# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-648**

# ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

## 15.0 PATENT CERTIFICATION

Paragraph II Certification [21 CFR 314.94(a)(12)(i)]

In accordance with the Federal Food, Drug and Cosmetic Act, Patent Certification is hereby provided for our 505 (b)(2) New Drug Application for Digoxin Elixir USP, 0.05 mg/mL.

Roxane Laboratories, Inc. hereby certifies that, in its opinion, and to the best of its knowledge, there are no unexpired patents for the reference listed drug, LANOXIN® Tablets, 0.25 mg (Orange Book, 21st Edition and supplements, copy attached). This certification is made in accordance with Section 505(j)(2)(A))(vii)(III) of the Federal Food, Drug and Cosmetic Act and CFR 314.94(a)(12)(i)(A)(3).

Statement of Exclusivity [21 CFR 314.94(a)(3)(ii)]

In the opinion of Roxane Laboratories, Inc. and to the best of its knowledge, in accordance with the list published in the Approved Drug Products with Therapeutic Equivalence (Orange Book, 21st Edition and supplements, copy attached to Section II), there is no unexpired exclusivity for the reference listed drug, LANOXIN® Tablets, 0.25 mg.

Elizabeth Ernst
Associate Director, DRA-Multisource Products

4/7/03
Date

EXCLUSIVITY SUMMARY FOR NDA # 21-648 SUPPL #_____

Trade Name: Generic Name: Digoxin Elixir USP 0.05 mg/ml

Applicant Name: Roxane Laboratories HFD # 110

Approval Date If Known: 8/26/04

**PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /_X__/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /_X__/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /_X__/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /___/ NO /_X __/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /___/ NO /_X__/

If yes, NDA #_____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

**PART II FIVE YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product. (Not Applicable-Digoxin Tablets were approved via NDA 20-405)

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /_ __/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /__/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X__/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently

would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X__/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

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(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /_X__/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_X__/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X__/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval: Published Literature

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /_X__/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

__NDA 20-405_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"): Published Literature

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

YES /___/ NO /_X__/ Explain: _Applicant submitted published literature to support approval of drug.

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain __as above_____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /_X__/ NO /___/

If yes, explain: this is a 505(b)(2) submission in which the applicant submitted published literature to support the labeling, but conducted no clinical studies of their own, other than a Bioequivalence study.

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Signature Date
Title:

Signature of Office/ Date
Division Director

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

/s/

Norman Stockbridge
8/26/04 12:31:36 PM

# PEDIATRIC PAGE

**(Complete for all filed original applications and efficacy supplements)**

**NDA/BLA # :** 21-648 **Supplement Type (e.g. SE5):** _____ **Supplement Number:**

**Stamp Date:** April 25, 2003 **Action Date:** August 26, 2004

**HFD** 110 **Trade and generic names/dosage form:** Digoxin Elixir USP, 0.05 mg/mL

**Applicant:** Roxane Laboratories **Therapeutic Class:** 7S

**Indication(s) previously approved:**

**Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.**

**Number of indications for this application(s):** 1

**Indication #1:** Heart Failure

**Is there a full waiver for this indication (check one)?**

X **Yes: Please proceed to Section A.**

☐ **No: Please check all that apply:** ____Partial Waiver ____Deferred ____Completed
**NOTE: More than one may apply**
**Please proceed to Section B, Section C, and/or Section D and complete as necessary.**

## Section A: Fully Waived Studies

**Reason(s) for full waiver:**

X **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Other:**_____

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

## Section B: Partially Waived Studies

**Age/weight range being partially waived:**

**Min**____ **kg**____ **mo.**____ **yr.**____ **Tanner Stage**____
**Max**____ **kg**____ **mo.**____ **yr.**____ **Tanner Stage**____

**Reason(s) for partial waiver:**

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Adult studies ready for approval**
☐ **Formulation needed**
☐ **Other:**_____

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

## Section C: Deferred Studies

**Age/weight range being deferred:**

**Min _____ kg_____ mo._____ yr._____ Tanner Stage_____**
**Max_____ kg_____ mo._____ yr._____ Tanner Stage_____**

**Reason(s) for deferral:**

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

**Other:**_____

**Date studies are due (mm/dd/yy):** _____

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

## Section D: Completed Studies

**Age/weight range of completed studies:**

**Min _____ kg_____ mo._____ yr._____ Tanner Stage_____**
**Max_____ kg_____ mo._____ yr._____ Tanner Stage_____**

**Comments:**

*If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**This page was completed by:**

**Edward Fromm**
***{See appended electronic signature page}***

_____
**Regulatory Project Manager**

**cc: NDA 21-648**
**HFD-960/ Grace Carmouze**

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.**

**(revised 12-22-03)**

## Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

**Indication #2:** Atrial Fibrillation

**Is there a full waiver for this indication (check one)?**

X **Yes: Please proceed to Section A.**

☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
**NOTE: More than one may apply**
**Please proceed to Section B, Section C, and/or Section D and complete as necessary.**

### Section A: Fully Waived Studies

**Reason(s) for full waiver:**

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
X **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Other:**_____

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

### Section B: Partially Waived Studies

**Age/weight range being partially waived:**

**Min** _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
**Max**_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

**Reason(s) for partial waiver:**

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Adult studies ready for approval**
☐ **Formulation needed**
☐ **Other:**_____

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

## Section C: Deferred Studies

**Age/weight range being deferred:**

**Min _____ kg_____ mo._____ yr._____ Tanner Stage_____**
**Max_____ kg_____ mo._____ yr._____ Tanner Stage_____**

**Reason(s) for deferral:**

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

**Date studies are due (mm/dd/yy): _____**

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

## Section D: Completed Studies

**Age/weight range of completed studies:**

**Min _____ kg_____ mo._____ yr._____ Tanner Stage_____**
**Max_____ kg_____ mo._____ yr._____ Tanner Stage_____**

**Comments:**

***If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.***

**This page was completed by:**

**Edward Fromm**
***{See appended electronic signature page}***

**Regulatory Project Manager**

**cc: NDA 21-648**
**HFD-960/ Grace Carmouze**

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.**

**(revised 10-14-03)**

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

/s/

Edward Fromm
8/27/04 08:06:32 AM

## 16.0 DEBARMENT CERTIFICATION

### 16.1 Roxane Laboratories

Certification of Compliance with Generic Drug Enforcement Act

In compliance with the Generic Drug Enforcement Act of 1992, Roxane Laboratories, Inc. hereby certifies that (1) we did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [section 306 (a) or (b)], in connection with this application, and (2) there are no convictions of the applicant and affiliated persons at Roxane Laboratories, Inc. responsible for the development or submission of the application.

Elizabeth Ernst
Associate Director, DRA-Multisource Products

Date 4/3/03

# NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

| Application Information | | | |
|---|---|---|---|
| NDA 21-648 | Grandfathered Drug-7S<br>Indication-treatment of Heart Failure | | |
| Drug: Digoxin Elixir USP, 0.05 mg/ml | | Applicant: Roxane Laboratories | |
| RPM: E. Fromm | | HFD-110 | Phone # 594-5332 |
| Application Type: ( ) 505(b)(1) **(X)** 505(b)(2) | | Reference Listed Drug (NDA #, Drug name): Lanoxin (digoxin) Tablets, 0.25 mg | |

| | |
|---|---|
| ❖ Application Classifications: | |
| • Review priority | (X ) Standard ( ) Priority |
| • Chem class (NDAs only) | 7S |
| • Other (e.g., orphan, OTC) | |
| ● User Fee Goal Dates | September 29, 2004 |
| ❖ Special programs (indicate all that apply) | **(X)** None<br>Subpart H<br>( ) 21 CFR 314.510 (accelerated approval)<br>( ) 21 CFR 314.520 (restricted distribution)<br>( ) Fast Track<br>( ) Rolling Review |
| ❖ User Fee Information | |
| • User Fee | (X ) Paid |
| • User Fee waiver | ( ) Small business<br>( ) Public health<br>( ) Barrier-to-Innovation<br>( ) Other |
| • User Fee exception | ( ) Orphan designation<br>( ) No-fee 505(b)(2)<br>( ) Other |
| ❖ Application Integrity Policy (AIP) | |
| • Applicant is on the AIP | ( ) Yes ( X) No |
| • This application is on the AIP | ( ) Yes ( X) No |
| • Exception for review (Center Director's memo) | |
| • OC clearance for approval | |
| ● Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent. | (X ) Verified |
| ❖ Patent | |
| • Information: Verify that patent information was submitted | (X ) Verified |
| • Patent certification [505(b)(2) applications]: Verify type of certifications submitted | 21 CFR 314.50(i)(1)(*i*)(A)<br>( ) I (x) II ( ) III ( ) IV<br><br>21 CFR 314.50(i)(1)<br>( ) (ii) ( ) (iii) |
| • For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice). | ( ) Verified<br>Not Applicable |

| | |
|---|---|
| ❖ Exclusivity (approvals only) | |
| • Exclusivity summary | X (will place in DFS when approved) |
| • Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!* | ( ) Yes, Application #_____<br>(X) No |
| ❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)* | PM-February 23, 2004, August 16, 2004 |
| [redacted] | |
| ❖ Actions | |
| • Proposed action | (X) AP ( ) TA ( ) AE ( ) NA |
| • Previous actions (specify type and date for each action taken) | AE-February 25, 2004 |
| • Status of advertising (approvals only) | (X) Materials requested in AP letter<br>( ) Reviewed for Subpart H |
| ❖ Public communications | |
| • Press Office notified of action (approval only) | (X) Yes ( ) Not applicable |
| • Indicate what types (if any) of information dissemination are anticipated | (X) None<br>( ) Press Release<br>( ) Talk Paper<br>( ) Dear Health Care Professional Letter |
| ❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable) | |
| • Division's proposed labeling (only if generated after latest applicant submission of labeling) | NA |
| • Most recent applicant-proposed labeling | NA |
| • Original applicant-proposed labeling | X |
| • Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)* | DMETS- January 23, 2004 |
| • Other relevant labeling (e.g., most recent 3 in class, class labeling) | X |
| ❖ Labels (immediate container & carton labels) | |
| • Division proposed (only if generated after latest applicant submission) | NA |
| • Applicant proposed | X |
| • Reviews | CMC-August 12, 2004, PM-August 16, 2004 |
| ❖ Post-marketing commitments | |
| • Agency request for post-marketing commitments | NA |
| • Documentation of discussions and/or agreements relating to post-marketing commitments | NA |
| ❖ Outgoing correspondence (i.e., letters, E-mails, faxes) | X |
| ❖ Memoranda and Telecons | X |
| ❖ Minutes of Meetings | |
| • EOP2 meeting (indicate date) | NA |
| • Pre-NDA meeting (indicate date) | NA |
| • Pre-Approval Safety Conference (indicate date; approvals only) | NA |
| • Other (Guidance) | March 27, 2002 |

| | |
|---|---|
| ❖ Advisory Committee Meeting | |
| • Date of Meeting | NA |
| • 48-hour alert | NA |
| ❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable) | June 29, 2004 |
| **Summary/Application Review** | |
| ❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)* | NA |
| **Clinical Information** | |
| ❖ Clinical review(s) *(indicate date for each review)* | December 11, 2003 |
| ❖ Microbiology (efficacy) review(s) *(indicate date for each review)* | NA |
| ● Safety Update review(s) *(indicate date or location if incorporated in another review)* | NA |
| ● Pediatric Page(separate page for each indication addressing status of all age groups) | X-Full Waiver |
| ❖ Statistical review(s) *(indicate date for each review)* | NA |
| ❖ Biopharmaceutical review(s) *(indicate date for each review)* | February 20, 2004 |
| ❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)* | NA |
| ❖ Clinical Inspection Review Summary (DSI) | |
| • Clinical studies | Not Requested |
| • Bioequivalence studies | December 9, 2003 |
| **CMC Information** | |
| ● CMC review(s) *(indicate date for each review)* | February 20 and August 12, 2004 |
| ❖ Environmental Assessment | |
| • Categorical Exclusion *(indicate review date)* | Yes-February 20, 2004 |
| • Review & FONSI *(indicate date of review)* | NA |
| • Review & Environmental Impact Statement *(indicate date of each review)* | NA |
| ● Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)* | NA |
| ● Facilities inspection (provide EER report) | Date completed: February 17, 2004<br>( X) Acceptable<br>( ) Withhold recommendation |
| ❖ Methods validation | ( ) Completed<br>(x ) Requested<br>( ) Not yet requested |
| **Nonclinical Pharm/Tox Information** | |
| ● Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)* | November 28, 2003 |
| ❖ Nonclinical inspection review summary | NA |
| ❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)* | NA |
| ● CAC/ECAC report | NA |

## Fromm, Edward J

**From:** Haffer, Andrew
**Sent:** Wednesday, April 21, 2004 10:50 AM
**To:** Fromm, Edward J
**Subject:** RE: Roxane Digoxin Labeling

Ed,

I took a quick look at the Roxane digoxin label and compared it with the [redacted] the current GSK Lanoxin PI. Sorry that this took a little longer then I had suggested.

