

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205383Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)

MEMORANDUM



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 24 April 2013

TO: NDA 205-383

FROM: Jessica G. Cole, PhD

THROUGH: Bryan Riley, PhD Microbiology Team Lead

cc: James Moore CDER/OND/DMIP

SUBJECT: Product Quality Microbiology assessment of Microbial Limits for (b) (4) (Iohexol) (b) (4) Oral Solution” [Submission Date: 11 March 2013]

The Microbial Limits specification for (b) (4) (Iohexol) (b) (4) Oral Solution” is acceptable from a Product Quality Microbiology perspective. Therefore, this submission is recommended for approval from the standpoint of product quality microbiology.

“(b) (4) (Iohexol) (b) (4) Oral Solution” is a powder for oral administration after reconstitution with tap water or other appropriate liquid. The labeling instructs the user to (b) (4). The applicant conducted post-constitutional hold studies where the drug product was reconstituted in tap water. Growth was enumerated at 48 hours and compared to tap water alone. The results in Table 1 demonstrate the microbiological safety of short-term storage of the reconstituted solution at room temperature.

Table 1- Microbiological stability of reconstituted drug product (Sponsor Table 3.2.P.8.3.11)

Time	Microbial Count (cfu/plate)			Tap Water
	Drug Product Constituted with Tap Water (Drug Product Batch Number)			
	(USC04106010)	(USC05602010)	(USC05702010)	
Immediately after solution preparation	140	154	174	232
After 2 days of standing at room temperature	403	417	413	365

Source: Interpharma Praha report number MB/IOHEXOL/R-1/12.

Reviewer’s Comment: The CFU recovered per plate are above the conventional limits for countable colonies (~250-300 CFU/per plate). However, the study clearly demonstrates that the reconstituted solution poses no greater microbial risk than standard tap water after 48 hours incubation.

MEMORANDUM

The drug product is tested for Microbial Limits at release using USP Chapter <61> (Microbiological Examination of Non-sterile Products: Microbial Enumeration Tests) and <62> (Microbiological Examination of Non-sterile Products: Tests for Specified Microorganisms). The Microbial Limits acceptance criteria are consistent with USP Chapter <1111> (Microbiological Examination of Non-sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use). The drug product will contain NMT (b) (4) CFU/g total aerobic microbial count, NMT (b) (4) CFU/g total combined yeast and mold count, and absence of *Escherichia coli* in 1 gram.

The Microbial Limits test methods were verified to be appropriate for use with the drug product following procedures consistent with those in USP Chapters <61> and <62>.

The drug product will also be tested for Microbial Limits annually as part of the post-approval stability protocol. The release specification will be tested for conformance at 36 months (b) (4) under long-term conditions and at 6 months under accelerated conditions.

ADEQUATE

Reviewer Comment – The microbiological quality of the drug product is controlled via a suitable testing protocol.

END

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/s/

JESSICA COLE
04/24/2013

BRYAN S RILEY
04/24/2013
I concur.

PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

NDA Number: 205-383 **Applicant:** Otsuka novel Products for Interpharma Praha, a.s. **Letter Date:** 11 March 2013

Drug Name: Iohexal
(b) (4) Oral Solution **NDA Type:** Original 505(b)(2) **Stamp Date:** 11 March 2013

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		The drug product is composed of 100% drug substance (b) (4) .
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	X		Manufacturing information is in DMF 26641.
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?		X	Not applicable for a non-sterile powder fill.
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	Not applicable.
5	Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity studies?		X	Not applicable.
6	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	X		Reference to USP methods.
7	Has the applicant submitted the results of analytical method verification studies?		X	Applicant states verification studies can be found in DMF 26641.
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?		X	Not applicable.
9	If sterile, are extended post-constitution and/or post-dilution hold times in the draft labeling supported by microbiological data?		X	There are no extended post-constitution hold times.
10	Is this NDA fileable? If not, then describe why.	X		

Additional Comments: The associated IND is 114,359 and there are no previous product quality microbiology reviews in DARRTS.

17 April 2013

Jessica G. Cole/Microbiologist Date

Bryan Riley/Microbiology Team Leader Date

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/s/

JESSICA COLE
04/18/2013

BRYAN S RILEY
04/18/2013
I concur.