# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-648**

# CHEMISTRY REVIEW(S)

CHEMISTRY REVIEW

Chemistry Review Data Sheet

# NDA 21-648

## Digoxin Elixir USP

## Digoxin

## Roxane Laboratories, Inc.

**Stuart Zimmerman**
**Division of Cardio-Renal Drug products**

# Table of Contents

## *Chemistry Review Data Sheet*

1. NDA 21-648

2. REVIEW # 3:

3. REVIEW DATE: 8/9/04

4. REVIEWER: Stuart Zimmerman, Ph.D.

5. PREVIOUS DOCUMENTS:

None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed /Document Date

| Document | Date | Receipt Date |
|---|---|---|
| Amendment | 3/10/04 | 3/11/04 (Response to CMC Issues) |
| Amendment | 3/22/04 | 3/23/04 |
| Amendment | 3/4/04 | 3/5/04 (Labeling) |
| Amendment | 6/17/04 | 6/18/04 (Drug substance impurity controls) |
| Amendment | 6/25/04 | 6/28/04 (FPL) |
| Amendment | 7/7/04 | 7/8/04 (Delineated impurity controls) |
| Amendment | 7/28/04 | 7/29/04 |

7. NAME & ADDRESS OF APPLICANT:

Name: Roxane Pharmaceuticals

Address: 110 Allen Road, Liberty Corner NJ 07938

Representative: Elizabeth Ernst

Telephone: 908-542-4403

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None (Name used is Digoxin Elixir USP)
b) Non-Proprietary Name (USAN): Digoxin
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: Type 7
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Cardiac glycoside

11. DOSAGE FORM: Elixir

12. STRENGTH/POTENCY: 0.05 mg/mL

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: x Rx ___OTC

15. **SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):**

_____SPOTS product – Form Completed

__x__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

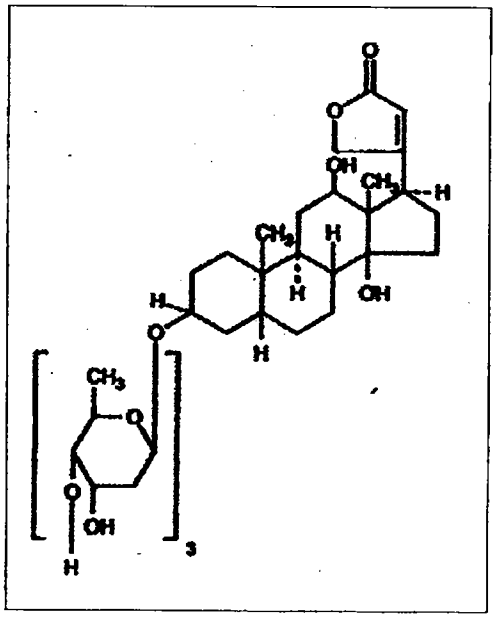
**Chemical Name:** 3ß-[(*0*-2,6-Dideoxy-ß-*D-ribo*-hexopyranosyl-(1-4)-*0*-2,6-dideoxy-ß-*D-ribo*-hexopyranosyl-(1-4)-2,6-dideoxy-ß-*D-ribo*-hexopyranosyl)oxy]-12ß,14-dihydroxy-5ß-card-20(22)-enolide.

**Molecular Formula:** $C_{41}H_{64}O_{14}$

**Molecular Weight:** 780.95

**CAS** [20830-75-5]

**Structural Formula** (Chemical Structure) (v. 1.4, p. 1644)



17 RELATED/SUPPORTING DOCUMENTS:

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE[1] | STATUS[2] | DATE REVIEW COMPLETED | COMMENTS |
|---|---|---|---|---|---|---|---|
| | II | | | 1 | Adequate | 2/18/04 | Updated to include comments - recent inspection |
| | III | | | 4 | Adequate | 9/23/03 (in NDA) | COAs with |
| | III | | | 4 | Adequate | **9/23/03 –as part of this NDAreview** | **Certificate for** |
| | III | | | 3 | Adequate | **9/23/03 –as part of NDA review** | **COA includes** |
| | III | | | 3, 7a | Adequate | 11/12/96 - Chemistry Review | Cross-reference - DMF |
| | III | | | 5, 7b | Adequate | 2/18/04 | Update of review status |
| | III | | | 3, 7b | Adequate | 3/18/89 for DMF | 1st Review of |
| | III | | | 3 | Adequate | 7/24/99 Rev. Date before use of e-filing | **See by James Vidra HFD –540** |
| | III | | | 1 | Adequate | 2/18/04 | Includes supporting information |
| | III | | | NA | Not relevant anymore | 9/12/03 | Updated to DMF |