Andy

++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++

I have a few general comments:

[redacted]

Some Specific Comments/concerns:

[redacted]

-----Original Message-----
**From:** Fromm, Edward J
**Sent:** Tuesday, April 20, 2004 9:38 AM
**To:** Haffer, Andrew
**Subject:** RE: Roxane Digoxin Labeling

**DIVISION OF CARDIO-RENAL DRUG PRODUCTS**
**FOOD AND DRUG ADMINISTRATION**

*US Mail address:*
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852



| | |
|---|---|
| **Transmitted to FAX Number:** | (614) 276-2470 |
| **Attention:** | Ms. Elizabeth Ernst |
| **Company Name:** | Roxane Laboratories |
| **Phone:** | (614) 272-4785 |
| **Subject:** | **Confirmation of Telecon w/FDA**<br>**March 31, 2004**<br>**NDA 21-648**<br>**Digoxin Elixir** |
| **Date:** | March 10, 2004 |
| **Pages including this sheet:** | **2** |
| **From:** | **Edward Fromm** |
| **Phone:** | **301-594-5332** |
| **Fax:** | **301-594-5494** |

Confirmation of Telecon

| | |
|---|---|
| Drug: | Digoxin Elixir<br>NDA 21-648 |
| Sponsor: | Roxane Laboratories |
| Subject: | Discussion of Labeling Issues |
| Date Requested:<br>Date Confirmation Faxed: | March 8, 2004<br>March 10, 2004 |
| Telecon Time & Date: | March 31, 2004<br>3:00-4:00 P.M. |

FDA Participants:

Douglas C. Throckmorton, M.D., HFD-110, Director, Division of Cardio-Renal Drug Products
Norman Stockbridge, M.D., Ph.D., HFD-110, Deputy Division Director
Abraham Karkowsky, M.D., Ph.D., HFD-110, Medical Team Leader
Mehul Desai, M.D., HFD-110, Medical Officer
Patrick Marroum, Ph.D., HFD-860, Team Leader, Clinical Pharmacology and Biopharmaceutics
Joga Gobburu, Ph.D., HFD-860, Team Leader, Pharmacometrics
Atul Bhattaram, Ph.D., HFD-860, Clinical Pharmacologist and Biopharmaceuticist
Stuart Zimmerman, Ph.D., HFD-810, Chemist
Edward Fromm, R.Ph., HFD-110, Regulatory Health Project Manager

**DIVISION OF CARDIO-RENAL DRUG PRODUCTS**
**FOOD AND DRUG ADMINISTRATION**

***US Mail address:***
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852



| | |
|---|---|
| **Transmitted to FAX Number:** | (614) 276-2470 |
| **Attention:** | Ms. Elizabeth Ernst |
| **Company Name:** | Roxane Laboratories |
| **Phone:** | (614) 272-4785 |
| **Subject:** | **Confirmation of Telecons w/FDA**<br>**March 8 & 18, 2004**<br>**NDA 21-648**<br>**Digoxin Elixir** |
| **Date:** | February 25, 2004 |
| **Pages including this sheet:** | **2** |
| **From:** | **Edward Fromm** |
| **Phone:** | **301-594-5332** |
| **Fax:** | **301-594-5494** |

Confirmation of Telecons

| | |
|---|---|
| Drug: | Digoxin Elixir<br>NDA 21-648 |
| Sponsor: | Roxane Laboratories |
| Subject: | Discussion of Labeling Issues |
| Date Requested:<br>Date Confirmation Faxed: | February 20, 2004<br>February 25, 2004 |
| Telecon Times & Date: | March 8, 2004, 3:00-4:00 P.M.<br>March 18, 2004, 3:00-4:00 P.M. |

FDA Participants:

Douglas C. Throckmorton, M.D., HFD-110, Director, Division of Cardio-Renal Drug Products
Norman Stockbridge, M.D., Ph.D., HFD-110, Deputy Division Director
Abraham Karkowsky, M.D., Ph.D., HFD-110, Medical Team Leader
Mehul Desai, M.D., HFD-110, Medical Officer
Patrick Marroum, Ph.D., HFD-860, Team Leader, Clinical Pharmacology and Biopharmaceutics
Joga Gobburu, Ph.D., HFD-860, Team Leader, Pharmacometrics
Atul Bhattaram, Ph.D., HFD-860, Clinical Pharmacologist and Biopharmaceuticist
Stuart Zimmerman, Ph.D., HFD-810, Chemist
Edward Fromm, R.Ph., HFD-110, Regulatory Health Project Manager

RHPM NDA Overview
February 23, 2004

| | |
|---|---|
| **NDA 21-648** | Digoxin Elixir USP, 0.05 mg/ml |
| **Sponsor:** | Roxane Laboratories |
| **Classification:** | 7S |
| **Indication:** | Treatment of Heart Failure |
| **Date of Application:** | April 10, 2003 |
| **Date of Receipt:** | April 25, 2003 (application originally received April 14, 2003, but user fee was not fully paid and received in entirety until April 25, 2003). |
| **10-Month Goal Date:** | February 25, 2004 |

**Background**

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 proposed a rule in the Federal Register on November 24, 2000, that would require approved applications for all digoxin products, including digoxin elixir.

Roxane filed an ANDA Suitability Petition to the Agency in October 2001, asking that digoxin elixir be considered for an ANDA in relation to the reference listed drug (RLD) product (Lanoxin Tablets). The Agency, however, denied their request in December of 2001 because pediatric studies would be needed.

The firm met with the Division on March 27, 2002, to discuss the requirements for filing a successful 505(b)(2) application for digoxin elixir, 0.05 mg/mL. With the suspension of the Pediatric Rule, the firm again filed a Suitability Petition, which the Office of Generic Drugs indicated that they would deny because of the need for extensive revisions of the labeling.

Roxane filed a 505(b)(2) application on April 10, 2003, that unfortunately, did not contain the full user fee required for this application. The full fee was received by the Agency on April 25, 2003 and therefore this becomes the "official" receipt date for the application.

Meetings

| | |
|---|---|
| June 11, 2003 | Filing Meeting |
| March 27, 2002 | Clinical Guidance |

**Review**

Medical

| | |
|---|---|
| Division Director: | Douglas C. Throckmorton, M.D |
| Conclusion: | Approvable, subject to agreement on labeling |

Secondary Medical: Not applicable

Medical Reviewers: Mehul Desai, M.D.
Conclusion: Dr. Desai notes in his December 11, 2003 review, that the pediatric dosing instructions for the current elixir are not identical to those in the approved tablet (NDA 20-405) labeling. Moreover, the basis and rationale for the dosing instructions in the tablet labeling are not clear. The applicant submitted published literature to support their proposed changes to the labeling, but he opines that the "majority of studies in the literature are uncontrolled, unblinded studies looking at endpoints that are not clinically meaningful or are retrospective studies."

Dr. Desai outlines three possible options with regard to the safety and efficacy information in the current labeling for the product:

(1). Leave the current labeling as is. He rejects this possibility as there is little evidence from the published literature that supports the current labeling in a drug that clearly has a narrow therapeutic index.

(2). Remove the dosing instructions for the pediatric population and state in the labeling that there are no adequate data to support efficacy in this population. Thus, the labeling would only reflect the use in adult patients who have trouble swallowing. Dr. Desai worries, however, that physicians would still prescribe the elixir for children without sound dosing guidelines.

(3). Have the sponsor conduct adequate and well-controlled trials that conform to the standards used by the Agency today. Potential difficulties with this option are that parents may be hesitant to enroll children in a placebo-controlled trial. In addition, atrial fibrillation is not common in children so enrolling sufficient patients would be problematic for this indication. In heart failure, the pathophysiology of this disease is different in adults compared to children, so extrapolation of data from a pharmacokinetic/pharmacodynamic study in children to data with adults would be difficult.

Labeling: None, see comments above.

Statistical Not applicable

Biopharmaceutics
Reviewer: Atul Bhattaram, Ph.D.
Conclusion: Approvable, Dr. Bhattaram notes in his February 20, 2003 review that the elixir formulation has been found to be bioequivalent to the RLD, Lanoxin Tablets, under fasted and fed conditions in healthy volunteers.

Dr. Bhattaram notes that the sponsor proposed a dosing scheme for pediatrics less than 2 years of age based solely on pharmacokinetics. However, he notes that the "target population is not well defined and no reasoning has been provided by the sponsor why the target concentration in adults and pediatrics should be identical." Dr. Bhattaram suggests that dosing instructions not be included for children < 2 years of age until the

applicant conducts a trial using relevant biomarkers in patients < 2 years of age and why these biomarkers are relevant. In addition, he encouraged the sponsor to develop and validate a digoxin-specific assay for use in neonates and infants.

A complete update of the Drug-Drug interaction section was done by the Biopharmaceutic's team and is currently being discussed with the applicant.

Labeling: See Dr. Bhattaram's February 20, 2004 review for suggested changes to the **CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS** and **DOSAGE AND ADMINISTRATION** sections of the labeling.

Chemistry

Reviewer: Stuart Zimmerman, Ph.D.

Conclusion: Dr. Zimmerman stated in his February 20, 2004 review, that the submission 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."

Labeling: Drs. Zimmerman and Srinivasachar suggested changes to the **DESCRIPTION, HOW SUPPLIED,** and carton and container labeling.

CGMP Inspections: Acceptable, February 17, 2004

Methods Validation: Pending

Environmental Assessment: Acceptable (Categorical Exclusion)

Pharmacology

Reviewer: Belay Tesfamariam, Ph.D.

Conclusion: Approvable

Labeling: None

Safety Update: There has not been a Safety Update since the original NDA submission of April 10, 2003.

Patent info: acceptable

DSI Audits: A bioequivalence audit was conducted by DSI on —— —— from September 29 to October 3, 2003. They recommended that "due to unjustified reassay for PK reasons, the original rather than PK repeat results from Studies DIGO-01 and DIGO-02 should be used for the bioequivalence determination."

DDMAC: Not applicable

Debarment Certification: included in package

Pediatrics: A full waiver will be granted to this application as pediatric dosing information will be detailed in the labeling.

DMETS Review: In a review dated January 23, 2004, DMETS recommended changes to the packaging labels as well as to the **DOSAGE AND ADMINISTRATION** section of the labeling.

Comments: A telecon was held with the sponsor on February 20, 2004 to discuss the status of the application. Dr. Throckmorton said that an approvable letter would be issued by the February 25, 2004 goal date, but would not include marked-up draft labeling as there are substantive issues yet to be resolved. These include the following:

1. Dosing instructions for children under 2 years of age.
2. Drug-Drug Interactions section of the labeling.
3. Indications section-probably only an indication in heart failure, similar to adults for this indication.
4. [redacted]
5. Changes in the labeling, carton and container labels suggested by DMETS. Roxane has agreed to many of these changes, but there are some not yet resolved.
6. CMC deficiencies related to impurity issues and specifications for the drug substance and product. There are also some minor labeling issues to be resolved.

I will draft an approvable letter for Dr. Throckmorton's signature.

Edward J. Fromm
Regulatory Health Project Manager

dr-ef-2-23-04

**RHPM Approval/Labeling Review**

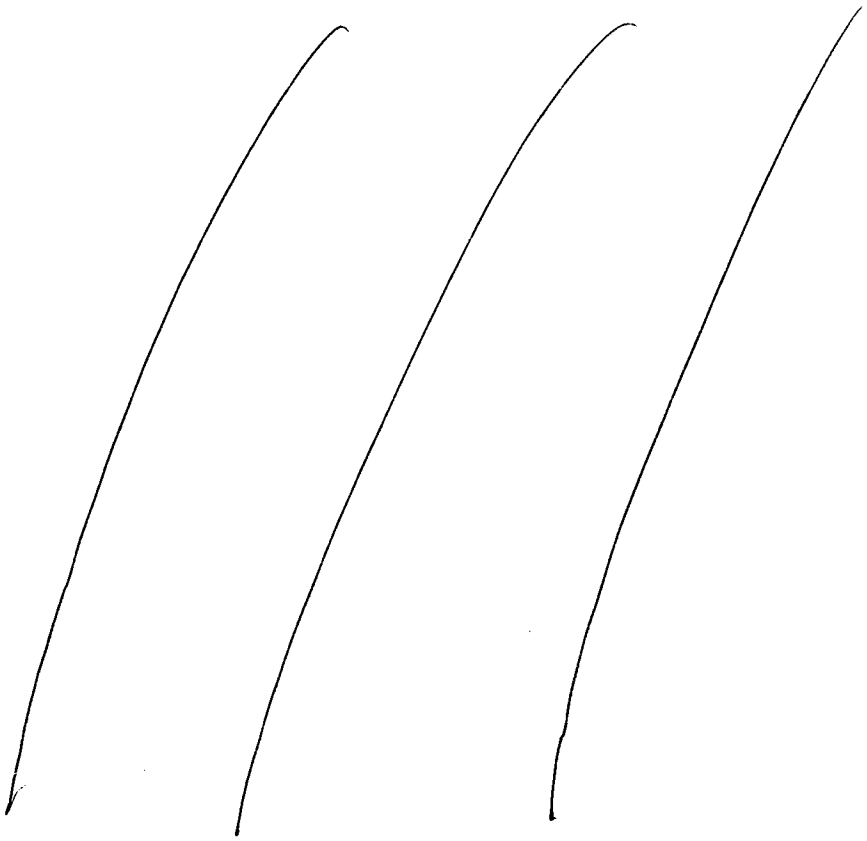
Application: NDA 21-648
Digoxin Elixir USP, 0.05 mg/mL

Applicant: Roxane Laboratories

| | |
|---|---|
| Date of FPL: | June 25, 2004 |
| Receipt of FPL: | June 28, 2004 |
| Date of Major (Chem) Amendment: | July 28, 2004 |
| Receipt of Major (Chem) Amendment: | July 29, 2004 |
| 60 day due date: | September 29, 2004 |

**Background:** An approvable letter was issued for NDA 21-648 on February 25, 2004. At the time the approvable letter was issued, the following issues still had to be resolved:

1) Labeling



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✓ Draft Labeling

_____ Deliberative Process

**Minutes of a Meeting between Roxane Laboratories and the FDA**

Date: January 26, 2004

Applications: Digoxin Elixir

Applicant: Roxane Laboratories

Subject: 505(b)(2) NDA Submission and Use of the Elixir in Children

FDA Participants:

Robert Temple, M.D., HFD-101, Director, Officer of Drug Evaluation 1 (via phone)
Douglas C. Throckmorton, M.D., HFD-110, Director, Division of Cardio-Renal Drug Products
Abraham Karkowsky, M.D., Ph.D., HFD-110, Medical Team Leader
Mehul Desai, M.D., HFD-110, Medical Officer
Patrick Marroum, Ph.D., HFD-860, Team Leader, Clinical Pharmacology and Biopharmaceutics
Atul Bhattaram, Ph.D., HFD-860, Clinical Pharmacologist and Biopharmaceuticist
Edward Fromm, HFD-110, Regulatory Health Project Manager

Roxane Laboratories

Elizabeth A. Ernst, Associate Director, Regulatory Affairs, DRA-Multisource Products
Gregory Hicks, Pharm.D., Clinical Research Manager , DRA-Multisource Products
Randall S. Wilson, Vice President, Scientific Affairs

**Background**

NDA 21-648 for Digoxin Elixir was submitted on April 10, 2003 and officially received by the Agency on April 25, 2003. This 505(b)(2) application was submitted in response to a Federal Register notice that went into effect on July 26, 2002; the notice requires current manufacturers of digoxin elixir to obtain approved applications of their products by June 28, 2004 or face regulatory action. The drug is indicated for the treatment of heart failure and control of atrial fibrillation.

