NAME:** N/A

7. **NONPROPRIETARY NAME:** Digoxin Tablets USP

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

9. **AMENDMENTS AND OTHER DATES**

Firm:

10-29-01	Original Submission
12-17-01	Firm response to telephone conversation
03-11-02	Bioequivalence amendment
05-06-02	Minor amendment
07-01-02	Telephone Conversation
07-01-02	Minor amendment
07-23-02	Minor amendment

FDA:

11-07-01	Acceptance to File
12-10-01	Telephone conversation
01-07-02	Acknowledgement letter.

02-21-02	Bioequivalence deficiency letter
03-27-02	Chemistry deficiency letter Rev # 1
06-24-02	Chemistry deficiency letter Rev # 2
07-01-02	Telephone Conversation
07-15-02	Discussion of the 7-01 amendment deficiencies during the PAI at Jerome Stevens facility by N. Samaan. This discussion was permitted by Dr. Venkatram, and Florence Fang chemistry division II director.

10. **PHARMACOLOGICAL CATEGORY:** Cardiotonic glycoside

11. **HOW DISPENSED: Rx**

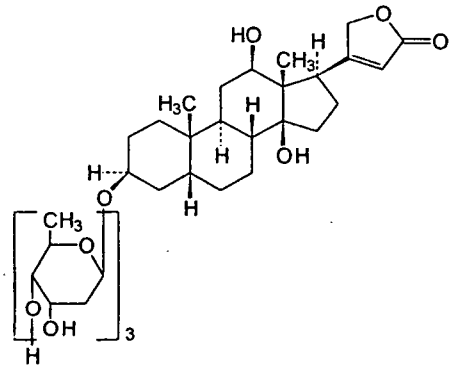
12. **RELATED IND/NDA/DMFs:**

NDA 20-405 Glaxo Wellcome (RLD-Lanoxin®), also See item # 37

13. **DOSAGE FORM/ROUTE OF ADMINISTRATION:** Tablets/Oral

14. **STRENGTH(s):** 0.125 mg & 0.25 mg

15. **CHEMICAL NAME AND STRUCTURE**



3ß-[(*O*-2,6-Dideoxy-ß-*D*-*ribo*-hexopyranosyl-(1→4)-*O*-2,6-dideoxy-ß-*D*-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-ß-*D*-*ribo*-hexopyranosyl)oxy]-12ß,14-dihydroxy-5ß-card-20(22)-enolide.

CAS [20830-75-5]

$C_{41}H_{64}O_{14}$ 780.96

16. **RECORDS AND REPORTS:** N/A

17. **COMMENTS**

A draft federal register notice declared digoxin tablets to be a new drug and on 9/30/97 FDA approved Glaxo Wellcome's NDA for Lanoxin Tablets. Prior to this, digoxin tablets were considered a "grandfather drug" by the Agency and had been legally marketed without an approved application since 1936. Although Jerome Stevens and other firms are presently marketing the product under the batch certification program. When the federal register notice is finalized, all firms will have to have an approved application in order to market this product.

a. Chemistry review: Recommend approval
b. Bio-review: Acceptable by J. Chaney on 04-30-02
c. Micro-review: N/A
d. Labeling review: Acceptable by A.Vezza on 5-23-02.
e. Method validation: Both the API and drug product have USP monographs.
f. EERs: Inspection conducted on 7-15-02. The inspector Dr. Robert Haron recommend approval for this ANDA (see attached e-mail)

18. **CONCLUSIONS/RECOMMENDATIONS**

Recommend Final Approval

19. **REVIEWER**	**DATE COMPLETED**
Nashed I. Samaan, Ph.D.	7-12-02 & 7-24-02

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Chem. Review #3

Applicant's Responses to Review #2
Minor amendment dated July 1, 2002

ANDA: 76-268

APPLICANT: Jerome Stevens Pharmaceuticals

DRUG PRODUCT: Digoxin Tablets USP 0.125 mg and 0.250 mg.

The following deficiencies were sent to the applicant per review # 2 and represent MINOR deficiencies. Each response made by the applicant follows the reviewer's comment.

FDA comment # 1

Your response to our comment # 1 is not satisfactory. In this regard:

a. You have cited the variable potency of digoxin lots as the rationale for using a % overage in the manufacture of this drug product. The lot to lot variation in assay potency of the active is not a good reason for including the overage in the manufacturing formula. An equation that calculates actual amounts to be used in the manufacture of the drug product (DP), based on the active "as is potency", will provide the assurance that the product is always formulated to 100% potency as required in the regulations. Please revise your formula cards (p. 4486 and p. 4496) and resubmit.

b. You cited the possibility of a loss of API during the manufacturing process as another reason for including an overage for the drug substance digoxin. Please provide data, identifying the production/process step(s), to support your claim that loss of API occurs during the manufacturing process.

