# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**022036Orig1s000**

# CHEMISTRY REVIEW(S)

**CMC BRANCH CHIEF MEMORANDUM**

| | |
|---|---|
| **To:** | NDA 22-036 |
| **From:** | Ramesh Sood, Ph.D., Branch Chief, ONDQA |
| **Date:** | 2-Dec-2008 |
| **Drug:** | Doxepin hydrochloride tablets |
| **Route of administration:** | Oral |
| **Strength:** | 1, 3 and 6 mg. |
| **Subject:** | **Approval** recommendation for NDA 22-036 |

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**Introduction:** Doxepin Hydrochloride has been marketed by Pfizer since 1969 for the treatment of depression, anxiety, and psychotic depressive disorders. It is available, under the tradename Sinequan®, as 10-, 25-, 50-, 75-, 100-, and 150 mg capsules and 10 mg/mL oral concentrate. In the current NDA, Somaxon proposes to market doxepin, under the tradename Silenor™, for treatment of insomnia. The product will be available as 1-, 3-, and 6 mg tablets. Silenor Tablets will be packaged in 30-, 100- and 500-count HDPE bottles, 4-count blister packs (physician sample), and 30-count blister packs.

**Drug Substance:** The active ingredient, Doxepin Hydrochloride, USP, [chemical name: 3-dibenz[*b,e*]oxepin- 11(6*H*)ylidene-*N*,*N*-dimethyl-1-propanamine hydrochloride] is a member of the tricyclic class of antidepressants. It is a well characterized small molecule with molecular formula $C_{19}H_{21}O$•HCl and molecular weight 315.84. Doxepin hydrochloride is readily soluble in water. The active moiety, doxepin, exists as an approximately (b) (4) mixture of *E*- and *Z*-isomers. The relative amounts of the two geometric isomers are controlled through drug substance specification. The drug substance CMC information is referenced to DMF (b) (4). The DMF was reviewed and found to be inadequate to support this NDA. Subsequently, the DMF holder provided adequate responses to the communicated CMC deficiencies and the DMF is found to be adequate to support this NDA.

The quality of the drug substance is assured through drug substance specification by the applicant. The drug substance acceptance specification established by the applicant includes testing for Description, identification (by IR and UV), loss on drying, residue on ignition, melting range, quantification of counter ion chloride, assay, limit of two geometric isomers, heavy metals, residual solvents, particle size distribution and related substance.

**Drug product:** The drug product is (b) (4) (1 mg), blue (3 mg) or green (6 mg) oval-shaped tablets debossed (b) (4) "3" or "6" on one side and "SP" on the other side. The drug product is manufactured at a (b) (4) The excipients used in the manufacture of the drug product are (b) (4) (b) (4) magnesium stearate, colloidal silicon dioxide, yellow no. 10 (b) (4), Blue no. 1 (b) (4) All tablets have the same excipients and a target weight of (b) (4). The manufacturing process includes (b) (4) The quality of the drug product is assured through appropriate in-process controls and the final product specification. The final drug product specification include tests and limits for description, identification (by HPLC), assay and

limits for each geometric isomer (HPLC), impurities (HPLC), uniformity of dosage form (HPLC), dissolution and moisture content. All analytical methods used for drug product testing have been adequately described and validated.

Based on the 24 months of long term stability data and 6 months of accelerated stability data for the nine batches in the registration stability study the applicant has concluded that the drug product packaged in (b) (4) blister or in the HDPE bottles (30-count/40mL, 100-count/60 mL or 500-count/150 mL) can be stored at controlled room temperature or up to 36 months. As such, the applicant has requested a 36-month expiry for the drug product. A 36-month expiration date is recommended for the drug product stored at 25 °C (77 °F) with excursions permitted to 15-30 °C (59-86 °F) (USP Controlled Room Temperature) based on the evaluation of provided stability data for the registration batches and supporting stability data.

(b) (4)

The Office of Compliance has provided an overall acceptable recommendation for all the manufacturing sites.