The Division requested a meeting with the applicant to discuss the clinical utility of digoxin in children, either for rate control or for heart failure.

**Meeting**

Dr. Throckmorton opened the meeting by noting that we have reviewed the data for use of digoxin elixir in children as it is currently being indicated, and we still have concerns about the suggested use of digoxin in CHF and atrial fibrillation. It is important to understand how the drug is currently being used in children and whether these uses can be linked to the adult data supporting the indications for CHF and atrial fibrillation. Dosing instructions would then need to be written, a task especially difficult for children under the age of 2 years old, given the paucity of data in this population. Roxane replied that digoxin is still being used in children for heart failure and rate control, but agreed that controlled-trial data is lacking. They presented slides detailing the history of digoxin elixir use and proposed revision of the labeling.

Heart Failure

Roxane consultants said that heart failure etiology and pathophysiology is often different in children and adults. Most heart failure in children is due to structural abnormalities in the heart, although there are a small percentage of children that have left ventricular contractility problems. This decrease in contractility in children can result from volume overload, ischemic heart disease, cardiomyopathy, and viral illnesses. Dr. Throckmorton said this subset of children with heart failure seemed similar to adult patients and asked what percentage of children with heart failure are in this subset. Roxane consultants said they believed that 10% was a reasonable estimate, although the rate increases as children progress in age, as heart failure following surgical repair of congenital heart defects occurs more frequently in older children. Dr. Throckmorton suggested that if we knew that digoxin improved outcomes in adults (based on DIG) and also had effects on a biomarker for ventricular function in both adults and children, this could support the use of digoxin in that pediatric population, even without clinical outcome data.

If that were to be shown, the next issue would be to describe the dose-response effects of digoxin on contractility in children, to provide adequate dose information for the label. Dr. Throckmorton asked what dose or serum concentrations of digoxin are used to treat contractility problems in children. Roxane consultants replied that a 0.5 to 2.0 ng/ml range is generally used for children, but that titration of digoxin is generally done by clinical effect and ECG readings. Digoxin levels are not routinely drawn in infants as there are frequently false positives thought to result from endogenous substances in the blood, which cross-react in the assay. Roxane consultants said that a dosing range of 10 mcg/kg/day is generally effective for these patients. Dr. Throckmorton said that a Japanese paper supports a 10-15 mcg/kg/day range in patients under 2 years of age, but noted that the applicant's revised dosing table [redacted] He also noted that impaired renal function occurs in this age group and asked that the sponsor submit arguments on why and how often it is used in this population. Dr. Throckmorton encouraged Roxane and the members of the Clinical Pharmacology and Biopharmaceutics team to talk about correlating adult serum concentrations and dosing of digoxin elixir with that of children, based on the most recent data available. It may not be possible to formulate dosing instructions for children less than 2 years of age; [redacted] Dr. Throckmorton also noted that there are safety concerns with the current [redacted] and the Division would likely remove this from the labeling. Roxane agreed that the [redacted] should be removed from the labeling.

Atrial Fibrillation

Dr. Throckmorton asked if the applicant was able to find controlled trial data linking the adult data for atrial fibrillation and children. Roxane consultants replied that their search to date has not located controlled data to support its use in children for this indication. They noted, however, that digoxin is used clinically to treat children with atrial tachyarrythmias (atrial flutter and fibrillation) and that it is effective in this regard. Digoxin is thought to act by decreasing AV node conduction by at least 2 different mechanisms.

Dr. Temple asked if it was possible to describe the concentration-dose relationship between adults and children in atrial fibrillation. Roxane said that they did not have data to support such a relationship, but noted that the effects of digoxin on the AV node were identical to those seen in adults. Dr. Throckmorton said that showing that digoxin lowered the ventricular response rate would not be enough by itself; outcome data linking adult and children with atrial fibrillation would be needed, given the adult indications. Roxane consultants replied that verapamil appeared to have been approved based on rate control alone, with little or no outcome data. They also noted that a recent paper noted that verapamil appeared to be not effective in children with atrial tachyarrythmias, although this was not due to heart block as originally thought, but rather problems associated with ventricular contractililty caused by the drug. Dr. Throckmorton said he was not familiar with the data supporting verapamil's approval but would review it and the paper describing the safety concern in children.

Dr. Throckmorton said that absent outcome data linking atrial fibrillation in adults with children, an indication in heart failure for children and adults was more plausible [redacted]

Drug-Drug Interaction Update

Dr. Throckmorton noted that the drug-drug interaction section of the labeling had been thoroughly updated by the Biopharmaceutic's team. Roxane said they welcomed this update and asked if the Division would try to make the labeling consistent for other digoxin products. Dr. Throckmorton replied that he recognizes the importance of consistency in labeling and will try to do this when possible. The Division will get these proposed changes to the sponsor as soon as possible for their review.

ODS

Dr. Throckmorton noted that the Office of Drug Safety had reviewed the labeling, including the carton and container labels for NDA 21-648, and had recommended revisions to certain parts of the labeling. We will forward their comments to you and ask that you reply formally in a submission to the Division.

**Conclusion**

Both the FDA and Roxane agreed that an indication could be crafted for digoxin elixir in children who have heart failure due to contractility problems in the left ventricle. Dr. Throckmorton asked that the applicant supply further information about this subset of heart failure in children, including concentration-response data for effects on contractility that could be linked to the adult population with heart failure. He encouraged Roxane to talk with members of the Biopharmaceutics team to formulate dosing guidelines for this subset of children with heart failure, particularly those less than 2 years of age.

Dr. Throckmorton said that an indication for digoxin elixir in children for atrial fibrillation is less likely, based on what he knows at this time, unless the applicant can furnish outcome data linking adult and children with atrial fibrillation.

The Drug-Drug Interactions section of the labeling has been extensively updated by the Biopharmaceutics team and the Division would discuss these and other revisions in the labeling prior to the action date for the application. Mr. Fromm will contact the sponsor to setup telecons to discuss these issues.

Minutes Preparation:

Edward Fromm

Concurrence Chair:

Robert Temple, M.D.

ef/dr-2/04/04-2/10/04-2/19-04

Rd: AKarkowsky-02-05-04
PMarrouom-02/04/04
ABhattaram-02/04/04
DThrockmorton-02/05/04

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

/s/

Robert Temple
2/23/04 06:53:00 PM

**CONSULTATION RESPONSE**
**Division of Medication Errors and Technical Support**
**Office of Drug Safety**
**(DMETS; HFD-420)**

| **DATE RECEIVED:** JUL-24-2003 | **DESIRED COMPLETION DATE:** SEPT-24-2003<br>**PDUFA DATE:** FEB-25-2004 | **ODS CONSULT #:**<br>03-0215 |
|---|---|---|

**TO:** Douglas Throckmorton, MD
Director, Division of Cardio-Renal Drug Products
HFD-110

**THROUGH:** Edward Fromm
Project Manager, Division of Cardio-Renal Drug Products
HFD-110

| **PRODUCT NAME:**<br>Digoxin Elixir, USP<br>0.05 mg/mL<br><br>**NDA #** 21-648 | **NDA SPONSOR:**<br>Roxane Laboratories, Inc. |
|---|---|

**SAFETY EVALUATOR:** Marci Lee, PharmD

**RECOMMENDATIONS:** DMETS recommends the labeling revisions outlined in Section III of this review to promote the safe use of this product.


Carol Holquist, RPh
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax (301) 443-9664

Jerry Phillips, RPh
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

**Division of Medication Errors and Technical Support**
**Office of Drug Safety**
**HFD-420; Parklawn Building Room 6-34**
**Center for Drug Evaluation and Research**

## LABELING AND PACKAGING REVIEW

**DATE OF REVIEW:** October 2, 2003

**NDA NUMBER:** 21-648

**NAME OF DRUG:** Digoxin Elixir, USP 0.05 mg/mL

**NDA SPONSOR:** Roxane Laboratories, Inc.

## I. INTRODUCTION

This consult was written in response to a request from the Division of Cardio-Renal Drug Products (HFD-110) for an assessment of the proposed container labels, carton and package insert labeling for Digoxin Elixir, USP for identification of possible interventions in an effort to minimize potential user error with this medication.

A Federal Register Notice was published on November 24, 2000 stating that manufacturers who wish to begin or continue marketing digoxin products for oral use must submit new drug applications (NDA's) or abbreviated new drug applications (ANDA's). This notice addresses digoxin tablets and elixir.

Roxane currently markets digoxin elixir and has submitted this NDA in response to the Federal Register Notice.

PRODUCT INFORMATION

Digoxin Elixir is currently marketed by Roxane in the United States. Digoxin Elixir is available as 2.5 mL unit dose cup containing 0.125 mg digoxin, 5 mL unit dose cup containing 0.25 mg digoxin, and 60 mL bottles containing 0.05 mg/mL of digoxin (with a calibrated dropper).

Digoxin elixir is indicated for the treatment of mild to moderate heart failure, and the control of ventricular response rate in patients with chronic atrial fibrillation.

Recommended dosages of digoxin may require considerable modification because of individual sensitivity of the patient to the drug. Therefore, in selecting the dose of digoxin such factors like, ideal body weight, renal function, age, concomitant disease state, current medications, must be considered.

The recommended [redacted]

Digoxin is generally administered once daily.

## II. RISK ASSESSMENT

### A. ADVERSE EVENT REPORTING SYSTEM (AERS) and DRUG QUALITY REPORTING SYSTEM SEARCHES

Digoxin Elixir has been marketed since 1934, therefore DMETS conducted a search of the FDA Adverse Event Reporting System (AERS) and the Drug Quality Reporting System. The searches yielded eight AERS and 32 DQRS medication error cases. Seven of the eight AERS cases involved actual errors. An actual error is defined as an error that actually occurred that may or may not have caused harm to the patient. The eight cases involve look-alike labels and labeling (5), look-alike names (1), dropper concerns (1), and inactives not listed on the labels and labeling (1). The remaining AERS case was a potential error in which a nurse noted that the labels and labeling of Digoxin Elixir and Furosemide Elixir looked identical.

Eighteen of the thirty-two DQRS cases will not be discussed because they involved manufacturing or product problems (e.g., missing lot numbers, color changes, etc). Three additional cases will also not be discussed because they involve labeling issues that the sponsor has already addressed (e.g., added concentration to the labels and labeling). The remaining eleven cases are distributed as follows: look-alike labels and labeling (4), calculation errors/confusion between micrograms and milligrams (4), wrong strength given [0.25 mg given instead of 0.125 mg or vice versa] (3), dropper concerns (2), and administration via an incorrect route (1). See Appendix A for a listing of all of the report narratives.

### B. SAFETY EVALUATOR RISK ASSESSMENT

Following a root cause analysis of the medication error cases identified in AERS and DQRS, the cases can be categorized into five areas of concern.

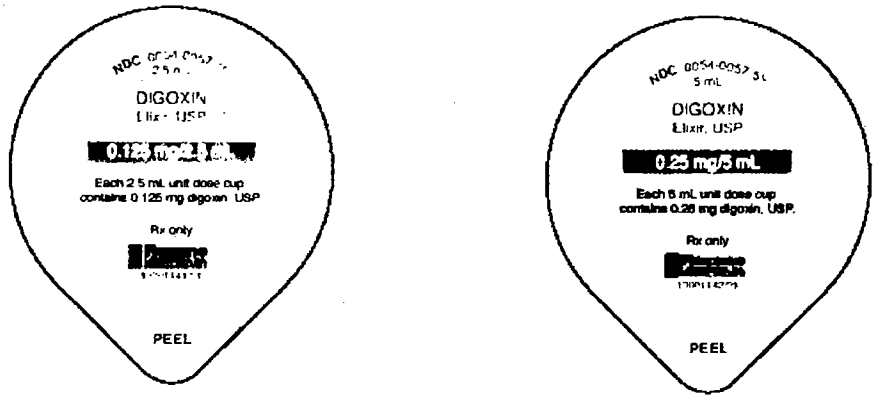
1. Look-alike Packaging with Furosemide

   a. There were seven cases of potential for confusion between Digoxin Elixir and Furosemide Oral Solution. Roxane's product line includes both digoxin elixir and furosemide oral solution (see figure 1 on page 4). The factors that increase the risk for confusion include the shared 60 mL bottle size with droppers, the similarity in the NDC numbers (0054-3192-46 and 0054-3294-46), similar size carton, and can be stored near each other on the shelf. The coloring of the labels and labeling are similar, a mixture of browns and tans found which is found on all Roxane packaging. A representative sample of this type of medication error follows.

> A patient received doses of digoxin (15 mcg) daily instead of furosemide for three consecutive days, in error. He experienced respiratory arrest and cyanosis. He was resuscitated and will require surgery. It should be noted that the patient was already taking digoxin as a concomitant medication. The product was dispensed in a manufacturer's bottle labeled Digoxin, NDC 0054-3192-48 Lot 981993A and the description of the product matches that of Digoxin Elixir. The pharmacy had labeled the product "Furosemide 10 mg/mL".