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

7a. This DMF (i.e., DMF — is a nested DMF relating to DMF — and is not directly referenced in terms of a COA. It is considered to be acceptable via supporting information included in the primary DMF —

7b. These DMFs — are both nested/referenced in DMF — which is now cited by issue for the — but remains satisfactory for the —

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

***Summary of Information:*** There is no IND associated with this NDA since this submission was the result of a request by the agency to file an NDA for this drug product that was already marketed without an NDA.

17. STATUS:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| Biometrics | N/A | | |
| EES | Adequate | 2/17/04 | Adams |
| Pharm/Tox | N/A (no need - old drug) | | |
| Biopharm | N/A Solution formulation- no consult | | |
| LNC | N/A | | |
| Methods Validation | To be submitted | | |
| DMETS | Applicant's responses to queries are adequate. | 7/12/02 –PM (Ed Fromm) | Report entered into DFS by Marci Lee covers issues. |
| EA | Acceptable (categorical Exclusion) | 6/7/02 see review section | Stuart Zimmerman |
| Microbiology | N/A | | |

# The Chemistry Review for NDA 21-438

## *The Executive Summary*

## I. Recommendations

### A. Recommendation and Conclusion on Approvability:

All deficiencies identified in the approvable letter of February 25, 2004 have been satisfactorily addressed. This application may be approved from the standpoint of chemistry, manufacturing and controls.

### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

## II. Summary of Chemistry Assessments

### A. Description of the Drug Product(s) and Drug Substance(s)

The drug product has been marketed for many years by the applicant without the support of an approved NDA. As background perspective, on September 30, 1997, the Agency approved an NDA for digoxin tablets, NDA 20-405. Because of this approval, ANDAs were now allowed for digoxin tablets. The Agency then proposed a rule in the Federal Register on November 24, 2000, that would require approved applications for all digoxin products, including digoxin elixir. In this connection, it is recognized that there is a USP monograph available for this elixir and that the applicant refers to this drug product as a USP article. The current USP standard for Digoxin Elixir (i.e., USP 25, p. 572) does not include any specifications for the control of the potential degradants that are known to exist and increase with time mainly by —

The drug product is an elixir formulation. There is one dosage strength of 0.05 mg/mL. The elixir is packaged in 60 ml — bottles having child resistant screw caps that are then replaced with dropper caps, and in unit dose — , cups provided in both 2.5 mL and 5.0 mL size.

The manufacturing process assures that each batch of the drug product can be consistently manufactured to acceptable performance standards. Also considered is the fact that chemical impurities and degradation is tightly controlled to very low limits throughout the entire process train - starting with drug substance manufacture.

Validated analytical control methods have been developed that can adequately monitor the critical control attributes to acceptable quality levels. For example, at

Adequate attention is given to the design of the in-process control tests and their respective acceptance criteria for step - by - step monitoring of the performance attributes at each critical unit process operation.

Packaging configurations have been appropriately designed to adequately protect the drug product's performance characteristics against changes for the shelf-life of the product. Appropriately designed stability studies have been planned to permit the conclusion that the drug product would be predicted to maintain its performance characteristics over the duration of its proposed expiry period which is 12 months. To date, of real time primary stability data has been submitted at the time of this review.

The drug substance, Digoxin USP is a well known active ingredient that has been marketed for many years. It is a white, crystalline solid that is readily soluble in water and ethanol. In the USA, it is regulated by a USP monograph. It is also the subject of other monographs such as the EP and BP monographs. It has a retest date of

The drug substance is manufactured by . Most of the critical drug substance chemistry and manufacturing information is in the drug master file (DMF) of the supplier. This DMF has been reviewed and found to be adequate from the standpoint of the critical control aspects. Additionally, the applicant has established individual analytical control limits for their own in-house control of process impurities in digoxin in a manner that exceeds the current USP requirements

**B. Description of How the Drug Product is Intended to be Used**

This application for digoxin elixir contains a liquid formulation that provides administration to a population of patients that may experience difficulty taking the solid oral dosage form. This formulation is expected to enable dose administration to patients who may have difficulty swallowing tablets, and will facilitate dose titration not currently possible with fixed-tablet dosage forms. It has a dose of administration

**C. Basis for Approvability or Not-Approval Recommendation:**

There are no pending chemistry and manufacturing controls (CMC) issues and the application may be approved from a CMC standpoint. The applicant has addressed the appropriate CMC requirements as detailed in the respective chemistry assessment sections of this review. This includes reference to the overall approval of the various manufacturing, packaging and testing facilities involved by the Office of Compliance.