**Recommendation:** All CMC related issues had been resolved for this application. The application is recommended for **"Approval"** from the CMC perspective.

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/s/

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Ramesh Sood
12/2/2008 10:29:55 AM
CHEMIST

# NDA 22-036

## Silenor (doxepin HCl) Tablets

## Somaxon Pharmaceuticals, Inc

**Sherita D. McLamore, Ph.D.**
Division of Pre-Marketing Assessment 1
Office of New Drug Quality Assessment

# Table of Contents

Executive Summary Section

# Chemistry Review Data Sheet

1. NDA: 22-036

2. REVIEW: #1

3. REVIEW DATE: August 15, 2008

4. REVIEWER: Sherita D. McLamore, Ph.D.

5. PREVIOUS DOCUMENTS:

| Previous Documents | Document Date |
|---|---|
| n/a | |

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
|---|---|
| Original Submission | January 30, 2008 |
| Amendment | July 24, 2008 |
| Amendment | August 29, 2008 |
| Amendment | August 11, 2008 |

7. NAME & ADDRESS OF APPLICANT:

| | |
|---|---|
| Name: | Somaxon Pharmaceuticals, Inc. |
| Address: | 3721 Valley Centre Drive, Suite 500<br>San Diego, CA 92130 |
| Representative: | James L'Italien, Ph.D. |
| Telephone: | 858-480-0400 |

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Silenor
b) Non-Proprietary Name (USAN): doxepin HCl
c) Code Name/# (ONDC only): n/a
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Insomnia

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 1 mg, 3 mg and 6 mg

13. ROUTE OF ADMINISTRATION: Oral

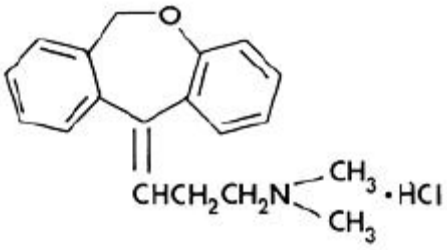
14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X___Not a SPOTS product

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

Chemical Names: 1-Propanamine,3-dibenz[*b,e*]oxepin-11(6*H*)ylidene-*N,N*-dimethyl-hydrochloride
Molecular Weights: 315.84
Molecular Formula: $C_{19}H_{21}NO$•HCl
CAS Registry Number:1229-29-4



## 17. RELATED/SUPPORTING DOCUMENTS:

### A. DMFs:

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE [1] | STATUS [2] | DATE REVIEW COMPLETED | COMMENTS |
|---|---|---|---|---|---|---|---|
| (b) (4) | II | (b) (4) | Doxepine HCl | 1 | Inadequate | 8/15/08 | |
| | III | | (b) (4) | 3 | adequate | 9/24/07 | |
| | III | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |
| | II | | | | | | |

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

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

### B. Other Documents:

Executive Summary Section

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|---|---|---|
| | | |
| | | |
| | | |

18. STATUS:

**ONDC:**

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| Biometrics | N/A | N/A | N/A |
| EES | Acceptable | 04/15/08 | Sherita McLamore, Ph.D. |
| Pharm/Tox | N/A | N/A | N/A |
| Biopharm | N/A | N/A | N/A |
| LNC | N/A | N/A | N/A |
| Methods Validation | Acceptable | Acceptable | Sherita McLamore, Ph.D. |
| DMETS | N/A | N/A | N/A |
| EA | Categorical Exclusion 21 CFR 25 31(b) *Acceptable* | 1/30/08 | Sherita McLamore, Ph.D. |
| Microbiology | N/A | N/A | N/A |

# The Chemistry Review for NDA 22-036

## *The Executive Summary*

### A. Recommendation and Conclusion on Approvability

The Chemistry, Manufacturing, and Controls (CMC) section of NDA 22-036 is approvable. The approval of this application from a CMC perspective is contingent on an acceptable response to the following CMC deficiencies:

1. [redacted]