**FIGURE 1.**

b. In addition, the potential for confusion between digoxin and furosemide exists for inpatient settings because both are available from Roxane as **5 mL patient cups** (see below). No AERS cases, were identified. The DQRS search identified three reports where one strength of Lanoxin was ordered but the other strength dispensed. However, DMETS cannot verify whether these cases involve the elixir formulation or tablet formulation. Despite this, due to the similar appearance one can perceive the same confusion among the unit dose cups.




2. Look-alike Similarity with Doxepin

Prescriptions for Digoxin Elixir may have look-alike similarity to Doxepin Oral Concentrate. The names begin and end with the same letters (D and i,n). Although, these names may look-alike when scripted, similar labels and labeling may also contribute to the potential for medication errors (see above).

> A pharmacist dispensed Digoxin instead of Doxepin. In this scenario, store #1 was out of "Digoxin" and they called store #2 to locate the product. The patient received "Digoxin" from store #2 in error. The patient discovered the error when he was at home and did not take any doses.

3. Calculation Errors and Confusion Between Micrograms and Milligrams

There have been calculation errors and errors associated with conversion from micrograms and milligrams. The labels and labeling for Digoxin contain both micrograms and milligrams, which may increase the potential for confusion.

Additionally, when prescribing for adults the doses are usually ordered in milligrams whereas orders for pediatric patients are usually prescribed in micrograms. These types of errors occur by both the prescribers and dispensers. See the following examples.

> Dosing calculation errors have resulted in a patient receiving 12.5 mL instead of 1.25 mL, in error.
>
> An order was written for Lanoxin 0.625 mg instead of Lanoxin 0.0625 mg, in error. The drug was administered from floor stock while the pharmacy was closed. The patient expired likely due to digoxin toxicity.
>
> An infant received 0.17 mg instead of 0.017 mg, in error, due to misplacement of a decimal point during calculation by a pharmacist.

4. Oral Syringe (Dropper) Dosing Confusion and Concerns

Although, DMETS did not have an actual dropper to evaluate, there appears to be confusion when using the oral syringe that is supplied with Digoxin Elixir. Digoxin is generally prescribed in micrograms or milligrams; however, the oral syringe is calibrated in milliliters. This may be a problem in scenarios where the strength is indicated on the Medication Administration Record (MAR) in lieu of the volume (i.e., milliliters). For example, in hospitals and long-term care facilities the MAR will likely list 'Digoxin 0.125 mg' and not 'Digoxin 2.5 mL.' Thus increments of milliliters may require the user to calculate the dose resulting in possible calculation errors. Additionally, if the milliliter amount to be administered is not a part of the MAR, each time the medication is administered by a different person the dose has to be recalculated, increasing the potential of errors. See the following report.

> One report describes how the product is commonly used in long term care facilities and the dropper scale has contributed to confusion for nurses intending to administer 2.5 mL but measure .25 mL in error. The reporter suggests changing the scale to read milligrams instead of milliliters.

DMETS notes that increments of milliliters may be more beneficial in the outpatient scenario; however, it appears that errors may occur in this scenario as well. The oral syringe is currently calibrated in 0.1 mL increments. However, the numbers do not utilize a leading zero, which may lead some users to misinterpret the increments. See the report below.

> A patient was hospitalized after a parent gave 0.2 milliliters instead of 2 milliliters of digoxin for several weeks in error. One of the contributing factors in this error scenario was the scale on the dosing syringe, which contained no leading zero before the ".2 cc" mark.

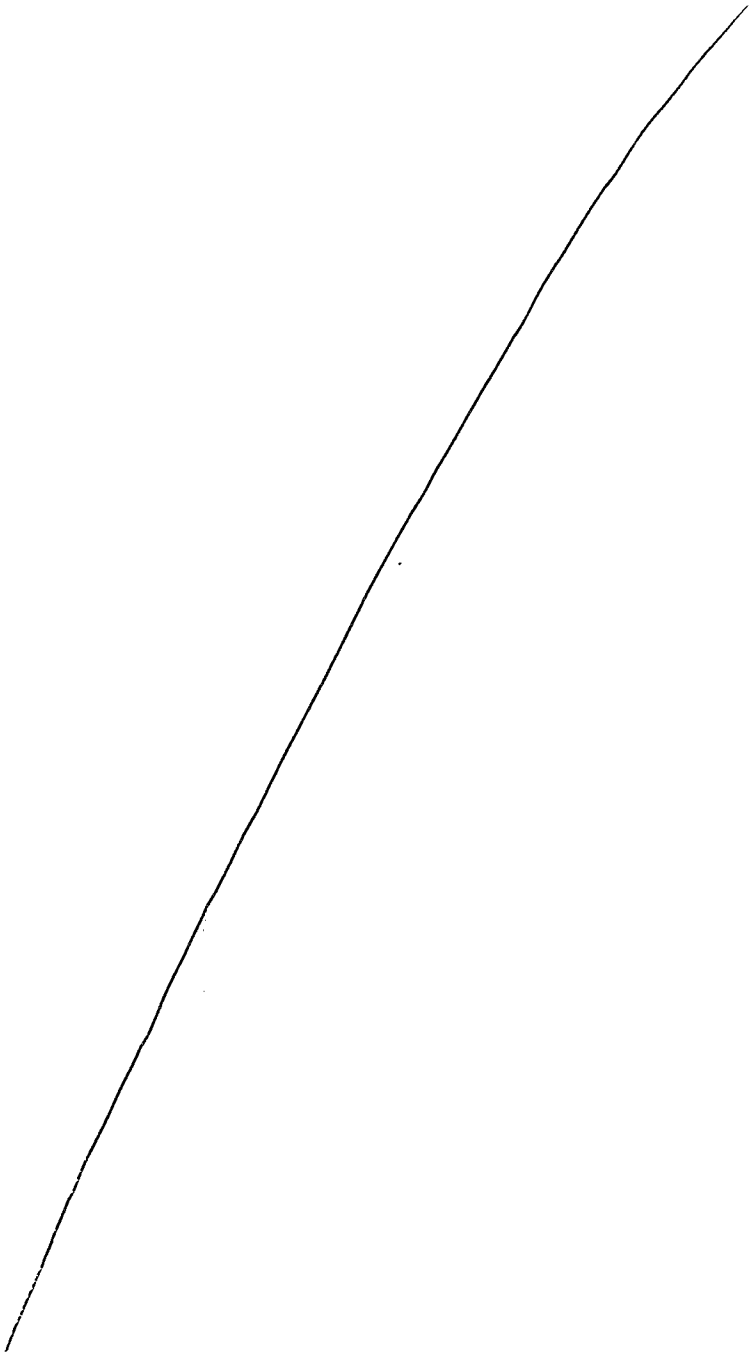
5. Inactive ingredient Issues

It does not appear that the inactive ingredients are listed on the container labels or carton labeling of Digoxin. DMETS notes that this information is not required by the Code of Federal Regulations. However, if space permits this may be useful information, especially if a patient has allergies or is sensitive to any of the inactive ingredients. An example of this type of report follows.

> A patient with a history of allergy to food dye and preservatives experienced an adverse reaction after taking digoxin elixir. The inactive ingredients listed on the bottle included only

10% alcohol and methyl paraben. The patient contacted the manufacturer and found it also contained propylene glycol, FD&C yellow #10, green #5 and some other things.

## III. LABELING, PACKAGING AND SAFETY RELATED ISSUES



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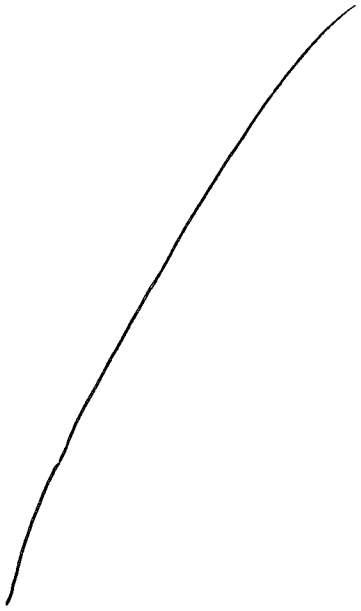
2 Page(s) Withheld

_____ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process



## IV. RECOMMENDATIONS

DMETS recommends the labeling revisions outlined in Section III to promote the safe use of this product.

DMETS would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam at 301-827-3242.

Marci Lee, PharmD
Safety Evaluator
Office of Drug Safety (DMETS)

Concur:

Denise Toyer, PharmD
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

# APPENDIX A

Post-Marketing Reports involving Digoxin Elixir from the AERS database

| ISR NUMBER<br>EVENT DATE<br>LOCATION<br>ACTUAL OR<br>POTENTIAL<br>OUTCOME | Summary of Digoxin Elixir Errors |
|---|---|
| 3489618<br>—<br>Huntsville, TX<br>Actual error<br>Patient experienced adverse events. | Urethra burned after three doses, bladder spasms after 10 doses, passed a fair amount of bright red blood from the bladder after the 16th dose on —. Bladder infection.<br>FULL DISCLOSURE OF CONTENTS WERE NOT LISTED ON THE BOTTLE, ONLY 10% alcohol, methyl paraben. Called Glaxo Wellcome, also contained propylene glycol, FD&C yellow #10, green #5 plus some other things. I NEVER WOULD HAVE TAKEN IT HAD I known what was in it. Relevant History: Highly allergic to food dyes and preservatives. |
| 3378906-4<br>Actual error<br>Patient was resuscitated and will require surgery. | An infant with congenital heart problem was hospitalized in Mexico. Furosemide Oral solution was ordered at a dose of 3 mg (0.3 mL) q24h but it was not available in Mexico. The drug was obtained from a pharmacy in the US and given to the infant in the hospital. He received doses on three consecutive days and experienced respiratory arrest and cyanosis. He was resuscitated and will require surgery.<br><br>The reporter said the product was dispensed in a manufacturer's bottle labeled Digoxin, NDC 0054-3192-48 Lot 981993A and the description of the product matches that of Digoxin Elixir. The pharmacy had labeled the product "Furosemide 10 mg/mL". Therefore the dose of digoxin potentially administered was 0.015 mg (15 mcg) daily for three days.<br><br>It should be noted that the patient was already taking digoxin as a concomitant medication.<br><br>A sample of the product was returned to Roxane for examination via visual appearance, it matches Digoxin Elixir. |
| 3518179-2<br>NOV-9-1999<br>Unknown location<br>Actual error<br>Patient required monitoring. | Expired drug was dispensed dated Sept 1999. Technician pulls medication from rx shelf. Verified by RPh. Usually any expired medication are discovered at verification, but for this particular instance the medicine's date was not discovered.<br><br>Error was detected by patient's mother 2 months later. The medication was used by the patient.<br><br>Digoxin level was monitored and the response was not optimal. |
| 4115740-1<br>—<br>Actual error<br>Patient was hospitalized.<br><br>Also in DQRS<br>U 000386 | Patient being discharged. Pharmacist instructed parent to give "2 cc" of Digoxin. Pharmacist did not remove dosing syringe provided with medication to show parent what "2 cc" is. Parent gave 0.2 cc for several weeks as syringe is labeled as ".1 cc", ".2 cc", etc. with no leading zero. The lack of leading zero was confusing to the parent.<br><br>We do not use the dosing syringe provided with the Lanoxin bottle. We use Baxa oral syringes and adapta-caps. The dose is marked on the syringe with a dose marker sticker. The Glaxo syringe WOULD BE |

| | |
|---|---|
| | safer if it said 0.1 cc and 0.2 cc, etc. We have also educated our staff about this error and the importance of effective counseling. |
| 3484926-1<br>Reported to ISMP<br>MAR-20-2000<br>Unknown location<br>Actual error<br>Patient did not take any doses of the wrong drug. | Pharmacist dispensed Digoxin instead of Doxepin when store #1 was out of "Digoxin" they called store #2 and the patient received "Digoxin" from store #2 in error.<br><br>Patient discovered error when he was at home and did not take any doses. |
| 3684086-8<br>Reported to ISMP<br><br>Actual error<br>Prolonged hospitalization<br>Temporary patient harm | An order for digoxin elixir, which is floor stock as 60 mL bottle was misinterpreted by a nurse as 60 mL of doxepin elixir, which was administered.<br><br>The patient has been in the ICU ever since the incident.<br><br>When the nurse attempted to give the "digoxin" elixir, the nurse scanned the bar code on the bottle, which generated an error window on the laptop "Drug not on profile or has already been given". But instead of resolving the problem, the fact that the nurse scanned the wrong medication bottle, the system allows the nurse to obtain the drug number and enter it manually... It is easy to simply type in the numbers that are designed to protect the integrity of the system.<br><br>Doxepin 10 mg/mL as 120 mL bottle.<br>Digoxin 0.05 mg/mL as 60 mL bottle (Roxane) |
| 4117283-8<br>Report date<br>APR-15-1999<br>Potential error | A nurse had been preparing to administer a dose of Furosemide solution, only to realize she had difficulty differentiating the Digoxin Elixir from the Furosemide at first glance. Three aspects of the packaging are similar for these two products: Outer box as well as front and side of the bottles. The coloring is similar as well, a mixture of brown and tans found on all Roxane packaging. |
| 3760262<br><br>Unknown location<br>Actual error<br>Hospitalization after patient received wrong medicine for ten days. | A pharmacist dispensed Lasix Oral Solution to a seven-month-old patient on a prescription calling for 60 mL Lanoxin Pediatric Elixir. The pharmacy's computer generated prescription label affixed to the manufacturer's box reflected that "Lanoxin Els Ped" had been dispensed. The manufacturer's box was labeled as "Lasix Oral Solution" The patient's mother administered the incorrect medicine to the patient for ten days.<br><br>Lasix oral solution (Aventis)<br>Lanoxin Elixir (Glaxo SmithKline) 60 mL |

Various ISR's listed with no specific info in narrative from annual report of the am assn of poison control centers toxic exposure surveillance system Am J Emer Med 2002;20(5)3.1-452.