**B. Reviewer's Signature**

**C. Endorsement Block**

Chemist Name/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

**D. CC Block**

APPEARS THIS WAY
ON ORIGINAL

36 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

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

/s/

Stuart Zimmerman
8/10/04 10:37:05 AM
CHEMIST

Kasturi Srinivasachar
8/12/04 06:02:08 PM
CHEMIST

# NDA 21-648

## Digoxin Elixir USP

## Digoxin

## Roxane Laboratories, Inc.

**Stuart Zimmerman**
**Division of Cardio-Renal Drug products**

# Table of Contents

## *Chemistry Review Data Sheet*

1. NDA 21-648

2. REVIEW # 2:

3. REVIEW DATE: 2/20/04

4. REVIEWER: Stuart Zimmerman, Ph.D.

5. PREVIOUS DOCUMENTS:

None

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | /Document Date |
|---|---|
| Original | 25-April-2003 |
| Amendment | 2-OCT-03 |
| Amendment | 03-DEC-2003 (In part) |
| Amendment | 2-FEB-04 |
| Amendment | 11-FEB-04 |
| Amendment | 12-FEB-04 |

7. NAME & ADDRESS OF APPLICANT:

Name: Roxane Pharmaceuticals

Address: 110 Allen Road, Liberty Corner NJ 07938

*Representative:* Elizabeth Ernst

Telephone: 908-542-4403

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: No (Name used is Digoxin Elixir USP)
b) Non-Proprietary Name (USAN): Digoxin
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: Type 3

- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Cardiac glycoside

11. DOSAGE FORM: Elixir

12. STRENGTH/POTENCY: 0.05 mg/mL

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: x Rx ___OTC

15. **SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):**

_____SPOTS product – Form Completed

__x__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

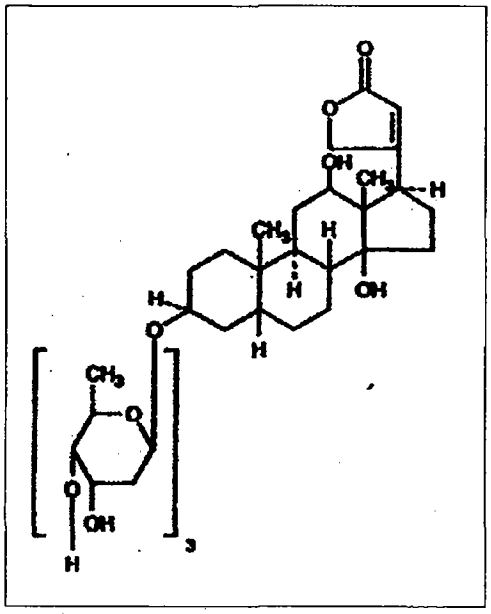
**Chemical Name:** 3ß-[(*0*-2,6-Dideoxy-ß-*D-ribo*-hexopyranosyl-(1-4)-*0*-2,6-dideoxy-ß-*D-ribo*-hexopyranosyl-(1-4)-2,6-dideoxy-ß-*D-ribo*-hexopyranosyl)oxy]-12ß,14-dihydroxy-5ß-card-20(22)-enolide.

**Molecular Formula:** $C_{41}H_{64}O_{14}$

**Molecular Weight:** 780.95

**CAS** [20830-75-5]

**Structural Formula** (Chemical Structure) (v. 1.4, p. 1644)



Chemistry Review Data Sheet

## 17 RELATED/SUPPORTING DOCUMENTS:

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE[1] | STATUS[2] | DATE REVIEW COMPLETED | COMMENTS |
|---|---|---|---|---|---|---|---|
| | II | | | 1 | Adequate | 2/18/04 | Updated to include comments - recent inspection |
| | III | | | 4 | Adequate | 9/23/03 (in NDA) | COAs with |
| | III | | | 4 | Adequate | **9/23/03 –as part of this NDAreview** | **Certificate for** |
| | III | | | 3 | Adequate | **9/23/03 –as part of NDA review** | **COA includes** |
| | III | | | 3, 7a | Adequate | 11/12/96 - Chemistry Review | Cross-reference - DMF |
| | III | | | 5, 7b | Adequate | 2/18/04 | Update of review status |
| | III | | | 3, 7b | Adequate | 3/18/89 for DMF | 1st Review of |
| | III | | | 3 | Adequate | 7/24/99 Rev. Date before use of e-filing | **See by James Vidra HFD –540** |
| | III | | | 1 | Adequate | **2/18/04** | Includes supporting information |
| | III | | | NA | Not relevant anymore | 9/12/03 | Updated to DMF |