Firm response on 7-01-02: Not Satisfactory

The firm eliminated the % overage of digoxin in the manufacture of the drug product. To assure that the product is manufactured to a potency of 100.00%, the firm will adjust the target compression unit dosage to 100.00% potency based on the in-process assay that is conducted on each batch. The firm submitted revised blend COAs to incorporate this change.

FDA comment:

Your response to our comment # 1 is not satisfactory.

You stated "***To assure that the product is manufactured to a potency of 100.00%, we will adjust the target compression unit dosage to 100.00% potency based on the in-process assay that is conducted on each batch***". This method to achieve 100 % potency is not acceptable. The quantity needed for each lot to achieve 100.00% potency should be based on the drug substance "as is potency". Please revise your formula cards (p. 4486 and p. 4496) and resubmit.

FDA comment # 2 in rev. # 2:

Your response to our comments # 10 is not satisfactory. Your proposed limit for an individual unknown degradant at stability of NMT % is not acceptable. The current office practice is to require identification of impurities/ degradants observed at >0.2%. In this regard, please also note the General Notices of the USP 25/NF 20 under title "Foreign Substances and Impurities". Please revise and resubmit.

Firm response on 7-01-02: Satisfactory

The firm reduced the limit for individual unknown degradant at release and stability to 0.2%.

FDA comment # 3 in rev. # 2:

In addition to , you have proposed a limit of NMT % for Individual known impurity/degradant Please identify this known impurity/degradant. Your long term room temperature data, for up to 12 months, showed % for individual known and unknown impurity/ degradant. Please tighten the limit.

Firm response on 7-01-02: Satisfactory

The firm eliminated the limit for individual known degradant. The firm submitted revised release and stability specifications to incorporate this change.

Review of
Minor amendment dated July 23, 2002

Due to minor deficiencies found in the firm's amendment dated July 1,02. And the Agency's Final Rule regarding revocation of conditions for marketing digoxin products for oral use. Dr. Venkataram, and Florence Fang chemistry division II director gave permission to the review chemist of this application, N. Samaan, to discuss these deficiencies with the firm's authorized persons during the pre-approval inspection. The firm's response to the deficiencies and other related issues are as follow:

1. The firm eliminated the % overage of digoxin in the manufacture of the drug product. The firm will adjust the amount of digoxin added to 100.00% potency based on the assay of each digoxin raw material lot. The firm provided revised batch production records to include formula to calculate the quantity of digoxin drug substance needed for each production lot. In addition, the firm revised the digoxin blend COAs to reflect the fact that the firm not adjusting the tablet target weight based on the inprocess blend assay as previously stated in July 1,02 amendment. Also, the revisedformula card indicates correct unit dose weight. **Satisfactory.**

   N.B.

   The elimination of the % overage of the drug substance was discussed on July 12, 02 with Dr. Chaney, the bioequivalence reviewer, to determine its impact on the bioequivalence study of this product. Dr chaney response is:

   "After consideration of the data from the bioequivalence studies in this ANDA I do not expect that a % decrease in potency (elimination of overage) relative to the potency of the biobatch would impact the acceptability of the fasting or fed biostudies". Please see attached.

2. The firm increased the limit for individual unknown degradant at release and stability to NMT %. The firm referred to "Guidance for Industry, Q3B Impurities in New Drug Product". The guidance has established the following limits:

Thresholds for Identification of Degradation Products in New Drug Products

Maximum Daily Dose	Threshold
< 1 mg	1.0% or 5 mcg whichever is lower
1 mg - 10 mg	0.5% or 20 mcg whichever is lower
10 mg - 2 g	0.2% or 2 mg whichever is lower
> 2 g	0.1%

The proposed limit of NMT % complies within the above limits. In addition, the proposed limit was discussed with the division director, Florence Fang" and it is acceptable. **Satisfactory**

3. The firm added a specification at release and stability for total Known and unknown degradant including The proposed limit is NMT %. **Satisfactory**

4. The firm revised the accelerated and long-term stability tables to incorporate the proposed impurity limits.

5. In addition, The firm submitted a revised SOP for the storage and re-testing of raw materials to include a provision to retest the inactive ingredients 18 months after the release date. **Satisfactory**

MAR 27 2002

38. Chemistry Comments to be provided to the applicant

ANDA: 76-268

APPLICANT: Jerome Stevens Pharmaceuticals

DRUG PRODUCT: Digoxin Tablets USP 0.125 mg and 0.250 mg.

