CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-412

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review
Review for HFD-120
6 June 2002

NDA: 21-412

Drug Product Name
Proprietary: Zolpidem Tartrate Rapidly Dissolving Tablets
Non-proprietary: Zolpidem Tartrate Rapidly Dissolving Tablets
Drug Product Classification: Treatment for Insomnia

Review Number: 1

Subject of this Review
Submission Date: 12/29/01
Receipt Date: 2/4/02
Consult Date: 2/14/02
Date Assigned for Review: 2/28/02

Applicant/Sponsor
Name: Biovail Technologies, Inc.
Address: 5701 Concorde Parkway
Chantilly, VA 20151
Representative: Wayne Kreppner
Telephone: (703) 995-2444

Niall Morrissey, Regulatory Affairs Associate (Ireland)
Phone +353 1-294 1887

Name of Reviewer: James L. McVey

Conclusion: The application is recommended for approval from a product quality microbiology perspective.

Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUPPLEMENT:** n.a.

2. **SUPPLEMENT PROVIDES FOR:** n.a.

3. **MANUFACTURING SITE:** Biovail Technologies Limited
3725 Concorde Parkway
Chantilly, VA 20151

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Tablet, 10 mg.

5. **METHOD(S) OF STERILIZATION:** n.a.

6. **PHARMACOLOGICAL CATEGORY:** for treatment of insomnia

B. **SUPPORTING/RELATED DOCUMENTS:** FAXed response to phone call request for clarification. FAX dated May 17, 2002.

C. **REMARKS:** Components s [redacted] b(4)

[redacted] No microbial limits release testing is required (ICH Q6a).

filename: 21412r1

APPEARS THIS WAY
ON ORIGINAL

Executive Summary

I. **Recommendations**

A. **Recommendation on Approvability** - The application is recommended for approval from a product quality microbiology perspective.

B. **Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – n.a.

II. **Summary of Microbiology Assessments**

A. **Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** – Microspheres are formed using

b(4)

specifications include a test for moisture and the limit is NMT —%. b(4)

B. **Brief Description of Microbiology Deficiencies – none.**

C. **Assessment of Risk Due to Microbiology Deficiencies – n.a.**

III. **Administrative**

A. **Reviewer's Signature** _____

B. **Endorsement Block**
Review Microbiologist: James L. McVey
Microbiology Supervisor; P.H. Cooney

C. **CC Block**
DFS, NDA 21-412
HFD- 805/Division File/21412r1

Product Quality Microbiology Assessment

A. TERMINAL MOIST HEAT STERILIZATION – n.a.

B. OTHER TERMINAL STERILIZATION PROCESSES – n.a.

C. ASEPTIC FILL MANUFACTURING PROCESS – n.a.

D. MISCELLANEOUS – n.a.

E. MAINTENANCE OF MICROBIOLOGICAL CONTROL AND QUALITY: STABILITY CONSIDERATIONS

The three exhibit batches were all put on stability testing. Monthly data is collected for packages stored at 40°C/75% RH for 3 months. Product stored at 25°C/60% RH and 30°C/60% RH were tested at 0,1, and 3 months. The 25°C/60% RH study will continue for 36 months. The 30°C/60% RH study will continue for 12 months. The 40°C/75% RH study will continue for 6 months. Based on the currently submitted data, expiration dating of 24 months at temperature at or below 30°C is proposed. Residual moisture is specified in the testing requirements to be ≤ —%. Microbial growth would not occur at this moisture level. b(4)

E.1. Container Closure Integrity - The tablets are packaged in ——— ——— blisters with child resistant lidstock. The package conforms to USP<661> parameters (p.80). b(4)

E.2. Pyrogen/Endotoxin Testing – n.a.

E.3. Microbial Limits Testing – not specified. Not needed if moisture levels are measured and remain within specifications.

F. RELEASE TESTS

F.1. Pyrogen/Endotoxin Testing – n.a.

F.2. Sterility Test – n.a.

F.3. Microbial Limits Testing –The product is a dry dosage form (tablet) and is manufactured under conditions which prevent contamination with microorganisms and may even reduce the level . The finished product specifications require that the moisture be NMT —%. Tablets with moisture at NMT —% are not likely to support microbial growth. This conclusion should be made by the applicant and provided to us. Several phone call requests were made and not answered. Finally, the applicant called from Ireland to respond. This FAX response was timely and satisfactory. The applicant is well aware of the conditions necessary to establish and maintain low or no microbial load in the finished product. Points made in the FAX are:

b(4)

- **All critical surfaces are sanitized with —— prior to a production run.**
- **CGMP practices are employed, including microbiological monitoring and control of facilities and ingredients.**
- **HEPA air systems and gowning are employed during manufacturing.**
- **——————————————**

b(4)

- **—————— are not conducive to microbial growth.**
- **The package is highly moisture resistant.**

Acceptable

G. LABELING – n.a.

H. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENT - None

2 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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

/s/

James McVey
6/17/02 01:53:42 PM
MICROBIOLOGIST

Peter Cooney
6/17/02 03:59:21 PM
MICROBIOLOGIST