

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-306

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

05 May 2009

NDA: 22-306/N-000

Drug Product Name

Proprietary: So-Aqueous.
Non-proprietary: Sotalol Injection.
Drug Product Priority Classification: S.

Review Number: 1

Dates of Submission(s) Covered by this Review

Letter	Stamp	Review Request	Assigned to Reviewer
25 JUL 2008	25 JUL 2008	25 AUG 2008	28 AUG 2008
29 JAN 2009	05 FEB 2009	N/A	N/A

Applicant/Sponsor

Name: Academic Pharmaceuticals, Inc.
Address: 21 N. Skokie Hwy. G-3
Lake Bluff, IL 60044
Representative: Not provided in review materials.
Telephone:

Name of Reviewer: John W. Metcalfe, Ph.D.

Conclusion: Recommend approval.

Product Quality Microbiology Data Sheet

- A. 1. **TYPE OF SUBMISSION:** Original NDA.
2. **SUBMISSION PROVIDES FOR:** A new drug product.
3. **MANUFACTURING SITE:**
Bioniche Teoranta
Coill Rua
Inverin
Co. Galway, Ireland
4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
➤ Solution in glass vial.
➤ Intravenous injection.
➤ 15 mg/mL.
5. **METHOD(S) OF STERILIZATION:** — filtration followed by
— processing. **b(4)**
6. **PHARMACOLOGICAL CATEGORY:** The subject drug product is intended to be a substitute for oral sotalol in patients who are unable to take oral medication.
- B. **SUPPORTING/RELATED DOCUMENTS:** Microbiology Review (dated 05 DEC 2006) of DMF 10953; *Helvoet Pharma, Rubber Compounds Manufactured in Pennsauken, New Jersey, Alken, Belgium, and Pregnana Milanese, Italy.*
- C. **REMARKS:**
The subject NDA is a paper submission. Four red jackets (Module 3, Volume 1.1 through Module 3, Volume 1.4) were provided for review.
- An Initial Quality Assessment was performed by the ONDQA PAL (review date: 15 August 2008). No specific issues pertaining to the microbiological quality of the subject drug product were raised in the IQA.
- The following Request for Information was provided to the OND Project Manager to be forwarded to the applicant on 07 January 2009:
A sterility assurance review of NDA 22-306 is on-going.
- The following is stated in Module 3.2.P.3.5, Section B.2 of the subject submission regarding holding periods:
“Validated hold times, as required according to CFR 211.111, will be established as part of process validation prior to marketing of this product.”
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b(4)

└ Include data or a rationale in support of these holding periods.

The applicant amended the application on 29 January 2009 with a commitment regarding the maximum holding periods. The amendment is summarized and reviewed in appropriate sections of this review.

An additional request for information was forwarded to the applicant on 11 February 2009. Following is this reviewer's comment and information request:

Reviewer Comment

The draft labeling states that the drug product will be diluted in one of three diluents and administered by infusion over — hours. However, the labeling makes no statement regarding how long, or at what storage conditions the final prepared solution may be held prior to the initiation of patient administration. Further, it is unknown as to whether the final solutions will support the growth of adventitious microorganisms which may contaminate the drug solution during final preparation.

b(4)

Please amend the application with the following:

- Modify Section 2.3 of the draft labeling information with a statement which specifies the maximum holding time and storage conditions (e.g.: temperature(s)) of the final prepared solution(s) prior to patient administration.
- Provide a risk assessment report summarizing studies that show adventitious microbial contamination does not grow under the storage and infusion conditions. Reference is made to *Guidance for Industry: ICH Q8 Pharmaceutical Development*, Section II.E and *Guidance for Industry: ICH Q1A(R2) Stability Testing of New Drug Substances and Products*, Section 2.2.7. For this product, the holding period is defined as: ┌

b(4)

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The report should describe test methods and results that employ a minimum countable inoculum to simulate potential microbial contamination that may occur during product dilution. It is generally accepted that growth is evident when the population increases more than 0.5 Log₁₀. The test should be run at the label's recommended storage conditions and be conducted for 2 to 3-times the holding period

b(4)

and using the label-recommended fluids. Periodic intermediate sample times are recommended.

Challenge organisms may include strains described in USP <51> plus typical skin flora or species associated with hospital-borne infections.

The applicant amended the application with a study addressing this information request. A summary of the study was provided to this reviewer electronically on 01 May 2009. This study is summarized and reviewed in Section 2.A. of this review.

File Name: N022306R1.doc

Executive Summary

I. Recommendations

- A. **Recommendation on Approvability** – NDA 22-306/N-000 is recommended for approval on the basis of product quality microbiology.
- B. **Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – Not applicable.

II. Summary of Microbiology Assessments

- A. **Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** - The bulk drug solution is compounded and then filtered through _____ filters in series prior to being _____ filled into _____ glass vials and sealed with _____ stoppers. b(4)
- B. **Brief Description of Microbiology Deficiencies** – There are no microbiology deficiencies identified.
- C. **Assessment of Risk Due to Microbiology Deficiencies** – Not applicable.

III. Administrative

- A. **Reviewer's Signature** _____
John W. Metcalfe, Ph.D.
- B. **Endorsement Block** _____
Stephen Langille, Ph.D.
- C. **CC Block**
N/A

10 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

Withheld Track Number: Microbiology-1

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

/s/

John Metcalfe
5/7/2009 11:13:11 AM
MICROBIOLOGIST

Stephen Langille
5/7/2009 11:15:49 AM
MICROBIOLOGIST
I concur with the conclusions of this review.