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7a. This DMF (i.e., DMF ) a nested DMF relating to DMF and is not directly referenced in terms of a COA. It is considered to be acceptable via supporting information included in the primary DMF

7b. These DMFs are both nested/referenced in DMF which is now cited by issue for the but remains satisfactory for the

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

***Summary of Information:*** There is no IND associated with this NDA since this submission was the result of a request by the agency to file an NDA for this drug product that was already marketed without an NDA.

17. STATUS:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| Biometrics | N/A | | |
| EES | Adequate | 2/17/04 | Adams |
| Pharm/Tox | N/A (no need - old drug) | | |
| Biopharm | N/A Solution formulation- no consult | | |
| LNC | N/A | | |
| Methods Validation | To be submitted | | |
| DMETS | Provided for assessment and outcome advice provided to applicant for correction. | 7/12/02 –PM (Ed Fromm) | Report entered into DFS by Marci Lee covers issues. |
| EA | Acceptable (categorical Exclusion) | 6/7/02 see review section | Stuart Zimmerman |
| Microbiology | N/A | | |

# The Chemistry Review for NDA 21-438

## *The Executive Summary*

## I. Recommendations

### A. Recommendation and Conclusion on Approvability:

The Office of Compliance has provided an overall "acceptable" CGMP recommendation for all the facilities involved in the manufacturing and testing of this product. This NDA 21-648 is approvable from a CMC standpoint pending the resolution of some outstanding control issues (e.g., — levels in the drug substance and related substance limits in the drug product). These deficiencies, listed on page 48, should be incorporated in the action letter to the applicant.

### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

## II. Summary of Chemistry Assessments

### A. Description of the Drug Product(s) and Drug Substance(s)

The drug product has been marketed for many years by the applicant without the support of an approved NDA. As background perspective, on September 30, 1997, the Agency approved an NDA for digoxin tablets, NDA 20-405. Because of this approval, ANDAs were now allowed for digoxin tablets. The Agency then proposed a rule in the Federal Register on November 24, 2000, that would require approved applications for all digoxin products, including digoxin elixir. In this connection, it is recognized that there is a USP monograph available for this elixir and that the applicant refers to this drug product as a USP article. The current USP standard for Digoxin Elixir (i.e., USP 25, p. 572) does not include any specifications for the control of the potential degradants that are known to exist and increase with time mainly by — he closest USP standard that does address such degradants is the USP monograph for Digoxin Injection whereby there is reference to the more primary monograph for Digoxin drug substance and the criteria that no TLC spot is more intense than that of Gitoxin standard solution (i.e., not more that 3% of any related glycoside as gitoxin). The applicant does provide for the control of potential degradants on a more individualized "specific/known" category-control basis. This approach is considered an advantage relative to the Current USP controls that do not delineate specific degradants in terms of any chemical structures.

The drug substance is manufactured by ——— ———. Most of the critical drug substance chemistry and manufacturing information is in the drug master file (DMF) of the supplier. This DMF has been reviewed and found to be adequate from the standpoint of the critical control aspects. There is a more current ——— issue that impacts on the particular patient population involved for drug product which is addressed to the applicant for resolution.

Digoxin USP is a well known active ingredient that has been marketed for many years. It is a white, crystalline solid that is readily soluble in water and ethanol. In the USA, it is regulated by a USP monograph. It is also the subject of other monographs such as the EP and BP monographs. It has a retest date of ———

The drug product is an elixir formulation. There is one dosage strength of 0.05 mg/mL. The elixir is packaged in 60 mL — bottles having child resistant screw caps that are then replaced with dropper caps, and in unit dose — , cups provided in both 2.5 mL and 5.0 mL size.

The manufacturing process assures that each batch of the drug product can be consistently manufactured to acceptable performance standards. Also considered is the fact that chemical impurities and degradation is tightly controlled to very low limits throughout the entire process train - starting with drug substance manufacture.