# APPENDIX B

## NCCMERP Dangerous Abbreviations – Partial List

http://www.nccmerp.org/dangerousAbbrev.htmL

### Dangerous Abbreviations

| Abbreviation | Intended meaning | Common Error |
|---|---|---|
| U | Units | Mistaken as a zero or a four (4) resulting in overdose. Also mistaken for "cc" (cubic centimeters) when poorly written. |
| µg | Micrograms | Mistaken for "mg" (milligrams) resulting in a one thousand-fold overdose. |

APPEARS THIS WAY
ON ORIGINAL

# APPENDIX C

DQRS Searching for Lanoxin, Digoxin (elixir) January 15, 2004

DIGOXIN

040286 16-JUL-92 Infant received 0.17 mg instead of **0.017 mg** due to misplacement of decimal point during calculation by a pharmacist.

041652 12-OCT-95 Digoxin 0.25 mg ordered, dispensed, and administered. **Not ordered in mcg/kg**. No other information is available.

042044 13-AUG-96 A Baxa oral syringe (clear plastic) was used to **inject Digoxin Elixir** 0.125 mg intravenously. The patient had a nasogastric tube with a two-way stopcock attached to an infusion so that it could run constantly or oral liquids could be given with a syringe. An oral syringe was sent but there was no "oral" sticker on the plunger. The prescription label contained the name of the patient, bed number, drug name and "po". The nurse prepared the clear Baxa oral syringe from the prescription with an adapter for the stopcock. The nurse who prepared the medication had to leave the floor so she asked another nurse present to give the Digoxin. She did not mention that it was via tube. The second nurse, who had given Digoxin IV in the past, thought it was supposed to be given intravenously and gave the green elixir via a butterfly.
Recommendation from reporter to USPC to prevent recurrence:
The hospital will now use amber oral syringes.

080087 24-JAN-94 A pharmacist erroneously entered into a computerized prescription recording system a prescription for **17 micrograms** of Digoxin as 0.17 mg, to be dispensed to an infant in a future medication.

DIGOXIN ELIXER PEDIATRIC D 100540 16-FEB-89 PRODUCT NOT LISTED IN APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUA TIONS, 8TH ED. OR SUPPLEMENTS

DIGOXIN ELIXIR D 103630 02-AUG-90 This product has lot numbers and expiration dates missing on 2/3 of the package.

M 128601 07-FEB-00 **Digoxin 50ug/mL**.....(NDC 0054-3192-46)
Furosemide oral sol 10 mg/mL (NDC 0054-3294-46)
1. Packages of 60mL bottles are too close in "look like"
2. Both NDC # end as "46"
3. Are generics but both reflect brand names beginning with an "L" and are stored usually next to each other on shelf.
4. Too easy to mix up
5. Outer package should be more unique to prevent any mis-dispensing.

129619 12-SEP-00 Found a tray of unit dose Digoxin **elixir** to have **no imprinted lot number or expiration date** anywhere on the packaging.

U 000264 29-MAR-00 A nurse had been preparing to administer a dose of Furosemide solution, only to realize she had difficulty differentiating the **Digoxin Elixir** from the Furosemide at first glance. Three aspects of the packaging are similar for these two products; the outer box as well as the front and side of the bottles. The coloring is similar as well, a mixture of browns and tans found on all Roxane packaging. See attached copy of the boxes and bottles.

024641 30-OCT-97 The problem was observed on 10/24/97. **Elixir** is yellow instead of clear.

025635 21-OCT-98 The problem was observed on 10/1/98. Containers are empty. All liquid is gone; tops are not sealed correctly. The reporter has **3x10 plus 2x5 mL** or 32x5mL containers that are empty.

040782 07-JAN-94 Reporter concerned that **Roxane 60 mL** products (Digoxin and Furosemide) look alike and are in danger of mix-up. See attached.

042151 31-OCT-96 The **amber bottles** of Furosemide and Digoxin are identical in shape with similar looking brown, tan, and white labels. If a patient was on both products and a nurse gave the Digoxin by mistake instead of the Furosemide after the patient already had taken the Digoxin, there is a potential for Digoxin toxicity. Recommendation from reporter to USPC to prevent recurrence: Change the bottle shape or labeling look of one of the products.

DIGOXIN ELIXIR PEDIATRIC M 115954 30-AUG-94 **Calibrated dropper** does not have safety cap. This is potentially dangerous to child on the Digoxin Elixir and to other siblings, due to possible ingestion/overdose.

DIGOXIN PEDIATRIC ELIXIR M 112426 23-AUG-93 On inspection of a bottle of Digoxin Pediatric **Elixir**, reporter has noted that there is no concentration of medication on the label. Specifically, the label states 0.05 mg but does not state the volume in which this 0.05 mg is contained. This is a very dangerous situation since an overdose could easily be given.

113091 03-NOV-93 Labeling not sufficient. **Does not give concentration by volume only 0.05 mg.**

U 017886 23-SEP-93 The label reads "50 mcg"; it does not state the strength per mL. The package insert does state that there are **50 mcg/mL**, but the package insert does not go to the floor.

LANOXIN ELIXIR PEDIATRIC D 107130 03-DEC-91 **Dropper calibrated by 1/10 cc (up to 1 cc).** Frequently used product in long term care facilities. Reporter has constantly observed nurses administering the wrong dose, ie: measures .25 on the dropper for 2.5 cc (.125 mg). Suggest that calibration on dropper be changed to mg instead of cc.

110962 25-FEB-93 **Discoloration** of Pediatric **Elixir**. Noticed back in December when prescription was filled. Called BW return and customer relations - got the "run around".

F 030128 28-JAN-03 On December 24, 2002 a pharmacist reported the discovery of two pieces of brown foreign material which resembled paper in a clear glass bottle of Lanoxin **Elixir** Pediatric.

G 083904 04-FEB-88 FOREIGN PARTICLES FLOATING IN THE **ELIXIR**

M 122115 06-JUN-96 The reporter stated that 2 bottles of Lanoxin pediatric **elixir** were found unlabeled. There was no tamper seal evident on one of the bottles. Both bottles were found inside intact boxes.

123656 22-JAN-97 Bottle of **elixir** inside of package has no label.

124430 22-MAY-97 Product dispensed with dropper supplied by manufacturer (included in package). Black **ink** signifying calibration/dose on dropper comes off in liquid when immersed. Remaining elixir has black flecks floating in it; markings have completely **"washed off" dropper into elixir**. Infant's mother concerned about black flecks ingested by patient.

134161 04-JUN-02 Hospital pharmacy personnel unsealed bottle of Lanoxin **Elixir** Pediatric manufactured by Glaxo, lot number is 1K618, exp date May 04. The liquid was found to have a white precipitate floating in the bottle.

U 000386 — Patient being dischared. Pharmacist instructed parent to given "2cc" of Digoxin. Pharmacist did not remove dosing syringe provided with medication to show parent what '2cc' is. Parent gave 0**.2cc for several weeks as syringe is labelled as 0/cc, .2cc etc. With no leading "0" (0.1cc, 0.2cc). Lack of "0" was confusing to parent.**

001177 01-JAN-88 UPON OPENING PRODUCT, NOTED **PARTICLES SUSPENDED IN LIQUID**

010450 19-FEB-91 The sealed bottle supposed to contain 60 mL of **elixer**. The bottle actually contains approximately 5 to 10 mL.

011333 10-JUN-91 A PARTIALLY USED BOTTLE OF DIGOXIN **ELIXIR** CHANGED COLOR TO A DARK, CLEAR GREEN. REPORTER IS QUESTIONING WHAT CAUSED THIS, SINCE THIS COLOR CHANGE HAS NEVER BEEN NOTICED IN THE PAST.

013906 24-MAR-92 Lanoxin elixir pediatric is noted "Protect from light". The bottle is a clear bottle. The reporter feels that the product **should be in the dark bottle** because the covering box is normally thrown away. See file for photocopy of manufacturer's letter to reporter on market withdrawal of this product.

022410 07-FEB-96 There is a "gnat" **floating in the liquid** of a sealed container. At the request

of the manufacturer, the container is to be returned.

042005 ——, A Digoxin **Elixir** order was called in for **0.625 mg/12.5 mL** daily by gastrostomy tube. This dose was administered from —— at which time, the patient's digoxin level came back at 6. The correct dose should have been **0.0625 mg or 1.25 mL**. The patient received a 10 times overdose for over two months. Interesting to note that this chart was reviewed by two different pharmacists for three months. The error was picked up on the third month review. The patient's digoxin level on —, was 1. On recheck, the digoxin level was 3.8. From that time, the Digoxin Elixir was held; it was restarted on —. The staff had been lulled into security because the patient and his drug regimen were being followed closely by the physician and pharmacist. (The patient was post-cardiac arrest and was on Cordarone). Recommendation from reporter to USPC to prevent recurrence: Everyone was made aware of the error.

000955 ——, Order was written for Lanoxin **0.625 mg**; intended dose was **0.0625mg**. Drug was administered from floor stock, while pharmacy was closed, beofre error was realized. Patient expired likely due to Digoxin toxicity.

080339 01-AUG-95 Lanoxin 0.25 mg was dispensed incorrectly for Lanoxin 0.125 mg.
Lanoxin 0.25 mg was dispensed incorrectly for Lanoxin 0.125 mg.

080504 02-APR-96 Patient was prescribed Lanoxin 0.125 and RPh read Rx wrongly as Lanoxin 0.25.
Patient was prescribed Lanoxin 0.125 and RPh read Rx wrongly as Lanoxin 0.25.

080900 17-NOV-97 Rx for Lanoxin 0.25 mg was incorrectly dispensed with Lanoxin 0.125 mg.
Rx for Lanoxin 0.25 mg was incorrectly dispensed with Lanoxin 0.125 mg.

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

/s/

Denise Toyer
1/23/04 02:58:31 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
1/23/04 03:28:07 PM
DRUG SAFETY OFFICE REVIEWER

Jerry Phillips
1/23/04 03:43:41 PM
DRUG SAFETY OFFICE REVIEWER

**DIVISION OF CARDIO-RENAL DRUG PRODUCTS**
**FOOD AND DRUG ADMINISTRATION**

*US Mail address:*
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852



| | |
|---|---|
| **Transmitted to FAX Number:** | (614) 276-2470 |
| **Attention:** | Ms. Elizabeth Ernst |
| **Company Name:** | Roxane Laboratories |
| **Phone:** | (614) 272-4785 |
| **Subject:** | **Confirmation of meeting w/FDA, January 26, 2004**<br>**Digoxin Elixir**<br>**NDA 21-648** |
| **Date:** | February 28, 2002 |
| **Pages including this sheet:** | **2** |
| **From:** | **Edward Fromm** |
| **Phone:** | **301-594-5332** |
| **Fax:** | **301-594-5494** |

Confirmation of Meeting

| | |
|---|---|
| Drug: | Digoxin Elixir |
| Sponsor: | Roxane Laboratories |
| Subject: | Discussion of Pediatric Use of the Elixir in Children |
| Date Requested: | January 6, 2004 |
| Date Confirmation Faxed: | January 9, 2004 |
| Meeting Date: | January 26, 2004 |
| Meeting Time: | 1:00-3:00 P.M. |
| Location: | conference Room "I", Sixth floor, Woodmont Office Complex 2<br>1451 Rockville, Pike, Rockville, MD |

FDA Participants:

Robert Temple, M.D., HFD-101, Director, Office of Drug Evaluation I
Douglas C. Throckmorton, M.D., HFD-110, Director, Division of Cardio-Renal Drug Products
Norman Stockbridge, M.D., Ph.D., HFD-110, Deputy Division Director
Thomas Marciniak, M.D., HFD-110, Medical Team Leader
Abraham Karkowsky, M.D., Ph.D., HFD-110, Medical Team Leader
Mehul Desai, M.D., HFD-110, Medical Officer
Patrick Marroum, Ph.D., HFD-860, Team Leader, Clinical Pharmacology and Biopharmaceutics
Atul Bhattaram, Ph.D., HFD-860, Clinical Pharmacologist and Biopharmaceuticist
Stuart Zimmerman, Ph.D., HFD-810, Chemist
Edward Fromm, R.Ph., HFD-110, Regulatory Health Project Manager

**Minutes of a Telecon between Roxane Laboratories and the FDA**

Date: January 6, 2004

Applications: Digoxin Elixir

Applicant: Roxane Laboratories

Subject: 505(b)(2) NDA Submission and Use of the Elixir in Children

FDA Participants:

Douglas C. Throckmorton, M.D., HFD-110, Director, Division of Cardio-Renal Drug Products
Mehul Desai, M.D., HFD-110, Medical Officer
Edward Fromm, HFD-110, Regulatory Health Project Manager

Roxane Laboratories

Elizabeth A. Ernst, Associate Director, Regulatory Affairs, DRA-Multisource Products
Gregory Hicks, Pharm.D., Clinical Research Manager , DRA-Multisource Products
Rebecca Braatz, Regulatory Associate

**Background**

NDA 21-648 for Digoxin Elixir was submitted on April 10, 2003 and officially received by the Agency on April 25, 2003. This 505(b)(2) application was submitted in response to a Federal Register notice that went into effect on July 26, 2002, which requires current manufacturers of digoxin elixir to obtain approved applications of their products by June 28, 2004 or face regulatory action. The drug is indicated for the treatment of heart failure and control of atrial fibrillation.

**Telecon**

Dr. Throckmorton opened the telecon by noting that the Division had recently met with Dr. Temple to review the Digoxin application, and although we have concluded that digoxin has a pharmacologic effect, this effect is not easily understood and one not linked to a clear clinical benefit. We also have had difficulties locating clear data on the clinical utility of digoxin in children, either for rate control or for heart failure. However, we are uncertain how digoxin is currently being used in children, and it would be helpful for the applicant and its consultants to meet with us and explain why this drug is needed in the pediatric population. Roxane said that it and physicians who have worked on the digoxin labeling would be available to meet with the Agency to provide information on the current use of digoxin in children.

Dr. Throckmorton noted that the action date for this application was February 25, 2004 and asked the applicant to make arrangements with Mr. Fromm to schedule this meeting as soon as possible. Roxane replied that they would be happy to meet with the Agency and would contact Mr. Fromm to make the appropriate arrangements for the meeting.