2. You indicate that the basis for manufacturing tablets with average hardness values of [redacted] were:
   - The multi-point dissolution profiles for uncoated tablets with average hardness values of [redacted] and [redacted] are similar with a $f_2$ value of [redacted].
   - Development multi-point dissolution profiles for colored, uncoated tablets with an average hardness of [redacted] and film-coated

tablets with an average hardness of [redacted] (b) (4) are similar with a $f_2$ value of [redacted] (b) (4)

You further indicate that the tablets will have a [redacted] (b) (4) that is spread further apart on the surface of the tablet. Indicate if the film coated tablets used in the above studies had a [redacted] (b) (4) that is spread further apart on the surface of the tablet.

3. Include a test and an acceptance criterion for the microbial limits in the drug product specification or justification for the exclusion as per ICH Q6A.

4. The acceptance criterion for the unidentified impurities should be based on the maximum daily dose and not the potency. As such, we request that you provide a single, uniform acceptance criterion for the individual unidentified impurities for the 1 mg, 3 mg and 6 mg drug product based on the maximum daily dose as per ICHQ3B (R)

5. The test method and acceptance criterion that you proposed for the identification of the drug substance in the drug product is not specific. Adopt a method that is specific for the drug substance or include a second chromatographic procedure that is based on a different separation method as outlined in ICH Q6A

6. The strength of the drug product is expressed as Doxepin; however, Doxepin HCl is listed on the label as an established name. Revise the label so that the established name corresponds to the strength.

7. [redacted] (b) (4)

8. The results of the multi-media dissolution study were [redacted] (b) (4) in 15 minutes for all samples tested. As such, we recommend that you revise the dissolution specification to Q=[redacted] (b) (4) in 15 minutes to be more reflective of the data and consistent with BCS Class 1 compounds.

9. Include a statement in the Precautions section of the draft package insert regarding the inclusion of [redacted] (b) (4) in the drug product formulation as per 21 CFR 201.20.

10. The limit that you propose for the total impurity is excessively broad and not reflective of the data. Revise the acceptance criteria for the total impurity to be more reflective of the data.

11. In the stability section of your application, you indicate that photostability studies were performed on the exposed drug product. ICH Q1B indicates the following:

    *…the studies on drug products should be carried out in a sequential manner starting with testing the fully exposed product then progressing as necessary to the product in the immediate pack and then in the marketing pack. Testing should progress until the results demonstrate that the drug product is adequately protected from exposure to light…*

As such, we request that you provide additional photostability data to demonstrate that the primary and or secondary packaging provides adequate protection for the drug product when exposed to light.

12. (b) (4) DMF (b) (4) for the manufacture of Doxepin HCl is deficient. The DMF holder has been notified of this by separate letter which includes a list of the deficiencies

Furthermore, DMF (b) (4) was reviewed in conjunction with this application for the manufacture and control of the drug substance. The DMF is inadequate to support this NDA. The DMF holder was sent a deficiency letter on August 15, 2008. Accordingly, approval of this applicant is also contingent on acceptable response to the deficiencies sent to the holder of DMF (b) (4).

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

N/A

## II. Summary of Chemistry Assessments

Doxepin Hydrochloride is the active pharmaceutical ingredient in this application. The drug substance is a tricyclic molecule that is marketed as a geometric isomeric mixture which contains between (b) (4) of the (*Z*)-isomer and between (b) (4) of the (*E*)-isomer. The drug substance is a white crystalline powder with an amine-like odor and is being manufactured and released by (b) (4) It is currently marketed for use in the use in the United States as an oral antidepressant and anxiolytic under NDAs 16-798 and NDA 17-516 (Sinequan® Capsules and Sinequan® Oral Concentrate) and as a topical cream used in the treatment of moderate pruritis under NDA 20-126 (Zolalon® 5% Cream). The applicant references DMF (b) (4) for all relevant information pertaining to the manufacture, control and release of the drug substance. DMF (b) (4) was reviewed in conjunction with this application and at this time is not adequate to support this application. A deficiency letter was sent to the holder on September 16, 2008. We are currently awaiting a response from the holder.

