CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202236Orig1s000

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

10 January 2012

NDA 202-236/N-000

Drug Product Name

Proprietary: Dymista (proposed)
Non-proprietary: Azelastine Hydrochloride (AH) 0.1% and Fluticasone Proprionate (FP) 0.037% (AH-FP)

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
01-APR-2011	01-APR-2011	01-JUN-2011	03-JUN-2011
07-DEC-2011	07-DEC-2011	NA	NA

Applicant/Sponsor

Name: Meda Pharmaceuticals, Inc.
Address: 265 Davidson Avenue, Suite 300
Somerset, NJ 08873-4120
Representative: Richard Fosko, RPH, MPH
Telephone: 732-564-2358

Name of Reviewers: Steven Fong, Ph.D.
Denise Miller, Microbiologist

Conclusion: CMC-Microbiology Recommends APPROVE.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Original NDA

2. SUBMISSION PROVIDES FOR: New drug product: non-sterile nasal spray (b) (4)

3. MANUFACTURING SITE:
Cipla Ltd.
Plot No. L139 to L146
Verna Industrial Estate
Verna, Salcette 403722
Goa, INDIA
Facility Establishment Identifier: 3004081307

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Non-sterile, (b) (4) multi-dose nasal spray containing 0.1% AH and 0.037% FP.

5. METHOD(S) OF STERILIZATION: N/A. Product is non-sterile.

6. PHARMACOLOGICAL CATEGORY: Allergic rhinitis therapeutic.

B. SUPPORTING/RELATED DOCUMENTS: None.

C. REMARKS:

1) The submission was submitted electronically in CTD format.

2) On 31-AUG-2011 the following IR (Communication 8) was submitted to the Applicant:

(1) Please amend the Microbial Quality section of the drug product Specification (Table 2 of Section 3.2.P.5.1) to include absence of Burkholderia cepacia and the method that will be used for B. cepacia detection. Your test method should be validated and a discussion of the test methods should be provided. Test methods validation should address multiple strains of the species and cells that are acclimated to the environments (e.g., warm or cold water) that may be tested.

(2) Please provide the manufacturing controls that will be implemented to limit contamination of the drug product with B. cepacia. We recommend that potential sources are examined and sampled as process controls. These may include raw materials and the manufacturing environment. A risk assessment for B. cepacia in the raw materials is recommended to develop sampling procedures and acceptance criteria.

An Amendment response, Supporting Document 14, was received 07-DEC-2011.

3) On 01-SEP-2011, Meda Pharmaceuticals sent an e-mail to RPM Philantha Bowen that contained questions regarding the 31-AUG-2011 microbiology quality IR. The questions are indicated below in italic font. Reviewer responses to the questions were provided in a 13-SEP-2011 communication to Meda Pharmaceuticals, and are indicated below the questions in regular font.

(1) *Regarding the request for multiple strains of B. cepacia, would three separate ATCC strains of the organism be appropriate? If the manufacturing site does not have an industrial isolate from their purified water system is it required that they still use cells that are acclimated to the environments (eg., warm or cold water).*

Microbiology Reviewer Response: For validation of the *B. cepacia* identification test, testing with three separate ATCC strains of the bacterium would be appropriate. If a *B. cepacia* isolate from the manufacturing site is not available, you are recommended to acclimate the ATCC strains to warm or cold water prior to conducting validation studies.

(2) *For process controls such as the manufacturing environment, is it acceptable to monitor the production surfaces for Total Aerobic Microbial Count (TAMC) and Total Yeasts and Molds Count (TYMC). Would the TAMC monitoring be adequate to show contamination control? Would the same be acceptable for air monitoring (TAMC and TYMC would be tested in the production areas).*

Agency Microbiology Reviewer Response: Monitoring of the air and production surfaces for TAMC and TYMC would be adequate to demonstrate contamination control. Testing for the specific presence of *B. cepacia* will not be necessary.

(3) *Is the following approach acceptable? The raw material risk assessment would include those materials (including purified water) which have the potential for microbiological contamination. This would include obtaining water activity data for dry materials, historical data* (b) (4) *and adding a B. cepacia screen to the purified water. For raw materials is USP <61> and <62> testing is appropriate or would a separate B. cepacia screen be required?*

Agency Microbiology Reviewer Response: The approach appears reasonable. The addition of a *B. cepacia* screen for purified water, and the performance of a risk assessment of the raw materials used for formulation, is appropriate and recommended.

4) On 17-NOV-2011 the following second IR was submitted to the Applicant:

Your proposed commercial product stability testing protocol should be amended to include a microbial limits *Burkholderia cepacia* detection assay and acceptance criterion.

The response was included in the 07-DEC-2011 Amendment (Supporting Document 14).

5) On 30-NOV-2011 the quality microbiology review of this application was transferred to Denise Miller. At this time, the review was substantially complete and was waiting for the response to the information request dated 31-AUG-2011. Denise Miller reviewed the response.

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