Minutes Preparation: Edward Fromm

Concurrence Chair: Douglas C. Throckmorton, M.D.

ef/dr-1/7/04-1/13/04

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 9, 2003

FROM: Nilufer M. Tampal, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D. CTV 12/11/03
Associate Director – Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIRs Covering NDA 21-648,
Digoxin Elixir USP, 0.05 mg/mL, Sponsored by
Roxanne Laboratories, Inc.

TO: Douglas C. Throckmorton, M.D.
Director
Division of Cardio-Renal Drug Products(HFD-110)

At the request of HFD-110, the Division of Scientific Investigations conducted an audit of the clinical and analytical portions of the following bioequivalence studies:

**Protocol # 1:** DIGO-01, A Single Dose, Two-Way Crossover Bioequivalence Study of Digoxin Elixir and Tablet Under Fasted Conditions.

**Protocol # 2:** DIGO-02, A Single Dose, Two-Way Crossover Bioequivalence Study of Digoxin Elixir and Tablet Under Fed Conditions.

The clinical portion of Study DIGO-01 was conducted at , and the clinical portion of Study DIGO-02 was conducted at The analytical portions for both studies were conducted at

Following the inspections, Form FDA 483 was issued at (**Attachment 1**). No Form FDA 483 was issued at (10/27-29/03) and at (10/28-30/03) The objectionable items and our evaluation are as follows:

**Analytical site:** [redacted]

1. **Data from acceptable runs (about 8% of the subject samples) in Studies DIGO-01 and DIGO-02 were replaced with results from re-assays requested by the Sponsor's consultant. There was no documented justification for rejecting and replacing the data.**

In response to the Form 483 **(see Attachment 2)**, the firm indicated that the re-assays were primarily conducted for pharmacokinetic (PK) reasons. Because the criteria used to determine the PK repeats has not been provided, there is no justification for rejecting the original data. The data from the PK repeat analyses **(see Attachment 3)** should not be used for the bioequivalence determination.

2. **Analytical runs that originally failed when results of QC specimens were outside the acceptance limits were re-processed by excluding selected calibration standards until the QC results passed.**

The firm biased run acceptance by manipulating standard curve regression parameters. For runs 6 and 11 in Study DIGO-01, the firm selectively excluded calibration standards to bring failing QCs into the acceptance limits. Therefore, the accuracy of the data from runs 6 and 11 has not been assured **(see Attachment 4)**. In their written response, the firm stated that they followed the standard industry practice. DSI rejects the firm's view because biased manipulation of the standard curve to pass failing QCs is unacceptable and does not assure the accuracy of the subject sample concentrations.

3. **Failure to demonstrate autosampler stability of digoxin in that data from pre-study validation run 5 was not acceptable when chromatograms were reintegrated consistently[1].**

Chromatograms for autosampler stability of digoxin at room temperature showed inconsistent manual reintegration for the 0.5 ng/mL and 0.1 ng/mL standards. When these chromatograms were reintegrated consistently the run failed to meet the acceptance criteria. Nonetheless, accuracy of the subject data from studies DIGO-01 and DIGO-02 was assured by the acceptable performance of the QCs interspersed throughout the study runs. In the written response, the firm proposed to repeat the autosampler stability studies **(see Attachment 2).**

**Conclusions:**

Following the above inspections, DSI recommends that:

1. Due to biased manipulation of the standard curve, all plasma concentrations from subjects 17, 18, and 20 (run 6) and all subject samples analyzed in run 11 (see table 1) for Study DIGO-01 be excluded from the bioequivalence determination.

[1] Please note that the Form 483 observation incorrectly stated bench top stability instead of autosampler stability

2. Due to unjustified reassay for PK reasons, the original rather than PK repeat results from Studies DIGO-01 and DIGO-02 should be used for the bioequivalence determination.

After you have reviewed this transmittal memo, please append it to the original NDA submissions.

Nilufer M. Tampal, Ph.D.

**Final Classifications:**

[redacted] **VAI**

[redacted] **NAI**

[redacted] **NAI**

Attachments*
*Due to the number of pages, attachments will be provided to the OCPB reviewer. These attachments are available upon request.

cc:
HFA-224
HFD-45/RF
HFD-48/Tampal(2)/Himaya/CF
HFD-110/Fromm/NDA 21-648
HFR-CE1515/Mechenbier/Bender
HFR-SW1450/Martinez
Drafted: NMT /12/09/03
Edited: JAO 12/11/03
FACTS: 44117
DSI:5478; O:\BE\eircover\21648rox.dig.doc

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-648

**DISCIPLINE REVIEW LETTER**

Roxane Laboratories, Inc.
Attention: Ms. Elizabeth Ernst
1809 Wilson Road
Columbus, OH 43228

Dear Ms. Ernst:

Please refer to your April 10, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Digoxin Elixir USP, 0.05 mg/mL.

We also refer to your submissions dated June 12, July 9, 11, September 4, and October 2, 2003.

During review of the Clinical, Chemistry, Manufacturing and Controls sections of your submission, the primary reviewers have identified, to date, the following potential review issues:

**CMC (Chemistry, Manufacturing and Controls)**

Drug Substance
Your statement (Volume 1.4, p. 1645) that digoxin does not have any chiral centers is erroneous and needs correction.

Please provide for the adoption of the following regulatory specifications (i.e., as given in the COA, Vol. 1.4, p. 1701-2) for your digoxin drug substance in addition to those in the current USP: (1) Specific Optical Rotation —, (2) Residual Solvents — and (3) Related Substances. Include supporting validation information for the test procedures and justification for the establishment of acceptance criteria. Consider tightening the currently utilized acceptance criteria (i.e., Vol. 1.5, Table 2, p. 1979) for the related substances in accord with the previously considered statistical model referenced for degradant control for the drug product (i.e., utilizing the —). Please include these newly adopted regulatory specifications to test the first — demonstration /validation drug substance batches (i.e., Vol. 1.4, p. 1704). Please provide information on what testing provisions are planned after these — batches?

Please provide for a consistency of understanding/categorical classification of potential drug substance and drug product impurities —

Please confirm that the results (i.e., Vol. 1.5, Table 2, p. 1979 provided by — — for Digoxin are derived utilizing the official USP test procedure since there is ambiguity concerning whether — testing could be utilized. Also, include full control

provisions (i.e., acceptance criteria and test procedures) related to their COA (i.e., Vol. 1.4, p. 1701-2).

Drug Product

Concerning your alternate drug product — test procedure, please justify why —

Please provide an alternate identification specification for your drug product that is based on your — test method in the event that you may expect to utilize the — for product identification.

In accord with the USP provisions to provide for a dosage form that delivers the expected label claim to the patient (e.g., see General Notices), please appropriately revise the amount of drug product placed in the cups to compensate for losses experienced by lack of delivery of all the solution to the patient. Such a revision should include studies to determine how much solution - on an average basis - remains in the cup after administration.

Concerning test methods for drug product impurity, there is inconsistency with reference to the analytical category "Unknown Related Compounds" (i.e., volume 1.4, p. 1665 that is expected to account for a number of different potential impurities) and its deletion with only reference to more restrictive category "Single Largest Unknown Related Compound". Please resolve this matter (e.g., include an accounting for any such other related compounds) to assure appropriate calculation of "Total Known and Unknown Related Compounds".

Please explain how your reference — " (i.e., Vol. 1.5, p. 1887) is determined and what its variability is in terms of batch-to-batch data. Does it change (e.g., owing to degradation) over time?

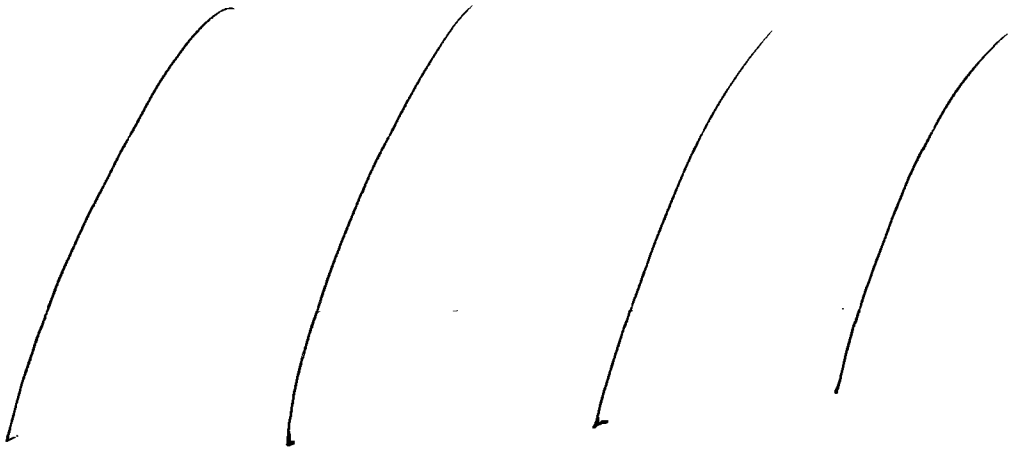
Please clarify whether the unknown peak at — (i.e., vol. 1.5, p. 1936) is the one that is considered to be the single major unknown peak that is normally observed in your reports on a batch-to-batch basis.

Please resolve the seemingly incorrect peak designation at — (i.e., Vol. 1.5, p. 1945) that is specified as digoxin and which could be for —

Container-Closure System

Please provide corrected LOAs from any relevant DMFs

Labeling



Environmental Assessment
Concerning your request for a categorical exclusion from the need to prepare an Environmental Assessment, please indicate if you have any knowledge of any extraordinary circumstances that exist relative to this action.

Methods Validation
Please include provision for the analytical profiling of all your critical degradation products in your methods validation package. For example, you could provide reference samples of specific degradants together with spiking instructions or a sample of the elixir that is known to contain significant amounts of such degradants (i.e., samples that were stressed beyond the normal expiry period).

**Clinical**

The medical officer reviewing this NDA application has had an opportunity to review the references that have been submitted supporting the use of Digoxin Elixir in a pediatric population. Based on the submitted references, it is the belief of the reviewer that there is inadequate evidence of efficacy of this drug in this population. This is of particular concern because digoxin is a drug with a narrow therapeutic index. The completed studies in the peer reviewed medical literature have major flaws. Examples of these include lack of appropriate control groups, unblinded patient assessments, lack of randomization, and evaluating endpoints that are not necessarily associated with meaningful outcomes (e.g. echocardiographic endpoints).

In addition, many other studies are retrospective in nature. In summary, the quality of pediatric studies that have been reviewed do not provide conclusive evidence of efficacy based on standards the Agency uses today. In order to further evaluate your application, please respond to the following:

1. Are there studies that support the use of digoxin (elixir and/or tablet) in a pediatric population that meet Agency's standards of establishing efficacy (e.g. prospective, randomized, placebo controlled, blinded, evaluating clinically relevant outcomes)?
2. If such studies exist, what specific pediatric populations and what indications do such studies support - Neonates? Infants? Children?
3. Do such studies adequately describe how digoxin should be administered in terms of loading dose and maintenance dose?

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can act on this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, please contact:

Mr. Edward Fromm
Regulatory Health Project Manager
(301) 594-5332

Sincerely,

*{See appended electronic signature page}*

Zelda McDonald
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Zelda McDonald
10/27/03 02:54:01 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

**FILING REVIEW LETTER**

NDA 21-648

Roxane Laboratories, Inc.
Attn: Ms. Elizabeth Ernst
1809 Wilson Rd.
Columbus, Ohio 43228

Dear Ms. Ernst:

Please refer to your new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act dated April 10, 2003 for Digoxin USP 0.05 mg/ml Elixir.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b)(2) of the Act on June 24, 2003 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

**Chemistry:**

1. Comparative Stability Data: The stability of the demonstration batch needs to be compared with those from previously manufactured batches of your elixir (e.g., those cited in Technical Report TR0662-023). Such data should include manufacturing scale, all monitored product specifications, and all packaging configurations. To facilitate the review of these data and enhance comparability of the three batches, structure the data presentations to allow specific statistical assessment of relevant variables. Include a rationale to support your proposed —— expiration date, based on this comparison.

2. Stability Testing: Your submitted accelerated stability studies —— — suggesting that additional information may be needed to support your proposed — expiration date. This could be in the form of stability testing under ICH intermediate conditions (30 degrees C, 60% relative humidity).

3. Drug-Container Interactions: No information has been submitted on the potential for interaction between components of the drug product and the proposed container, especially ——

4. Impurities and Degradents in the Drug Substance and Product: You have made a proposal regarding the acceptable limits of "other" and total impurities and degradents, but provided no rationale for these limits.

We are providing the above comments to give you preliminary notice of potential review issues. Submission of data relevant to these identified deficiencies is solicited to further the review. As the review of the NDA is not complete, this is not indicative of deficiencies that may be identified with a completed review. Issues may be added, deleted, expanded upon, or modified with a complete review of the submission.

If you have any questions, please contact:

Mr. Edward Fromm
Regulatory Health Project Manager
(301) 594-5332

Sincerely,

*{See appended electronic signature page}*

Douglas C. Throckmorton, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Doug Throckmorton
7/3/03 08:02:30 AM

## NDA REGULATORY FILING REVIEW
**(Includes Filing Meeting Minutes)**

NDA 21-648, Digoxin Elixir USP, 0.05 mg/ml.