The drug product, Silenor (doxepin HCl) Tablets, is being developed for treatment of insomnia. The drug product is manufactured at a (b) (4) The excipients used in the manufacture of the drug product are ) magnesium stearate, colloidal silicon dioxide, yellow no. 10 (b) (4) Blue no. 1 (b) (4) The oval shaped tablets are available in three strengths, 1 mg, 3 mg and 6 mg. All tablets have the same excipients and a target weight of (b) (4). The 1 mg tablets are (b) (4) The 3 mg tablets are blue with “SP” debossed on one side

and the number 3 on the other. The 6 mg tablets are green with "SP" debossed on one side and the number 6 on the other.

The drug product will be packaged into 40 mL, 60 mL or 150 mL HDPE bottles which correspond to 30, 100 and 500 tablets counts, respectively. The drug product will also be packaged into (b) (4) blister strips. The blister strips will be incorporated into a 4 count physician sample, a 7 count physician sample and a 30 count trade pack. Packaging into the HDPE bottles and blister strips will accomplished by (b) (4) and (b) (4) respectively. The applicant includes a complete description of each of the packaging component including manufacturers, certificates of analyses, drawings, diagrams and specifications for the components.

As indicated in the stability section of this review, the applicant includes 24 months of long term stability and 6 months of accelerated data for nine batches (3 batches each strength) of the drug product. Six months of data were also provided for three batches (1 batch each strength) of supportive data and three batches (1 batch each strength) for the drug product scale-up confirmation stability batches. The drug product was packaged in 30, 100 and 500 count HDPE bottles and in (b) (4) blisters. One batch of each strength was packaged in the 4-count blister strips to qualify (b) (4). as a commercial packager. Additionally, the three scale-up confirmation batches were packaged in 30-count/40 mL HDPE bottles. The stability protocol utilizes a (b) (4) design for the registration stability study. (b) (4) was applied to the container closure system and (b) (4) was applied to the testing points the long term study (see page 66 of this review). The applicant tests the following attributes on stability: assay, E-isomer, Z-isomer, impurities, appearance, hardness, friability, dissolution and moisture. The acceptance criteria for he tests on stability were identical to those proposed for the commercial product. There was a slight decrease in assay and hardness and an increase in moisture for samples stored in the (b) (4) blisters. The dissolution, *E*-isomer, *Z*-isomer, impurities, appearance, and friability remained virtually unchanged. All data for all batches in all packaging configurations were acceptable and within the prescribed acceptance criteria.

Based on the 24 months of long term stability data and 6 months of accelerated stability data for the nine batches in the registration stability study the applicant has concluded that the drug product packaged in (b) (4) blister or in the HDPE bottles (30-count/40mL, 100-count/60 mL or 500-count/150 mL) can be stored at controlled room temperature or up to 36 months. As such, the applicant has requested a 36-month expiry for the drug product. At this time, a decision on the expiry will not be made. We will defer setting an expiry for the drug product until all information pertaining to this application has been received and evaluated.

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

The drug product, Silenor (doxepin HCl) tablets, is being developed for treatment of insomnia. The drug product is manufactured as 1 mg, 3 mg and 6 mg immediate release tablets. The active is currently approved for use in a topical cream and in two oral formulations. The approved dose for the two oral formulations is 75- 100 mg/day. The maximum daily dose of the drug product is 6 mg.

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

NDA 22-036 is Approvable from a Chemistry standpoint due to chemistry, manufacturing and controls concerns related to the drug substance and the drug product as outlined in this review.

