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APPLICATION NUMBER:

201655Orig1s000

MICROBIOLOGY REVIEW(S)

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF PHARMACEUTICAL SCIENCES
NEW DRUG MICROBIOLOGY

M E M O R A N D U M

Date: 13 October 2010

TO: Craig Bertha, DARRTS

FROM: James L. McVey, Team Leader, New Drug Microbiology

Cc: Stephen Langille**,** Ph.D., Senior Microbiologist, New Drug Microbiology Staff

SUBJECT: NDA 201655 Oxymorphone HCl [redacted] (b) (4) extended-release tablets. Third Review

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From Second Review:

The applicant maintains that no microbial limits testing is needed based on their data.
Reviewer Comment: The response provided does not address the total microbiological load or in-process controls. Clearly microorganisms will not grow in the dry environment intended and some vegetative cells will die. The contract manufacturer has provided microbial limits for the coating solution [redacted] (b) (4) that should apply to the complete tablet. A microbial limits test should be included in the release specifications **.**

The following deficiency was provided in a discipline specific letter to the applicant dated 8 October 2010.

ICH Q6a states "it is advisable to test the drug product unless its components are tested before manufacture and the manufacturing process is known, through validation studies, not to carry a significant risk of microbial contamination or proliferation." Adequate information has been provided that the finished dosage form will not support growth but the introduction of contaminants during the manufacturing process has not been adequately addressed. The product specification should state that the product meets the requirements of USP <61>, <62>, and <1111> if tested. The batch release criteria should identify the specific manufacturing process tests and criteria used to assess the finished product as microbiologically suitable for release. These tests and criteria should include, for example:

- Microbial limits data for critical raw materials,
- Microbiological environmental monitoring data for critical processing steps, and
- In-process control parameters [redacted] (b) (4) that may affect product quality microbiology.

Third Review: The applicant responded in a letter dated 12 October 2010, SDN 0011.

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Endo agrees to amend the drug product specifications in include microbial limits testing. Section 3.2.P.5.1 has been updated to include the following. "Microbiological Examination, Total Aerobic Count [redacted] (b) (4) Total Yeasts and Mold [redacted] (b) (4) and absence of *Escherichia coli*, per USP<61> and <62>. The specification is footnoted to say that the testing is for release only.

Acceptable

END

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/s/

JAMES L MCVEY
10/14/2010
Added Microbial Limits testing to product release specification.

STEPHEN E LANGILLE
10/14/2010

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Memoranda

Date: 05 October 2010

TO: Craig Bertha, DARRTS

FROM: James L. McVey, Team Leader, New Drug Microbiology

Cc: Stephen Langille, Ph.D., Senior Microbiologist, New Drug Microbiology Staff

SUBJECT: NDA 201655 Oxymorphone HCl (b) (4) extended-release tablets. Second Review

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Previous Review dated 18 August 2010:

The applicant does not propose any microbial limits testing for the drug product. The reason for not doing so is reproduced below.

"Oxymorphone hydrochloride (b) (4) extended-release tablets are a non-sterile oral product."

The tablets are manufactured using (b) (4) (b) (4)

Research studies demonstrate that the final drug product does not promote microbial growth. Not less than 2, 7, 0.7 and 3, 7, 0.7 log reduction from the initial count of the bacteria *Staphylococcus aureus, Pseudomonas aeruginosa*, and *Bacillus subtilis*, respectively, was observed after 14 and 28 days of incubation. For the mold *Aspergillus niger*, no increase from the initial count was found after 14 and 28 days.

"Therefore, it is deemed appropriate not performing microbial test for the release and stability monitoring of the drug product."

Also from the application:

"Oxymorphone hydrochloride, a semi-synthetic opioid analgesic, is supplied in 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg (b) (4) extended-release tablet strengths for oral administration. The tablets contain the following inactive ingredients: hypromellose, polyethylene oxide, polyethylene glycol, α-tocopherol, citric acid, polyvinyl alcohol, titanium dioxide, macrogol and talc. In addition, the 5 mg, 7.5 mg, and 30 mg tablets contain iron oxide red. The 7.5 mg tablets contain iron oxide black, and iron oxide yellow. The 10 mg tablets contain FD&C yellow No. 6. The 20 mg tablets contain FD&C blue No. 1, FD&C yellow No. 6, and D&C yellow No. 10. The 40 mg tablets contain FD&C yellow No. 6, and D&C yellow
No. 10."

The manufacturing process steps include (b) (4)

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