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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-425

Microbiology Review(s)

Product Quality Microbiology Review

6 Aug. 2002

Review for HFD 160

NDA:	**21-425-BI**
Drug Product Name	
Proprietary:	Ultravist®
Non-proprietary:	Iopromide
Drug Product Classification:	502: Radiopharm
Review Number:	2
Subject of this Review	
Submission Date:	July 31, 2002
Receipt Date:	August 1, 2002
Consult Date:	August 5, 2002
Date Assigned for Review:	August 5, 2002
Submission History (for amendments only)	
Date(s) of Previous Submission(s):	November 20, 2001
Date(s) of Previous Micro Review(s):	April 8, 2002
Applicant/Sponsor	
Name:	Berlex Laboratories, Inc.
Address:	340 Changebridge Road P.O. Box 1000 Montville, NJ 07045-1000
Representative:	Patricia R. Mayer
Telephone:	(973) 487-2116
Name of Reviewer:	Stephen E. Langille, Ph.D.
Conclusion:	Recommended for approval

Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUPPLEMENT:** Original Submission

2. **SUPPLEMENT PROVIDES FOR:** N/A

3. **MANUFACTURING SITE:** Schering AG, Charlottenberg
Max-Dohrn-Strasse 8,
D-10589 Berlin, Germany

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

- Solution for injection
- Intravascular
- 300 mgI/mL and 370 mgI/mL

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

6. **PHARMACOLOGICAL CATEGORY:** Imaging agent

B. **SUPPORTING/RELATED DOCUMENTS:** None

C. **REMARKS:** NDA 21-425 is being submitted in support of a pharmacy bulk package for Ultravist® Injection. The drug product will be filled and sterilized according to the same processes and at the same production site as is currently approved for all other Ultravist® Injection presentations currently approved under NDA 20-220. Microbiology comments from the first review of this NDA were provided to the Applicant on July 10, 2002.

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Executive Summary

I. Recommendations

A. Recommendation on Approvability -
NDA 21-425 is recommended for appproval from the standpoint of microbial product quality.

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 -
500 mL pharmacy bulk packs will be in

B. Brief Description of Microbiology Deficiencies -
No deficiencies were identified based upon the information provided.

C. Assessment of Risk Due to Microbiology Deficiencies -
Not applicable

III. Administrative

A. Reviewer's Signature /S/

B. Endorsement Block
In DFS

C. CC Block
In DFS

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/s/

Stephen Langille
8/12/02 12:51:35 PM
MICROBIOLOGIST

Peter Cooney
8/12/02 01:03:42 PM
MICROBIOLOGIST

Product Quality Microbiology Review
Review for HFD-160

March 11, 2001

NDA:	**21-425**
Drug Product Name	
Proprietary:	Ultravist®
Non-proprietary:	Iopromide
Drug Product Classification:	502: Radiopharm
Review Number:	1
Subject of this Review	
Submission Date:	November 20, 2001
Receipt Date:	November 26, 2001
Consult Date:	November 27, 2001
Date Assigned for Review:	December 10, 2001
Submission History (for amendments only)	
Date(s) of Previous Submission(s):	N/A
Date(s) of Previous Micro Review(s):	N/A
Applicant/Sponsor	
Name:	Berlex Laboratories, Inc.
Address:	340 Changebridge Road P.O. Box 1000 Montville, NJ 07045-1000
Representative:	Patricia R. Mayer
Telephone:	(973) 487-2116
Name of Reviewer:	Stephen E. Langille, Ph.D.
Conclusion:	Approvable pending the resolution of microbiology issues.

Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUPPLEMENT:** Original Submission

2. **SUPPLEMENT PROVIDES FOR:** N/A

3. **MANUFACTURING SITE:** Schering AG, Charlottenberg
Max-Dohrn-Strasse 8,
D-10589 Berlin, Germany

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

- Solution for injection
- Intravascular
- 300 mgI/mL and 370 mgI/mL

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

6. **PHARMACOLOGICAL CATEGORY:** Imaging agent

B. **SUPPORTING/RELATED DOCUMENTS:** None

C. **REMARKS:** NDA 21-425 is being submitted in support of a pharmacy bulk package for Ultravist® Injection. The drug product will be filled and sterilized according to the same processes and at the same production site as is currently approved for all other Ultravist® Injection presentations currently approved under NDA 20-220.

filename: c:\reviews\21-425r1

Executive Summary

I. Recommendations

A. Recommendation on Approvability -

NDA 21-425 is approvable pending the resolution of microbiology deficiencies.

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 -

500 mL pharmacy bulk packs will be in

B. Brief Description of Microbiology Deficiencies -

The applicant failed to provide information regarding the reprocessing, endotoxin testing, integrity testing, and microbial challenge testing.

C. Assessment of Risk Due to Microbiology Deficiencies -

Proper container closure integrity testing must be conducted to insure against drug product contamination during the shelf life of the product. Clarification of the endotoxin limits and testing schedule is necessary to guard against drug product toxicity. Proper validation of the microbial challenge test is prudent for pharmacy bulk packs with a ten hour open container exposure time in order to evaluate the possibility of organism growth in the open container.

III. Administrative

/S/

A. Reviewer's Signature _____

B. Endorsement Block

In DFS

C. CC Block

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H. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS

1. **Please answer the following questions with regard to container closure integrity testing:**

   a. **Will Ultravist 300 or Ultravist 370 be reprocessed? If so, additional container closure integrity testing may be necessary.**

   b. **Were 50 ml bottles used for container closure integrity testing sealed with the same stoppers used for the 500 mL bottles of Ultravist?**

   c. **How many of the 50 ml bottles were used for the container closure integrity test?**

2. **According to Working Report NI44EB10, the Ultravist solutions were**

   aliquots were removed from the solutions at various time points in order to monitor microbial growth. How can ... mL aliquots detect microbial populations of . CFU/mL?

3. **Please address the following issues with regard to endotoxin testing:**

   a. **What is the schedule for testing stability batches for endotoxin levels?**

   b. **Working Report L816EB20 (volume 2) and the CMC summary (volume1) list the endotoxin limits for Ultravist at EU/mL and EU/mL respectively. What is the actual endotoxin limit for Ultravist?**

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/s/

Stephen Langille
4/8/02 09:35:05 AM
MICROBIOLOGIST

Peter Cooney
4/8/02 01:27:05 PM
MICROBIOLOGIST