## III. Administrative

**A. Reviewer's Signature**

**B. Endorsement Block**

SMcLamore/Date
RSood

**C. CC Block**

Orig. NDA 22-036

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/s/
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Sherita McLamore
9/24/2008 09:58:19 PM
CHEMIST

Ramesh Sood
9/26/2008 09:05:21 AM
CHEMIST

# Initial Quality Assessment
# Branch I
# Pre-Marketing Assessment Division I

| | |
|---|---|
| **OND Division:** | Division of Neurology Products |
| **NDA:** | 22-036 |
| **Applicant:** | Somaxon Pharmaceuticals |
| **Stamp Date:** | 31-Jan-2008 |
| **PDUFA Date:** | 30-Nov-2008 |
| **Trademark:** | Silenor™ |
| **Established Name:** | Doxepin (HCl) |
| **Dosage Form:** | Tablet |
| **Route of Administration:** | Oral |
| **Indication:** | Insomnia |
| **PAL:** | Martha R. Heimann, Ph.D. |

| | Yes | No |
|---|---|---|
| **ONDQA Fileability:** | ☒ | ☐ |
| **Comments for 74-Day Letter** | ☐ | ☒ |

## Summary and Critical Issues:

### *Summary*

Doxepin Hydrochloride has been marketed by Pfizer since 1969 for treatment of depression, anxiety, and psychotic depressive disorders. It is available, under the tradename Sinequan®, as 10-, 25-, 50-, 75-, 100-, and 150 mg capsules and 10 mg/mL oral concentrate. In the current NDA, Somaxon proposes to market doxepin, under the tradename Silenor™, for treatment of insomnia. The product will be available as 1-, 3-, and 6 mg tablets. Silenor Tablets will be packaged in 30-, 100- and 500-count HDPE bottles, 4-count blister packs (physician sample), and 30-count blister packs (trade).

*Drug Substance*

The active ingredient, Doxepin Hydrochloride, USP, [chemical name: 3-dibenz[*b,e*]oxepin-11(6*H*)ylidene-*N,N*-dimethyl-1-propanamine hydrochloride] is a member of the tricyclic class of antidepressants. It is a well characterized small molecule with molecular formula $C_{19}H_{21}O•HCl$ and molecular weight 315.84. Doxepin hydrochloride is readily soluble in water. The active moiety, doxepin, exists as an approximately (b) (4) mixture of *E*- and *Z*-isomers.

The bulk drug substance is manufactured by (b) (4). (b) (4) is cross-referenced for CMC information. The DMF has been reviewed previously and found adequate; however, the most recent DMF review is dated 14-Aug-2002. Acceptance testing performed by the drug product manufacturer (b) (4), acceptance criteria, and supporting validation data are included in the NDA itself. The applicant also provides drug substance

solubility and permeability data (b) (4)

*Drug Product*

The proposed product is a conventional, oval shaped, immediate release, tablet that will be available in three strengths, 1 mg (b) (4), 3 mg (blue) and 6 mg (green). The quantitative composition is given in the applicant's Table 2.3.P.1-1 below.

Best Possible Copy

**Table 2.3.P.1-1 Composition of Silenor Tablets (1 mg, 3 mg, and 6 mg)**

| Name of Ingredient | Reference to Standards | Function | Unit Formula (mg) | | |
|---|---|---|---|---|---|
| | | | 1 mg | 3 mg | 6 mg |
| Doxepin HCl | USP | Drug Substance | (b) (4) | 3.39 [b] | 6.78 [c] |
| (b) (4) | | | | | |
| Magnesium Stearate [d] (b) (4) | USP/NF | | | | |
| Colloidal Silicon Dioxide [e] | USP/NF | | | | |
| (b) (4) | D&C | | | | |
| | FD&C | | | | |
| Blue No. 1 (b) (4) | FD&C | | | | |
| **Total Tablet Weight** | | | **150 mg** | | |

[a] Equivalent to 1.0 mg of doxepin as the free base
[b] Equivalent to 3.0 mg of doxepin as the free base
[c] Equivalent to 6.0 mg of doxepin as the free base
[d] Silicified Microcrystalline Cellulose (*Microcrystalline Cellulose, USP/NF, Ph.Eur., JP, and Colloidal Silicon Dioxide, USP/NF, Silica Colloidal Anhydrous, Ph.Eur., Light Anhydrous Silicic Acid, JP*) (b) (4)

