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RESEARCH**

*APPLICATION NUMBER:*

**201277Orig1s000**

**MICROBIOLOGY REVIEW(S)**

# Product Quality Microbiology Review

13 JAN 2011

**NDA:** 201-277

**Drug Product Name**

**Proprietary:** Gadovist 1.0 (proposed)

**Non-proprietary:** Gadobutrol

**Review Number:** 1

**Dates of Submission(s) Covered by this Review**

<b>Submit</b>	<b>Received</b>	<b>Review Request</b>	<b>Assigned to Reviewer</b>
14 MAY 2010	14 May 2010	19 MAY 2010	24 MAY 2010
13 OCT 2010	13 OCT 2010	N/A	N/A
22 DEC 2010	22 DEC 2010	N/A	N/A

**Applicant/Sponsor**

**Name:** Bayer HealthCare Pharmaceuticals Inc.

**Address:** PO Box 1000  
Montville, NJ 07045-1000

**Representative:** Philip Johnson

**Telephone:** 973-487-2181

**Name of Reviewer:** Jessica G. Cole, Ph.D.

**Conclusion:** Recommended for approval.

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## Product Quality Microbiology Data Sheet

- A.
- 1. TYPE OF SUBMISSION:** NDA.
  - 2. SUBMISSION PROVIDES FOR:** New drug product. Gadovist is currently approved with a 0.5 M formulation and this submission proposes a 1.0 M formulation.
  - 3. MANUFACTURING SITE:**  
Bayer Schering Pharma AG, Wedding Site  
D-13342 Berlin, Germany
  - 4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
    - Solution for injection in glass vials, pre-filled syringes and pharmacy bulk packages
    - 1.0 mmol/mL
    - Intravenous
  - 5. METHOD(S) OF STERILIZATION:** (b) (4)
  - 6. PHARMACOLOGICAL CATEGORY:** Contrast agent for central nervous system MRI.

B. **SUPPORTING/RELATED DOCUMENTS:** Not applicable.

C. **REMARKS:** This application was in the eCTD format.  
An information request was sent to the RPM on 4 August 2010 with 17 questions/comments. A response was received on 13 October 2010 and the answers are incorporated into the relevant sections of this review.

1. This application proposes (b) (4). Please address the following:

(b) (4)



17. During the sterility test samples should be compared to the negative control and not the positive control to determine whether growth has occurred.

A follow-up question was received from the sponsor on 31 August 2010 a microbiology response was sent to the RPM on 1 September 2010 (this was not forwarded to the applicant until October 2010). The sponsors comment is italicized and the microbiology response follows.

*In the Microbiology Request 1, faxed to Bayer on 12 August 2010, comment #17 states the following*

*17. During the sterility test samples should be compared to the negative control and not the positive control to determine whether growth has occurred.*

*I can confirm that Bayer does compare the test samples to the negative control to determine if growth has occurred, and our complete reply to these comments will reflect this.*

***Question for the FDA reviewer:** Is this comment being provided to us because there is reference within our NDA to comparison to a positive control? If so, can the FDA reviewer please identify the specific section / report? Alternatively, is this comment being provided to us as guidance in case additional sterility testing is conducted?*

**Microbiology Reviewer Comment**

Please forward the following information to the applicant:

During review of NDA 201-277 the method for determining a negative sterility test was unclear. Document A45453 states on page 7/9 Section 4: (b) (4)

” We note that this document describes the sterility test validation method. Insufficient information was present in the description of the sterility test method to assess what criterion was used to determine the results from sterility test samples. Document K217E180 page 31/35 states: (b) (4)

From a microbiological perspective, shaking the sterility test sample could potentially dislodge and suspend a small but visible cluster of microbiological growth. Samples should be visually compared to the negative control prior to shaking but may be shaken after the initial observation. All samples should be compared to the negative control to assess potential microbial contamination.

A third information request was sent to the sponsor on 17 November 2010 and a response was received on 22 December 2010. The information has been incorporated into the relevant sections of this review.

**Microbiology Comment:**

Please provide the following information or a reference to its location in the subject submission.

1. Provide information to support (b) (4)  

4. Provide a description of the post-approval stability program.
5. Provide the final sterility test validation report.

**filename:** N201277R1.doc

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**Executive Summary**

**I. Recommendations**

- A. Recommendation on Approvability** – 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** – This product is broadly antimicrobial and undergoes (b) (4)
- B. Brief Description of Microbiology Deficiencies** – Not applicable.
- C. Assessment of Risk Due to Microbiology Deficiencies** – Not applicable.

**III. Administrative**

- A. Reviewer's Signature** \_\_\_\_\_  
Jessica G. Cole, Ph.D.
- B. Endorsement Block** \_\_\_\_\_  
Stephen Langille, Ph.D.  
Senior Microbiology Reviewer
- C. CC Block**  
N/A

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/s/  
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JESSICA COLE  
01/13/2011

STEPHEN E LANGILLE  
01/13/2011

# PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

**NDA Number:** 201277      **Applicant:** Bayer HealthCare Pharmaceuticals Inc.      **Letter Date:** 5/14/2010

**Drug Name:** Gadobutrol      **NDA Type:** New 505(b)(1)      **Stamp Date:** 5/14/2010  
 Gadovist 1.0 (proposed)

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		eCTD format but the headings are only study numbers with no description
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	X		3.2.P.3.4 -A44380
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?	X		
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		3.2.P.2 – A36069, A36092, A35203, A31742
6	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	X		Methods are in K217E180
7	Has the applicant submitted the results of analytical method verification studies?	X		Sterility-A45453 LAL- A25361
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?	X		A49730
9	Is this NDA fileable? If not, then describe why.	X		

Additional Comments: This product is (b) (4) after sterile filtration and is supplied in glass vials or syringes and as a pharmacy bulk pack in glass vials/bottles.

6/23/2010

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Jessica G. Cole, Ph.D. Date

6/25/2010

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David Hussong, Ph.D./Associate Director for Microbiology Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201277	ORIG-1	BAYER HEALTHCARE PHARMACEUTICALS INC	GADOBUTROL INJECTION

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/s/

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JESSICA COLE  
06/28/2010

DAVID HUSSONG  
06/28/2010

I concur with the primary reviewer's conclusion that the submission is reviewable.