Valid analytical control methods have been developed that can adequately monitor the critical control attributes to acceptable quality levels. For example, potential impurities and degradants are closely controlled to levels of quantitation between ——— depending on the nature of each specific degradant assessed - relative to active drug abundance.

Adequate attention is given to the design of the in-process control tests and their respective acceptance criteria for step - by - step monitoring of the performance attributes at each critical unit process operation.

Packaging configurations have been appropriately designed to adequately protect the drug product's performance characteristics against changes for the shelf-life of the product. Appropriately designed stability studies have been planned to permit the conclusion that the drug product would be predicted to maintain its performance characteristics over the duration of its proposed expiry period which is 12 months. To date, ——— of real time primary stability data has been submitted at the time of this review.

**B. Description of How the Drug Product is Intended to be Used**

This application for digoxin elixir contains a liquid formulation that provides administration to a population of patients that may experience difficulty taking the solid oral dosage form. This formulation is expected to enable dose administration to patients who may have difficulty swallowing tablets, and will facilitate dose titration not currently possible with fixed-tablet dosage forms. It has a dose of administration

**C. Basis for Approvability or Not-Approval Recommendation:**

The Office of Compliance has provided an overall cGMP approval for all facilities submitted for inspection. However, the applicant is approvable from a CMC standpoint because of pending issues relating to impurity issues and specifications for the drug substance and drug product. Since these matters relate to quality aspects for this narrow therapeutic index product which could be prescribed to neonates, their satisfactory resolution is necessary before the NDA may be approved.

The applicant now proposes an 12 month expiry date for the drug product that is currently supported by 12 months of real-time ambient stability data. This is acceptable since there is support by full term ambient stability data.

**B. Reviewer's Signature**

**C. Endorsement Block**

Chemist Name/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

**D. CC Block**

38 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

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

/s/

Stuart Zimmerman
2/20/04 02:45:01 PM
CHEMIST

Kasturi Srinivasachar
2/20/04 05:08:41 PM
CHEMIST

Chemistry Review Data Sheet

# NDA 21-648

## Digoxin Elixir USP

## Digoxin

## Roxane Laboratories, Inc.

**Stuart Zimmerman**
**Division of Cardio-Renal Drug products**

# Table of Contents

## *Chemistry Review Data Sheet*

1. NDA 21-648

2. REVIEW # 1:

3. REVIEW DATE: 2-17-04

4. REVIEWER: Stuart Zimmerman, Ph.D.

5. PREVIOUS DOCUMENTS:

None

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | /Document Date |
|---|---|
| Original | 10-APR-2003 |
| Amendment | 12-JUN-2003 |
| Amendment | 9-JUL-2003 |
| Amendment | 04-SEP-2003 |
| Amendment | 03-DEC-2003 (In part – stability update) |

7. NAME & ADDRESS OF APPLICANT:

Name: Roxane Pharmaceuticals

Address: 110 Allen Road, Liberty Corner NJ 07938

Representative: Elizabeth Ernst

Telephone: 908-542-4403

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Digoxin Elixir
b) Non-Proprietary Name (USAN): Digoxin
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: Type 3

- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Cardiac glycoside

11. DOSAGE FORM: Elixir

12. STRENGTH/POTENCY: 0.05 mg/mL

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: x Rx ___OTC

15. **SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):**

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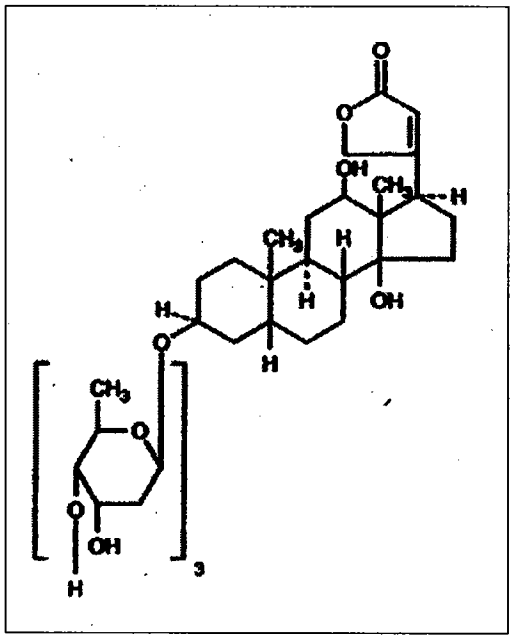
**Molecular Formula:** $C_{41}H_{64}O_{14}$