Differences between the compositions of the proposed commercial tablets, clinical trial materials used for Phase 2 and Phase 3 clinical studies, and registration stability batches are noted below:

- Phase 2 efficacy trials were performed using 1 mg, 3 mg, and 6 mg doxepin capsules rather than tablets.
- Phase 3 clinical tablets were white; the registration stability batches and commercial tablets include colorants in tablet matrix.
- (b) (4)

Silenor Tablets will be packaged for commercial distribution in 30-, 100- and 500-count HDPE bottles with (b) (4) child-resistant closures, and in 30-count (b) (4)/Aluminum blister cards. Physician samples will be packaged in 4-count (b) (4)/Aluminum blister cards.

The drug product is manufactured by (b) (4) using conventional (b) (4) techniques. Process flow diagrams and a brief narrative description of the manufacture of (b) (4) batch (b) (4) of 6 mg tablets are provided. The applicant states that the manufacturing process for all three strengths is the same. It is noted that the applicant has not identified any manufacturing steps or process controls as critical to ensure product quality.

The proposed regulatory specifications for Silenor Tablets are summarized in the applicant's Table 3.2.P.5.1-1 below.

**Table 3.2.P.5.1-1 Specification for Silenor Tablets (1 mg, 3 mg and 6 mg)**

| Test Name | Test Method Title | Method Number | Acceptance Criteria |
|---|---|---|---|
| Description | Organoleptic-Observation | (b) (4) | (b) (4) blue (3 mg) or green (6 mg) oval tablet debossed (b) (4) 3', or '6' on one side and 'SP' on the other side. |
| Identification | HPLC Release/Stability Assay, Content Uniformity, Blend Uniformity, Determination of E- and Z- Isomers, and Identification by HPLC | | The retention times of the peaks [Doxepin (E-Isomer) and Doxepin (Z-Isomer)] in the sample solution chromatogram must match those of the corresponding peaks in the standard solution chromatogram. |
| Doxepin Assay<br>E-Isomer<br>Z-Isomer | HPLC Release/Stability Assay, Content Uniformity, Blend Uniformity, Determination of E- and Z- Isomers, and Identification by HPLC | | (b) (4) of label claim |
| Identified Impurities<br>(b) (4) | Related Substances | | NMT (b) (4)<br>NMT<br>NMT |
| Unidentified Impurities | | | NMT (b) (4)<br>NMT |
| Total Impurities | | | NMT (b) (4) |
| Uniformity of Dosage Units (By Content Uniformity) | HPLC Release/Stability Assay, Content Uniformity, Blend Uniformity, Determination of E- and Z- Isomers, and Identification by HPLC | | Meets USP <905> requirements |
| Dissolution | Dissolution | | NLT (b) (4) Q) in 30 minutes |
| Moisture Content (Karl Fischer) | Water (b) (4) | | NMT (b) (4) |

The proposed analytical procedures are relatively straight-forward. Two closely related HPLC methods are used for determination of doxepin content, content uniformity and related substances. A separate, unrelated, HPLC method is used for quantitation of dissolution results. The analytical procedures that are proposed for control of Silenor Tablets are not derived from the compendial methods described in the USP monographs for Doxepin Hydrochloride and Doxepin Hydrochloride Capsules.

The application contains stability data through 6 months under accelerated storage conditions and 24 months under long term conditions. It is noted, however, that the applicant applied a combination of (b) (4) of container sizes and (b) (4) of testing time points to the design of the registration stability protocol. The resulting protocol includes both HDPE bottles and blister packaging within the same (b) (4) design. Additionally, testing at the 3, 6, 9 and 18 month test points is reduced by two thirds. The applicant did not consult with the Agency regarding the adequacy of the stability protocol prior to initiation of stability studies.

(b) (4)

## *Critical issues for review*

*Drug Substance*

No critical issues related to the drug substance are identified. The applicant's proposal to (b) (4)

*Drug Product*

Although this is a simple dosage form, there are a number of issues related to the adequacy of the documentation provided in the application to support product performance and quality.

