

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-536

MICROBIOLOGY REVIEW(S)

MEMORANDUM

To: NDA 22-536
From: Thomas M. Wong, Ph.D., Chemist
Date: 17-March-2010
Drug: Indomethacin for Injection
Route of administration: Intravenous injection
Strength: 1 mg/vial
Subject: **“Approval”** recommendation for NDA 22-536

The microbiology reviewer has completed the review and has given an approval recommendation. The CMC review of the drug product was completed on November 24, 2009 and all deficiencies have been resolved. There is no CMC outstanding issue pending. The office of Compliance has provided an overall acceptable recommendation for the manufacturing sites on June 22, 2009.

The application is recommended for “Approval” from CMC perspective.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22536	ORIG-1	APP PHARMACEUTICA LS LLC	INDOMETHACIN

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/s/

THOMAS M WONG
03/17/2010

RAMESH K SOOD
03/18/2010

Product Quality Microbiology Review

12 March 2010

NDA: 22-536

Drug Product Name: Indomethacin for Injection

Review Number: 1

Dates of Submission(s) Covered by this Review

Letter	Stamp	Review Request	Assigned to Reviewer
5/8/2009	5/8/2009	6/10/2009	2/29/2010
8/10/2009	8/10/2009	6/10/2009	2/29/2009
11/10/2009	11/10/2009	6/10/2009	2/29/2009

Submission History (for amendments only) N.A.

Applicant/Sponsor

Name: APP Pharmaceuticals
Address: 1501 East Woodfield Road
Suite 300 East
Schaumburg, IL 60173
Representative: Georgia Hizon, Senior Reg. Scientist
Telephone: 847-330-3950

Name of Reviewer: James L. McVey

Conclusion: Approve.

Product Quality Microbiology Data Sheet

- A.**
- 1. TYPE OF SUBMISSION:** New 505 (b)(2) application
 - 2. SUBMISSION PROVIDES FOR:** A complete NDA submission. It is indicated to close a hemodynamically significantly patent ductus arteriosus in premature infants.
 - 3. MANUFACTURING SITE:** APP Pharmaceuticals, LLC
Barceloneta, Puerto Rico
 - 4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** 1 mg/vial
 - 5. METHOD(S) OF STERILIZATION:** (b) (4)
processing.
 - 6. PHARMACOLOGICAL CATEGORY.** Indicated to close hemodynamically significant patent ductus arteriosus in premature infants.
- B. SUPPORTING/RELATED DOCUMENTS:** The reference listed drug is Indocin[®] IV marketed by Ovation Pharmaceuticals. DMFs referenced were:
(b) (4)
- Sufficient information for product quality microbiology review was provided in the application.
- C. REMARKS:** This assignment was assumed from the previous assigned micro reviewer on 2/29/2010. Microbiology requests for English translations of SOPs for sterility testing and validation, bioburden testing, filtration validation were provided in Amendment 2 dated 8/10/2009. Updated finished product specifications are provided in the amendment dated 11.10/2009.

filename: N22536r1.doc

Executive Summary

I. Recommendations

- A. **Recommendation on Approvability** - Approval is recommended from a product quality microbiology perspective. Please note the Label recommendation in section 2.A. at the bottom of this review.
- B. **Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – N.A.

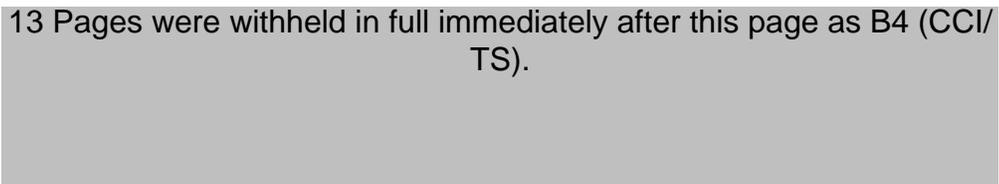
II. Summary of Microbiology Assessments

- A. **Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** –  (b) (4)
- B. **Brief Description of Microbiology Deficiencies** – None.
- C. **Assessment of Risk Due to Microbiology Deficiencies** – No added risk.

III. Administrative

- A. **Reviewer's Signature** _____
James L. McVey
- B. **Endorsement Block**
Microbiology Supervisor _____
David Hussong, Ph.D.
- C. **CC Block**
NDA 22-536

13 Pages were withheld in full immediately after this page as B4 (CCI/TS).



Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22536	ORIG-1	APP PHARMACEUTICA LS LLC	INDOMETHACIN

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/s/

JAMES L MCVEY
03/16/2010

DAVID HUSSONG
03/16/2010

I concur that the application may be approved, and strongly endorse the reviewer's recommended amendment to the labeling concerning the limit of the use-period after reconstitution.

PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

NDA Number: 22-536

**Applicant: APP
Pharmaceuticals, Inc.**

Letter Date: 08 MAY 2009

**Drug Name: Indomethacin
for Injection, 1mg/vial**

NDA Type: 505 (b)(2)

Stamp Date: 12 MAY 2009

The following are necessary to initiate a review of the NDA application:

	Content Parameter	Yes	No	Comments
1	Is the product quality microbiology information described in the NDA and organized in a manner to allow substantive review to begin? Is it legible, indexed, and/or paginated adequately?	X		
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	X		Section 2.3.P.3; and Section 3.2.P.3.3
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?	X		Section 3.2.P.3.5
4	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		X	
5	Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity studies?	X		Container-Closure Integrity studies provided
6	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	X		
7	Has the applicant submitted the results of analytical method verification studies?	X		
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?	-	-	
9	Is this NDA fileable? If not, then describe why.	X		

Additional Comments: Due to either solubility or antimicrobial issues, sample preparation for sterility testing and raw materials bioburden testing may be problematic. Therefore, it is necessary to request several Standard Operating Procedures related to microbial control testing (see following page) in order to assess the submitted summary results of testing.

Robert J. Mello, Ph.D., Reviewing Microbiologist, NDMS

Date

Bryan S. Riley, Senior Reviewer, NDMS

Date

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/s/

Robert Mello
6/23/2009 07:45:47 AM
MICROBIOLOGIST

NDA is Fileable

Bryan Riley
6/23/2009 09:40:43 AM
MICROBIOLOGIST
I concur.