Applicant: Roxane Laboratories

Date of Application: April 10, 2003
Date of Receipt: April 25, 2003 (application originally received April 14, 2003, but user fee was not fully paid and not received in entirety until April 25, 2003).
Date of Filing Meeting: June 11, 2003
Filing Date: June 24, 2003
74 day ltr due: July 8, 2003

Indication(s) requested: Heart Failure, Atrial Fibrillation

Type of Application: Full NDA __X_____ Supplement _____
(b)(1) ____ _____ (b)(2) ___X_____

Therapeutic Classification: S___X____ P_____
Resubmission after a withdrawal or refuse to file __NA_____
Chemical Classification: (1,2,3 etc.)__7____
Other (orphan, OTC, etc.)___NA_____

Has orphan drug exclusivity been granted to another drug for the same indication? NO

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

NO

If the application is affected by the application integrity policy (AIP), explain. NO

User Fee Status: Paid ____X_____ Waived (e.g., small business, public health) _____
Exempt (orphan, government) __NA_____
Form 3397 (User Fee Cover Sheet) submitted: YES___X____ NO_____
User Fee ID#____4532_____
Clinical data? YES ___X____ NO _____ Referenced to NDA# __20-405____
Date clock started after UN _April 25, 2003___NA_____

User Fee Goal date: ___February 25, 2004____

Action Goal Date (optional) ___February 25, 2004_____

- Does the submission contain an accurate comprehensive index? YES
- Form 356h included with authorized signature? YES
  **If foreign applicant, the U.S. Agent must countersign.**
- Submission complete as required under 21 CFR 314.50? YES
- If electronic NDA, does it follow the Guidance? NA
  **If an electronic NDA: all certifications must be in paper and require a signature.**

- If Common Technical Document, does it follow the guidance? NA

- Patent information included with authorized signature? YES

- Exclusivity requested? NO; If yes, ____years

Note: An applicant can receive exclusivity without requesting it, therefore, requesting exclusivity is not a requirement.

- Correctly worded Debarment Certification included with authorized signature? YES
  **If foreign applicant, the U.S. Agent must countersign.**

  Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with the studies listed in Appendix ____." Applicant may not use wording such as, " To the best of my knowledge, ...."

- Financial Disclosure included with authorized signature? YES
  (Forms 3454 and/or 3455)
  **If foreign applicant, the U.S. Agent must countersign.**

- Has the applicant complied with the Pediatric Rule for all ages and indications? NA

- Field Copy Certification (that it is a true copy of the CMC technical section)? YES

**Refer to 21 CFR 314.101(d) for Filing Requirements**

PDUFA and Action Goal dates correct in COMIS? YES
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

List referenced IND numbers: NA

End-of-Phase 2 Meeting? NO

Pre-NDA Meeting(s)? YES, March 27, 2002 & December 13, 2002 (t-con)

**Project Management**

Copy of the labeling (PI) sent to DDMAC? YES

Trade name (include labeling and labels) consulted to ODS/Div. of Medication Errors and Technical Support? YES

MedGuide and/or PPI consulted to ODS/Div. of Surveillance, Research and Communication Support? NA

OTC label comprehension studies, PI & PPI consulted to ODS/ Div. of Surveillance, Research and Communication Support? NA

Advisory Committee Meeting needed? NO

**Clinical**

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? NA

**Chemistry**

- Did sponsor request categorical exclusion for environmental assessment? YES
  If no, did sponsor submit a complete environmental assessment? NA
  If EA submitted, consulted to Nancy Sager (HFD-357)? NA

- Establishment Evaluation Request (EER) package submitted? YES

- Parenteral Applications Consulted to Sterile Products (HFD-805)? NA

ATTACHMENT

MEMO OF FILING MEETING (June 11, 2003)

BACKGROUND:

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 proposed a rule in the Federal Register on November 24, 2000, that would require approved applications for all digoxin products, including digoxin elixir.

Roxane filed an ANDA Suitability Petition to the Agency in October 2001, asking that digoxin elixir be considered for an ANDA in relation to the reference listed drug (RLD) product (Lanoxin Tablets). The Agency, however, denied their request in December of 2001 because pediatric studies would be needed.

The firm met with the Division on March 27, 2002, to discuss the requirements for filing a successful 505(b)(2) application for digoxin elixir, 0.05 mg/mL. With the suspension of the Pediatric Rule, the firm again filed a Suitability Petition, which the Office of Generic Drugs indicated that they would deny because of the need for extensive revisions of the labeling.

Roxane filed a 505(b)(2) application on April 10, 2003, that unfortunately, did not contain the full user fee required for this application. The full fee was received by the Agency on April 25, 2003 and therefore this becomes the "official" receipt date for the application.

ATTENDEES:

Douglas C. Throckmorton, M.D., HFD-110, Director, Division of Cardio-Renal Drug Products
Norman Stockbridge, M.D., Ph.D., HFD-110, Deputy Division Director
Mehul Desai, M.D., HFD-110, Medical Officer
Angelica Dorantes, Ph.D., HFD-860, Clinical Pharmacologist and Biopharmaceuticist
Belay Tesfamariam, Ph.D., HFD-110, Pharmacologist
Kasturi Srinivasachar, Ph.D., HFD-810, Team Leader, Division of New Drug Chemistry I
Stuart Zimmerman, Ph.D., HFD-810, Chemist
Robert Shibuya, Ph.D., HFD-45, DSI, Pharmacologist
Sriam Subramaniam, Ph.D., HFD-48, Physiologist
Edward Fromm, HFD-110, Regulatory Health Project Manager

ASSIGNED REVIEWERS:

| Discipline | Reviewer | Expected |
|---|---|---|
| Medical | Mehul Desai, M.D | December 31, 2003 |
| Secondary Medical: | TBD | |
| Statistical: | James Hung, Ph.D. | No Review Required |
| Pharmacology: | Belay Tesfamariam, Ph.D. | November 30, 2003 |
| Statistical Pharmacology: | NA | |
| Chemist: | Stuart Zimmerman, Ph.D. | November 30, 2003 |
| Environmental Assessment (if needed): | Stuart Zimmerman, Ph.D. | November 30, 2003 |
| Clinical Pharmacology & Biopharmaceutics: | Angelica Dorantes, Ph.D. | December 31, 2003 |
| Microbiology: | NA | |
| DSI (clinical): | Robert Shibuya, Ph.D. | No Audit Req. |

| | | |
|---|---|---|
| DSI (GLP): | Sriram Subramaniam, Ph.D. | TBD |
| Project Manager: | Edward Fromm | |
| Other Consults: | NA | |

Per reviewers, all parts in English, or English translation? YES__X___ NO___

CLINICAL – File ____X_____ Refuse to file _____

- Clinical site inspection needed: YES_____ NO___X_____

MICROBIOLOGY CLINICAL – File____NA_____ Refuse to file_____

STATISTICAL – File ____NA_____ Refuse to file _____

BIOPHARMACEUTICS – File ____X_____ Refuse to file _____

- Biopharm. inspection Needed: YES____X_____ NO _____

PHARMACOLOGY – File ____X_____ Refuse to file _____

CHEMISTRY –

- Establishment(s) ready for inspection? YES__X___NO_____ File__X___ Refuse to file _____

REGULATORY CONCLUSIONS/DEFICIENCIES:

___X____The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

___X____ No filing issues have been identified.

_____ Filing issues to be communicated by Day 74.

ACTION ITEMS:

- Filing issues/no filing issues will be documented and conveyed to applicant in the 74-Day letter by July 8, 2003.

Mr. Edward Fromm
Regulatory Project Manager, HFD-110

Rd: RShibuya-6/12/03
S Subramaniam-6/12/03
SZimmerman-7/21/03
KSrinivasachar-7/21/03
BTesfamariam-7/21/03
ADorantes-7/22/03
MDesai-7/22/03
NStockbridge-7/23/03
DThrockmorton-7/23/03

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/s/

Edward Fromm
8/6/03 10:17:22 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-648

Roxane Laboratories, Inc.
Attention: Ms. Elizabeth Ernst
1809 Wilson Road
Columbus, OH 43228

Dear Ms. Ernst:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for (Digoxin Elixir USP) 0.05 mg/mL.

You were notified in our letter dated April 24, 2003, that your application was not accepted for filing due to non-payment of fees. This is to notify you that the Agency has received all fees owed and your application has been accepted as of April 25, 2003.

The review priority classification for this application is standard (S).

Unless we notify you within 60 days of the above date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on June 24, 2003, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be February 25, 2004.

Under 21 CFR 314.102(c), you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room, 5002
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room, 5002
1451 Rockville Pike
Rockville, Maryland 20852

If you have any questions, please call:

Mr. Edward Fromm
Regulatory Health Project Manager
(301) 594-5332

Sincerely,

*{See appended electronic signature page}*

Zelda McDonald
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Zelda McDonald
5/1/03 10:39:18 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-648

Roxane Laboratories, Inc.
Attention: Ms. Elizabeth Ernst
1809 Wilson Road
Columbus, OH 43228

Dear Ms. Ernst:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: (Digoxin Elixir USP) 0.05mg/mL Oral

Date of Application: April 10, 2003

Date of Receipt: April 14, 2003

Our Reference Number: NDA 21-648

We have not received the appropriate user fee for this application. An application is considered incomplete and cannot be accepted for filing until all fees owed have been paid. Therefore, this application is not accepted for filing. We will not begin a review of this application's adequacy for filing until FDA has been notified that the appropriate fee has been paid. Payment should be submitted to the following address:

Food and Drug Administration
P.O. Box 360909
Pittsburgh, PA 15251-6909

Checks sent by a courier should be addressed to:

Food and Drug Administration (360909)
Mellon Client Service Center, Room 670
500 Ross Street
Pittsburgh, PA 15262-0001

**NOTE: This address is for courier delivery only. Make sure the FDA Post Office Box Number (P.O. Box 360909) and user fee identification number are on the enclosed check.**

The receipt date for this submission (which begins the review for filability) will be the date the review division is notified that payment has been received by the bank.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room, 5002
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room, 5002
1451 Rockville Pike
Rockville, Maryland 20852

If you have any questions, please call:

Mr. Edward Fromm
Regulatory Health Project Manager
(301) 594-5332

Sincerely,

*{See appended electronic signature page}*

Zelda McDonald
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Zelda McDonald
4/25/03 09:55:17 AM

Boehringer Ingelheim
Roxane Laboratories



Food and Drug Administration
Center for Drugs and Biologics
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

April 10, 2003

NDA

**505 (b)(2) New Drug Application**
**Digoxin Elixir USP, 0.05 mg/mL**

**Elizabeth A. Ernst**
**Associate Director,**
**DRA-Multisource Products**

**Telephone (614) 272-4785**
**Telefax (614) 276-2470**
**E-Mail eernst@col.boehringer-ingelheim.com**

**1809 Wilson Road**
**Columbus, Ohio 43228**

Dear Madam/Sir:

In accordance with 21 CFR 314.50, Roxane Laboratories, Inc. is submitting a 505 (b)(2) New Drug Application (NDA) for Digoxin Elixir USP, 0.05 mg/mL. This NDA consists of fourteen (14) volumes.

The reference listed drug is LANOXIN® (digoxin) Tablets 0.25 mg , manufactured by Glaxo-Wellcome Inc. The active ingredient is digoxin.

Four complete copies of the draft labeling are contained in the Archival and CMC Review copies of this application. The drug product will be manufactured, tested, labeled, packaged and released by Roxane Laboratories, Inc. No contract manufacturers or packagers are used for the proposed drug product. *In vivo* bioequivalence study reports are also included in this application.

Roxane Laboratories, Inc. commits to provide full cooperation to resolve any problems that may arise during the methods validation testing as part of the "Post-Approval" for the above listed drug product.

We have also submitted a copy of the technical sections contained in the archival and review copies of this application to Ms. Kathleen Culver, Pre-Approval Manager, FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097.

Correspondence concerning this application should be directed to Elizabeth Ernst, Associate Director, DRA-Multisource Products, Roxane Laboratories, Inc. I can be reached at (614) 272-4785 and by telefax at (614) 276-2470.

Respectfully,

Elizabeth Ernst
Associate Director, DRA-Multisource Products

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

# APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

*(Title 21, Code of Federal Regulations, Parts 314 & 601)*

*Form Approved: OMB No. 0910-0338*
*Expiration Date: August 31, 2005*
*See OMB Statement on page 2.*

FOR FDA USE ONLY

APPLICATION NUMBER 21-648

## APPLICANT INFORMATION

| NAME OF APPLICANT | DATE OF SUBMISSION |
|---|---|
| Roxane Laboratories, Inc. | April 10, 2003 |
| **TELEPHONE NO.** *(Include Area Code)* | **FACSIMILE** *(FAX)* **Number** *(Include Area Code)* |
| 614-272-4785 | 614-276-2470 |
| **APPLICANT ADDRESS** *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* | **AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE |
| 1809 Wilson Rd.<br>Columbus, OH 43228 | N/A |

RECEIVED
APR 14 2003
CDR/CDER

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
APR 15 2003
HFD-110

## PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* NDA # 21-648

| ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)* | PROPRIETARY NAME *(trade name)* IF ANY |
|---|---|
| Digoxin Elixir USP | N/A |

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*
(3β,5β,12β)-3-[(O-2,6-dideoxy-β-*D*-*ribo*-hexopyranosyl-(1→ 4)-O-2,6-dideoxy-β-*D*-*ribo*-hexopyranosyl-(1→ 4)-2,6-dideoxy-β-*D*-*ribo*-hexopyranosyl)oxy]-12,14-dehydroxy-card-20(22)enolide

CODE NAME *(If any)*: N/A

| DOSAGE FORM: | STRENGTHS: | ROUTE OF ADMINISTRATION: |
|---|---|---|
| Elixir | 0.05 mg/mL | Oral |

(PROPOSED) INDICATION(S) FOR USE:
Treatment of mild to moderate heart failure, and control of ventricular response rate in patients with chronic atrial fibrillation.

## APPLICATION INFORMATION

APPLICATION TYPE *(check one)*
■ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ■ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug: LANOXIN® (digoxin) Tablets, 0.25 mg — Holder of Approved Application: Glaxo-Wellcome Inc.

TYPE OF SUBMISSION *(check one)* ■ ORIGINAL APPLICATION ☐ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Original Application

PROPOSED MARKETING STATUS *(check one)* ■ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 14 THIS APPLICATION IS ■ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

**ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)**
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready

See Attached.

**Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)**

DMF's:

NDA's: NDA 20-405, LANOXIN® (digoxin) Tablets, 0.25 mg

| This application contains the following items: *(Check all that apply)* | |
|---|---|
| X | 1. Index |
| X | 2. Labeling *(check one)* ■ *Draft Labeling* ☐ *Final Printed Labeling* |
| X | 3. Summary (21 CFR 314.50 (c)) |
| X | 4. Chemistry section |
| X | A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2) |
| X | B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request) |
| | C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2) |
| | 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2) |
| X | 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2) |
| | 7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4)) |
| X | 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2) |
| X | 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2) |
| X | 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2) |
| | 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2) |
| X | 12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2) |
| | 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c)) |
| X | 14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A)) |
| X | 15. Establishment description (21 CFR Part 600, if applicable) |
| X | 16. Debarment certification (FD&C Act 306 (k)(1)) |
| X | 17. Field copy certification (21 CFR 314.50 (l)(3)) |
| X | 18. User Fee Cover Sheet (Form FDA 3397) |
| | 19. Financial Information (21 CFR Part 54) |
| | 20. OTHER *(Specify)* |

**CERTIFICATION**

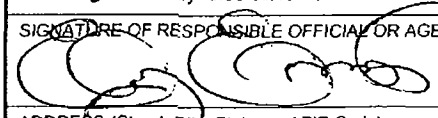
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

**Warning:** A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

| *SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT* | *TYPED NAME AND TITLE* | DATE: |
|---|---|---|
|  | Elizabeth Ernst,<br>Associate Director, DRA-Multisource Products | April 10, 2003 |

| *ADDRESS (Street, City, State, and ZIP Code)* | Telephone Number |
|---|---|
| Roxane Laboratories, Inc., 1809 Wilson Rd., Columbus, OH 43228 | (614) – 272-4785 |

**Public reporting burden for this collection of information** is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
od and Drug Administration
:ER, HFD-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

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REC'D
APR 15 2003
HFD-110

## 19.0 FINANCIAL INFORMATION

Roxane Laboratories, Inc. conducted pharmacokinetic studies to assess the single dose bioequivalence of Roxane's Digoxin Elixir USP, 0.05 mg/mL formulation to that of Glaxo SmithKline's LANOXIN® Tablets, 0.25 mg. The studies were conducted for Roxane Laboratories, Inc. by , a contract research organization located at

A copy of the financial certification form (FDA Form 3454) for the principal investigators, is provided.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

# CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

*TO BE COMPLETED BY APPLICANT*

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

*Please mark the applicable checkbox.*

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

| Clinical Investigators | |
|---|---|
| | |
| | |
| | |

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

| NAME | TITLE |
|---|---|
| Elizabeth Ernst | Associate Director, Regulatory Affairs |
| FIRM/ORGANIZATION: Roxane Laboratories, Inc. | |
| SIGNATURE | DATE: 4/7/03 |

**Paperwork Reduction Act Statement**

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

**DIVISION OF CARDIO-RENAL DRUG PRODUCTS**
**FOOD AND DRUG ADMINISTRATION**

***US Mail address:***
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852



| | |
|---|---|
| **Transmitted to FAX Number:** | (614) 276-2470 |
| **Attention:** | Ms. Elizabeth A. Ernst |
| **Company Name:** | Roxane Laboratories |
| **Phone:** | (614) 272-4785 |
| **Subject:** | **Minutes of Telecon w/FDA, December 13, 2002 Digoxin Elixir 505(b)(2) Application** |
| **Date:** | Jan. 10, 2003 |
| **Pages including this sheet:** | 3 |
| **From:** | **Edward Fromm** |
| **Phone:** | **301-594-5332** |
| **Fax:** | **301-594-5494** |

PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!

**Minutes of a Telecon between Roxane Laboratories and the FDA**

Date: December 13, 2002

Applications: Digoxin Elixir

Applicant: Roxane Laboratories

Subject: 505(b)(2) NDA Submission

FDA Participants:

Douglas C. Throckmorton, M.D., HFD-110, Director, Division of Cardio-Renal Drug Products
Michael Jones, HFD-005, Special Assistant, Office of Regulatory Policy
Edward Fromm, HFD-110, Regulatory Health Project Manager

Roxane Laboratories

Elizabeth A. Ernst, Associate Director, Regulatory Affairs, DRA-Multisource Products
Gregory Hicks, Pharm.D., Clinical Research Manager , DRA-Multisource Products

**Background**

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 proposed a rule in the Federal Register on November 24, 2000, that would require approved applications for all digoxin products, including digoxin elixir.

Roxane filed an ANDA Suitability Petition to the Agency in October, 2001, asking that digoxin elixir be considered for an ANDA in relation to the reference listed drug (RLD) product (Lanoxin Tablets). The Agency, however, denied their request in December of 2001 because pediatric studies would be needed.

The firm met with the Division on March 27, 2002 ,to discuss the requirements for filing a successful 505(b)(2) application for digoxin elixir, 0.05 mg/mL. The telecon today is to discuss the progress the firm has made in preparation for submission of this application.

**Telecon**

Roxane Laboratories opened the telecon by noting that their 505(b)(2) application for digoxin elixir is ready for submission but due to the suspension (at least temporarily) of the Pediatric Rule, the firm will likely file another Suitability Petition with the Office of Generic Drugs. The petition will again ask that the Agency make a determination their product is suitable for submission as an ANDA based on the RLD product (Lanoxin Tablet, 0.25 mg).

The firm noted that at the March 27, 2002 meeting with the Division, we asked that the labeling be updated. A draft of this labeling was recently sent to the Division and the firm asked

Dr. Throckmorton said he was appreciative of the work that has gone into the labeling, but said that he could not comment on the firm's request at this time.

Roxane noted that the data could support a "Class Labeling Guidance" for digoxin products. Dr. Throckmorton said he is aware of this regulatory strategy and how it might be used for digoxin products.

The firm noted that, based on the proposed draft labeling submitted to the Division for digoxin elixir, Mr. Michael Jones had notified them that a full User Fee would be required. They said that paying a full User Fee was hard to justify economically and asked for further clarification on this issue. Mr. Jones said the statute was clear; a 505(b)(2) application requesting new indications (new claims ) would require payment of the full fee if clinical data is required for approval. He added that clinical data (for User Fee purposes) could be defined as data from clinical studies the sponsor performs or from the literature.

Minutes Preparation: Edward Fromm

Edward Fromm

Concurrence Chair:

Douglas C. Throckmorton, M.D.

ef/dr-12/30/02/-1/08/03

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Rockville, MD 20852



| | |
|---|---|
| **Transmitted to FAX Number:** | (614) 276-2470 |
| **Attention:** | Ms. Elizabeth A. Ernst |
| **Company Name:** | Roxane Laboratories |
| **Phone:** | (614) 272-4785 |
| **Subject:** | **Minutes of Meeting w/FDA, March 27, 2002 Digoxin Elixir 505(b)(2) Application** |
| **Date:** | April 29, 2002 |
| **Pages including this sheet:** | **4** |
| **From:** | **Edward Fromm** |
| **Phone:** | **301-594-5313** |
| **Fax:** | **301-594-5494** |

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**Minutes of a Pre-IND Meeting between Roxane Laboratories and the FDA**

Date: March 27, 2002

Applications: Digoxin Elixir

Applicant: Roxane Laboratories

Subject: 505(b)(2) NDA Requirements

FDA Participants:

Douglas C. Throckmorton, M.D., HFD-110, Acting Division Director
Norman Stockbridge, M.D., Ph.D., HFD-110, Medical Team Leader
Gabriel Robbie, Ph.D., HFD-860, Clinical Pharmacologist and Biopharmaceuticist
Charles Resnick, Ph.D., HFD-110, Pharmacology Team Leader
Ram Mittal, Ph.D., HFD-810, Chemist
Ms. Natalia A. Morgenstern, HFD-110, Chief, Project Management Staff
Mr. Edward Fromm, HFD-110, Project Manager

Roxane Laboratories

Ms. Elizabeth A. Ernst, Associate Director, Regulatory Affairs, DRA-Multisource Products
Gregory Hicks, Pharm.D., Clinical Research Manager , DRA-Multisource Products

/ / /

**Background**

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 proposed a rule in the Federal Register on November 24, 2000, that would require approved applications for all digoxin products, including digoxin elixir.

Roxane filed an ANDA Suitability Petition to the Agency in October, 2001, asking that digoxin elixir be considered for an ANDA in relation to the reference listed drug (RLD) product (Lanoxin Tablets). The Agency, however, denied their request in December of 2001.

The firm is meeting with the Division today to discuss the requirements for a successful 505(b)(2) application for digoxin elixir, 0.05 mg/ml.

**Meeting**

Dr. Throckmorton opened the meeting by noting that there appear to be two main requirements for the digoxin elixir 505(b)(2) application:

1. Bioequivalence Studies-the firm will need to demonstrate bioequivalence to the RLD (Lanoxin) Tablets. Roxane asked if the bioequivalence studies should be done in both fed and fasted patients. Dr. Robbie replied that is our preference would be that the studies be done in both fed and fasted patients.

The firm noted that they had conducted pilot bioequivalence studies of their elixir to the Lanoxin Elixir and found to their surprise that their formulation was not equivalent. They theorize that

Dr. Throckmorton reaffirmed that demonstrating bioequivalence to the RLD would be sufficient to meet the Agency's standards for bioequivalence.

2. Pediatric Waiver-Dr. Throckmorton said that despite reports to the contrary, the Pediatric Rule was still in effect and the Division would not grant a waiver for doing studies pursuant to that Rule. The firm will need to supply data (although not necessarily the primary data) to justify the current pediatric labeling for digoxin Tablets. This means that both the efficacy and safety information included in the label and the bases for the instructions for use need to be justified by referencing available literature, or a very strong case made for why that is not possible/relevant. Material available for the first time since 1997 potentially will be very relevant. Furthermore, if the current pediatric information is not supportable, then the Division might ask the firm to obtain additional data.

   Roxane said they were planning on submitting their application in the last quarter of 2002 and asked if the pediatric information could be submitted later in the review period. Dr. Throckmorton said the pediatric information is critical to the application and therefore it would be needed when the firm is ready to submit the application. If there are difficulties obtaining the data the Division should be informed to see if it could be of assistance.

CMC Information

The firm said that they plan to produce of the elixir for the in vitro and in vivo studies. Stability information would be augmented with lots stability data) that were manufactured in the past. Dr. Mittal said this was acceptable but noted that the firm would need to commit to the production of 3 commercial lots at the time of approval.

Roxane said they plan on having of accelerated stability data at the time of NDA submission and asked if that was sufficient. Dr. Mittal said it was acceptable but noted that the product's expiration date will be based on the stability data received prior to approval. Dr. Throckmorton noted that stability data received too late in the review period would either not be considered by the Division or reviewed after extending the review clock. He added that the firm should submit a proposal for their planned CMC studies.

Preclinical Information

Roxane said that they plan on using the Agency's findings of safety for the preclinical sections of the labeling and would submit any pertinent literature references, especially those since 1997. Dr. Throckmorton said the firm's plan is reasonable; however, we cannot make a determination about the adequacy of the pharm/tox sections of the labeling until the NDA is submitted.

Clinical Data Section

The firm said that for the clinical data sections of the labeling, they plan of justifying the current labeling and will also look at literature sources since 1997 for updated information. Dr. Throckmorton said this was acceptable.

**Conclusion**

The Division said the firm would need to demonstrate the bioequivalence of digoxin elixir to the RLD. The Division will not grant a waiver for doing pediatric studies pursuant to the Pediatric Rule and the firm will need to conduct an extensive literature search to justify the current pediatric labeling for digoxin Tablets.

Roxane affirmed their commitment to do the appropriate bioequivalence studies and to collect the necessary information to justify the pediatric section of the labeling. They noted that they plan on submitting their application in the last quarter of 2002.

Minutes Preparation: Edward Fromm

Edward Fromm

Concurrence Chair: 4.25.02

Douglas C. Throckmorton, M.D.

cf/dr-4-02-02/4-29-02

Rd: RMittal-4-3-02
GRobbie-4-24-02
CResnick-4-24-02
NMorgenstern-4-25-02
NStockbridge-4-25-02
DThrockmorton-4-26-02

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| | |
|---|---|
| **Transmitted to FAX Number:** | (614) 276-2470 |
| **Attention:** | Mr. Gregory Hicks |
| **Company Name:** | Roxane Laboratories |
| **Phone:** | (614) 241-4106 |
| **Subject:** | **Confirmation of meeting w/FDA, March 27, 2002 Digoxin Elixir** |
| **Date:** | February 28, 2002 |
| **Pages including this sheet:** | **2** |
| **From:** | **Edward Fromm** |
| **Phone:** | **301-594-5313** |
| **Fax:** | **301-594-5494** |

Confirmation of Meeting

| | |
|---|---|
| Drug: | Digoxin Elixir |
| Sponsor: | Roxane Laboratories |
| Subject: | 505(b)(2) Requirements |
| Date Requested: | February 22, 2002 |
| Date Confirmation Faxed: | February 28, 2002 |
| Meeting Date: | March 27, 2002 |
| Meeting Time: | 10:30A.M.-12:00 P.M. |
| Location: | conference Room "F", Fifth floor, Woodmont Office Complex 2<br>1451 Rockville, Pike, Rockville, MD |

FDA Participants:

Douglas Throckmorton, M.D., HFD-110, Acting Division Director
Norman Stockbridge, M.D., Ph.D., HFD-110, Team Leader/Medical, HFD-110
Angelica Dorantes, Ph.D., HFD-860, Clinical Pharmacologist and Biopharmaceuticist
Gabriel Robbie, Ph.D., HFD-860, Clinical Pharmacologist and Biopharmaceuticist
Charles Resnick, Ph.D., HFD-110, Pharmacology Team Leader
Kasturi Srinivasachar, Ph.D., HFD-810, Team Leader, Division of New Drug Chemistry I
Natalia Morgenstern, HFD-110, Chief, Project Management Staff
Edward Fromm, HFD-110, Project Manager