- *Pharmaceutical development.* Initial clinical trials (through Phase 2) for the insomnia were performed using capsules rather than tablets. Consequently, the applicant has limited manufacturing experience with the tablet formulations. An apparent lack of formulation and process understanding is reflected by an abbreviated pharmaceutical development section. (b) (4)

- M*anufacturing process and controls:* As noted above, the applicant provides a very brief process narrative in lieu of master batch records. Whether the process narrative provides sufficient detail to allow for meaningful evaluation is unclear. It is noted that the applicant makes a number of general statements about manufacturing principles (e.g., (b) (4) without providing specific details.

- *Drug product specification:* The applicant provides minimal information to justify the proposed specification or choice of test methods. As an example, the proposed dissolution procedure uses (b) (4) No data to support the choice of test parameters, sampling time or proposed acceptance criteria are provided. The applicant does state that (b) (4) The referenced dissolution data could not be located within the application.

  There is minor problem with acceptance criteria for unidentified related substances. The applicant proposes limits on NMT (b) (4)% for individual unidentified impurities the 1 mg and 3 mg tablets versus NMT (b) (4)% in 6 mg tablets. This discrepancy appears to result from misinterpretation of the ICH guidance and application of the identification threshold to individual tablet strengths rather than to the maximum daily intake.

- *Container closure systems:* Results of photostability testing on exposed tablets indicate that the product is photolabile. The applicant recommends that a "protect from light" statement be included in the label. While the proposed HDPE bottle configuration would be expected to provide adequate protection from light, the blister package may not. For blister cards, the applicant is relying on secondary packaging (e.g., (b) (4) to provide light protection. The possibility that the blisters will be removed from the secondary packaging should be considered during the review.

- *Stability:* As noted, the applicant has used a (b) (4) approach in the design of the registration stability protocol. The adequacy of the stability protocol should be determined prior to use of the resulting stability data to establish the expiration dating period based on the primary stability studies.

## *Additional issues*

*Fileability.* Although the NDA provides limited CMC information, it contains the minimum documentation required under 21 CFR §314.50 to support filing the application for review.

*Administrative:* A claim for categorical exclusion is provided in Module 1. Categorical exclusion is claimed under 21 CFR §25.31(b).

*Establishment Evaluation:* All manufacturing facilities listed in Attachment 1 were entered into EES for compliance evaluation on 12-Feb-2008

*Labeling/Established Name*: Labeled potency of the proposed product is stated as content of doxepin (base). To assure consistency between label potency and the established name, the product should be labeled as 'doxepin tablets', rather than doxepin hydrochloride tablets'. It is noted that Doxepin Hydrochloride is recognized as USAN, and that the USP monographs for the capsule and oral solution include the salt form in the official name. It is anticipated that the USP will update the current monographs to ensure consistency between established name and labeled potency at some time in the future.

## *Comments for 74-Day Letter*

There are no comments for the 74 day letter. Although the NDA contains minimal CMC information; there do not appear be any major issues that could be addressed with the applicant prior to a detailed review of the supporting data.

## Review, Comments and Recommendation:

The NDA is marginally fileable from a CMC perspective. (b) (4) The submission does not appear to require a review by the Manufacturing Sciences Branch; however that reviewer may wish to consult with the Manufacturing Science Branch regarding process development issues and details of the (b) (4) Assignment of the NDA to a single reviewer is recommended.

Martha R. Heimann, Ph.D. 19-Feb-2008
Pharmaceutical Assessment Lead Date

Ramesh Sood, Ph.D. 19-Feb-2008
Branch Chief Date

# ATTACHMENT 1

## Manufacturing Sites for Doxepin HCl Tablets

| Facility Information | Function |
|---|---|
| (b) (4) | |

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

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/s/
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Martha Heimann
2/19/2008 09:56:05 AM
CHEMIST

Ramesh Sood
2/19/2008 11:11:44 AM
CHEMIST