**Molecular Weight:** 780.95

**CAS** [20830-75-5]

**Structural Formula** (Chemical Structure) (v. 1.4, p. 1644)



## 17 RELATED/SUPPORTING DOCUMENTS:

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE[1] | STATUS[2] | DATE REVIEW COMPLETED | COMMENTS |
|---|---|---|---|---|---|---|---|
| | II | | | NA | Other –under review | **Refer to review for comments** | Currently rechecking out certain tests and results |
| | III | | | 4 | Adequate | 9/23/03 (in NDA) | COAs with |
| | III | | | 4 | Adequate | **9/23/03 –as part of this NDAreview** | **Certificate for** |
| | III | | | 3 | Adequate | **9/23/03 –as part of NDA review** | **COA includes** |
| | III | | | 3, 7a | Adequate | 11/12/96 - Chemistry Review | Cross-reference - DMF |
| | III | | | 5, 7b | Other – Under Review | N/A at this point | Refer to review for comments |
| | III | | | 3, 7b | Adequate | 3/18/89 for DMF | 1st Review of |
| | III | | | 3 | Adequate | 7/24/99<br>Rev. Date before use of e-filing | **See by James Vidra HFD –540** |
| | III | | | NA | Other- Under review | 9/12/03 | Refer to review for comments |

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

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7a. This DMF (i.e., DMF — is a nested DMF relating to DMF — and is not directly referenced in terms of a COA. It is considered to be acceptable via supporting information included in the primary DMF

7b. These DMFs — are both nested/referenced in DMF — which is now cited by issue for the — but remains satisfactory for the —

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

***Summary of Information:*** There is no IND associated with this NDA since this submission was the result of a request by the agency to file an NDA for this drug product that was already marketed without an NDA.

17. STATUS:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| Biometrics | N/A | | |
| EES | Pending inspection results for DMF — | | |
| Pharm/Tox | N/A (no need - old drug) | | |
| Biopharm | N/A Solution formulation- no consult | | |
| LNC | N/A | | |
| Methods Validation | To be submitted | | |
| DMETS | Provided for assessment and outcome advice provided to applicant for correction. | 7/12/02 –PM (Ed Fromm) | Report entered into DFS covers control issues. |
| EA | Acceptable (categorical Exclusion) | 6/7/02 see review section | Stuart Zimmerman |
| Microbiology | N/A | | |

# The Chemistry Review for NDA 21-438

## *The Executive Summary*

## I. Recommendations

### A. Recommendation and Conclusion on Approvability:

This NDA 21-648 is approvable pending the satisfactory completion of the inspection of the sites involved and the resolution of some other outstanding control issues (e.g., drug product and in-process changes in the specifications, labeling changes and the assignment of an expiration date).

### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

## II. Summary of Chemistry Assessments

### A. Description of the Drug Product(s) and Drug Substance(s)

The drug product has been marketed for many years by the applicant without the support of an approved NDA. As background perspective, on September 30, 1997, the Agency approved an NDA for digoxin tablets, NDA 20-405. Because of this approval, ANDAs were now allowed for digoxin tablets. The Agency then proposed a rule in the Federal Register on November 24, 2000, that would require approved applications for all digoxin products, including digoxin elixir. In this connection, it is recognized that there is a USP monograph available for this elixir and that the applicant refers to this drug product as a USP article. The current USP standard for the exilir does not include any specifications for the control of the potential degradants that are known to exist and increase with time mainly by [redacted]. The closest USP standard that does address such degradants is the USP monograph for Digoxin Injection whereby there is reference to the more primary monograph for Digoxin drug substance and the criteria that no TLC spot is more intense than that of Gitoxin standard solution (i.e., not more that 3% of any related glycoside as gitoxin). The applicant does provide for the control of potential degradants on a more individualized "specific/known" category-control basis. This approach is considered an advantage relative to the Current USP controls that do not delineate specific degradants in terms of any chemical structures.

The drug substance is manufactured by [redacted] Most of the critical drug substance chemistry and manufacturing information

is in the drug master file (DMF) of the supplier. This DMF has been reviewed and found to be adequate.