The deficiencies presented below represent MINOR deficiencies:

A. Chemistry Deficiencies

1. The exhibit batches of Digoxin Tablets USP, 0.125 mg and 0.250 mg used in support of this ANDA and the proposed commercial batches are formulated with a % overage of Digoxin. Please eliminate this overage or justify.

2. In your original submission (p. 4485 and p. 4496), you provided Blank Manufacturing records batch sizes of tablets for Digoxin Tablets USP, 0.125 mg and 0.250 mg strength, respectively. However, in your submission dated 12-17-01, you provided Blank Manufacturing records batch sizes of tablets for Digoxin Tablets USP, 0.125 mg and 0.250 mg strength, respectively. Please clarify your commercial production batch size.

3. The USP monograph includes Identification tests B and C by for the drug substance. Please add these identification tests to your specifications for Digoxin drug substance.

4. The manufacturer of the drug substance, , has provided results for residual solvents by in their certificate of analysis (COA) (p. 4429). In this regard:

   a. The COA does not include limits for the test. Please request revised COA from that includes limits for each test and submit.

   b. Please include a test method and limits for the Organic Volatile Impurities and residual solvents

to your drug substance specifications. In this regard we note that the manufacturer's certificate of analysis for the drug substance, Digoxin (p. 4428), reported test results of % ppm) for . Please note that the ICH limit for is NMT ppm. Please comment.

5. In addition, has identified the related substance impurities in its certificate of analysis (p.4429). Please identify and establish a limit for each known related substance impurity in the drug substance.

6. You have proposed a re-test schedule of 18 months (p.4442 and p.4478). Please justify with data.

7. Please clarify the notations C and M in your packaging records. Additionally, please submit packaging and labeling reconciliation data. Submit your acceptance criteria.

8. The USP monograph for digoxin tablets includes two identification tests, ID(A) which is based on retention times and ID(B) which relies on Rf values. Please add the second ID test to your finished product specifications.

9. Please identify the known related substance impurities in your drug product at release and stability study. Establish test method and a limit for each and incorporate it in your release and stability specifications.

10. The limit for any unknown impurity in your drug product release and stability specifications is high. At the proposed levels they may need to be identified. Please tighten the limits.

11. Your proposed limits for total related substance impurities at release and stability are high. In this regard:

    a. Your long-term stability data of the exhibited batches do not support the proposed high limits of the related substance

impurities. Please tighten these limits. Alternatively, you can provide data including chromatograms comparing your drug product impurity profile with that of the RLD.

b. Your accelerated stability data do not include results for the related substance impurities. Please reanyalyze and submit the data. Data including chromatograms comparing your drug product impurity profile with that of the RLD.

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

1. Please include the primary function of each excipient in your components and composition statement.

2. Please be informed that all facilities involved in the production, packaging, labeling, testing, and/or release of this product should comply with cGMP requirements at the time of approval of this ANDA.

3. Please submit available updated room temperature stability data.

Sincerely yours,

/S/

for

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

JUN 24 2002

38. Chemistry Comments to be provided to the applicant

ANDA: 76-268

APPLICANT: Jerome Stevens Pharmaceuticals

DRUG PRODUCT: Digoxin Tablets USP 0.125 mg and 0.250 mg.

The deficiencies presented below represent MINOR deficiencies:

A. Chemistry Deficiencies

1. Your response to our comment # 1 is not satisfactory. In this regard:

a. You have cited the variable potency of digoxin lots as the rationale for using a % overage in the manufacture of this drug product. The lot to lot variation in assay potency of the active is not a good reason for including the overage in the manufacturing formula. An equation that calculates actual amounts to be used in the manufacture of the drug product (DP), based on the active "as is potency", will provide the assurance that the product is always formulated to 100% potency as required in the regulations. Please revise your formula cards (p. 4486 and p. 4496) and resubmit.

b. You cited the possibility of a loss of API during the manufacturing process as another reason for including an overage for the drug substance digoxin. Please provide data, identifying the production/process step(s), to support your claim that loss of API occurs during the manufacturing process.

2. Your response to our comments # 10 is not satisfactory. Your proposed limit for an individual unknown degradant at stability of NMT % is not acceptable. The current office practice is to require identification of impurities/degradants observed at %. In this regard, please also note the General Notices of the USP 25/NF 20 under title "Foreign Substances and Impurities". Please revise and resubmit.

3. In addition to you have proposed a limit of NMT for Individual known impurity/degradant. Please identify this known impurity/degradant. Your long-term room temperature data, for up to 12 months, showed % for individual known and unknown impurity/ degradant. Please tighten the limit.

Sincerely yours,

/S/

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research