Digoxin USP is a well known active ingredient that has been marketed for many years. It is a white, crystalline solid that is readily soluble in water and ethanol. In the USA, it is regulated by a USP monograph. It is also the subject of other monographs such as the EP and BP monographs. It has a retest date of —

The drug product is an elixir formulation. There is one dosage strength of 0.05 mg/mL. The elixir is packaged in 60 mL — bottles having child resistant screw caps that are then replaced with dropper caps, and in unit dose — cups provided in both 2.5 mL and 5.0 mL size.

The manufacturing process assures that each batch of the drug product can be consistently manufactured to acceptable performance standards. Also considered is the fact that chemical impurities and degradation is tightly controlled to very low limits throughout the entire process train - starting with drug substance manufacture.

Valid analytical control methods have been developed that can adequately monitor the critical control attributes to acceptable quality levels. For example, potential impurities and degradants are closely controlled to levels of quantitation between — - depending on the nature of each specific degradant assessed - relative to active drug abundance.

Adequate attention is given to the design of the in-process control tests and their respective acceptance criteria for step - by - step monitoring of the performance attributes at each critical unit process operation.

Packaging configurations have been appropriately designed to adequately protect the drug product's performance characteristics against changes for the shelf-life of the product. Appropriately designed stability studies have been planned to permit the conclusion that the drug product would be predicted to maintain its performance characteristics over the duration of its proposed expiry period which is — To date, however, only 12 months of real time primary stability data has been submitted at the time of this review. Additional stability data is expected to be provided in the future that would be expected to further support this proposed expiry date. A conservative expiration date of only — can be permitted at this time taking into account the allowance — based on supporting data.

**B. Description of How the Drug Product is Intended to be Used**

This application for digoxin elixir contains a liquid formulation that provides administration to a population of patients that may experience difficulty taking the solid

oral dosage form. This formulation is expected to enable dose administration to patients who may have difficulty swallowing tablets, and will facilitate dose titration not currently possible with fixed-tablet dosage forms. It has a dose of administration —

**C. Basis for Approvability or Not-Approval Recommendation:**

A final recommendation can only be given after the Office of Compliance has provided an overall cGMP status for all facilities submitted for inspection. The review issues identified in the list of deficiencies also need to be resolved.

The applicant proposes an — expiry date for the drug product that is currently supported by 12 months of real-time ambient stability data. This is not acceptable at this time. The accelerated stability data is found to be only marginally supportive of any extension of the more fundamental real-time data. It is recognized, however, that existing 12 month stability profiles for both the active drug substance and the preservatives do project out past — at this time so there is some assurance that the proposed — expiry period could be met with continued supporting stability data at the ambient condition of stress.

**B. Reviewer's Signature**

**C. Endorsement Block**

Chemist Name/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

**D. CC Block**

79 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

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

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/s/

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Stuart Zimmerman
2/17/04 10:06:25 AM
CHEMIST

Kasturi Srinivasachar
2/17/04 01:44:03 PM
CHEMIST

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 21648/000
Org Code : 110
Priority : S

Sponsor: ROXANE
1809 WILSON RD
COLUMBUS, OH 43228

Stamp Date : 14-APR-2003
PDUFA Date : 25-FEB-2004
Action Goal :
District Goal: 27-DEC-2003

Brand Name : DIGOXIN ELIXIR 0.05MG/ML
Estab. Name:
Generic Name: DIGOXIN ELIXIR
Dosage Form: (ELIXIR)
Strength : 0.05MG/ML

| FDA Contacts: | | | |
|---|---|---|---|
| E. FROMM | Project Manager | (HFD-110) | 301-594-5300 |
| S. ZIMMERMAN | Review Chemist | (HFD-110) | 301-594-5300 |
| K. SRINIVASACHAR | Team Leader | (HFD-110) | 301-594-5376 |

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Overall Recommendation: ACCEPTABLE on 17-FEB-2004by S. ADAMS (HFD-322) 301-827-9051

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Establishment : CFN : — FEI : —

DMF No: — AADA:

Responsibilities: —

Profile : CEX OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 17-FEB-04
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 1510690 FEI : 1510690

ROXANE LABORATORIES INC

1809 WILSON RD

COLUMBUS, OH 43228

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE RELEASE TESTER

FINISHED DOSAGE STABILITY TESTER

Profile : LIQ OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 19-DEC-03

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

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Establishment : CFN : 1527529 FEI : 1527529

ROXANE LABORATORIES INC

330 OAK ST

COLUMBUS, OH 43216

DMF No: AADA:

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Profile : LIQ OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 26-JUN-03

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

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