

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
201655Orig1s000

MICROBIOLOGY REVIEW(S)



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

MEMORANDUM

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

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.

Endo agrees to amend the drug product specifications to include microbial limits testing. Section 3.2.P.5.1 has been updated to include the following. “Microbiological Examination, Total Aerobic Count (b)(4) Total Yeasts and Mold (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

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

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)

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)

Reviewer comments:

(b) (4)

(b) (4) No

bioburden information is provided for the excipients used. Although the data summary provided demonstrates that the compendial organisms do not grow in the product, there is no evidence of the extent of microbiological contamination before or after manufacturing. The growth capabilities of the indigenous microorganisms may be more significant than the compendial testing demonstrates.

Recommended Comment to Applicant.

Include a test for microbial limits (USP<61>, <62>) in the release specifications for this product. USP <1111> provides recommendations for acceptable limits. The information provided does not address the microbiological load or in-process control. It is recommended that the appropriate ingredients also be tested for bioburden as part of the microbiological control of this manufacturing process.

Over time it is possible that the product may take on water and support growth. This issue should be addressed in the stability plan. Annual testing is recommended.

Second Review:

The applicant maintains that no microbial limits testing is needed based on their data. The above comment was provided to the applicant in a letter dated 2 September 2010 as question 4. A response was provided from the applicant dated 14 September 2010. The applicant states that the tablets and all the compendial excipients used in its manufacture meet current USP requirements and no USP requirements include at test for microbial limits. Decision tree #8 in ICH Q6a was consulted and the applicant determined that the tablets (b) (4) is a dry dosage form and that they have data that demonstrates microbial growth inhibition properties. (b) (4)

(b) (4)

An additional study was conducted at (b) (4) to qualify a (b) (4) for the (b) (4) coating suspensions. The total aerobic count was less than (b) (4) and the total yeasts and mold was less than (b) (4). No indicator organisms were found in the coating suspensions. The same conclusion was drawn as before. No testing for microbial limits is needed.

Reviewer Comment: The response provided does not address the total microbiological load or in-process controls.

Memoranda

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 (b)(4) (b)(4) that should apply to the complete tablet. A microbial limits test should be included in the release specifications .

ICH Q6a includes the following comment:

Section 1.2 "Specifications are one part of a total control strategy for the drug substance and drug product designed to ensure product quality and consistency. Other parts of this strategy include thorough product characterization during development, upon which specifications are based, and adherence to good manufacturing practices (GMP's), e.g., suitable facilities, a validated manufacturing process, validated test procedures, raw materials testing, in-process testing, stability testing."

And

Section 1.3 "The quality of drug substances and drug products is determined by their design, development, in-process controls, GMP controls, process validation, and by specifications applied to them throughout development and manufacture. This guidance addresses specifications, i.e., those tests, procedures, and acceptance criteria that play a major role in assuring the quality of the new drug substance and new drug product at release and during shelf life. Specifications are an important component of quality assurance, but are not its only component. All of the factors listed above are considered necessary to ensure consistent production of drug substances and drug products of high quality."

And

Section 2.3 "It may be possible to propose excluding or replacing certain tests on this basis. Some examples are:

Microbiological testing for drug substances and solid dosage forms that have been shown during development not to support microbial viability or growth (see Decision Trees #6 and #8)."

It is my interpretation that the accomplishment of section 2.3 is dependent on meeting the requirements of sections 1.2 and 1.3. The authors assumed that those requirements discuss in 1.2 and 1.3 had been fulfilled when they wrote section 2.3.

And

Section 3.3.1 Drug Substance (g) "The type of microbial test(s) and acceptance criteria should be based on the nature of the drug substance, method of manufacture, and the intended use of the drug product."

And

Section 3.3.2 New Drug Products:

"(f) Microbial limits: Microbial limit testing is seen as an attribute of GMP, as well as of quality assurance. In general, **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.** It should be noted that, whereas this guidance does not directly address excipients, the principles discussed here may be applicable to excipients as well as to new drug products. Skip testing may be an appropriate approach in both cases, where permissible (see Decision Tree #6 for microbial testing of excipients)."

"Acceptance criteria should be set for the total count of aerobic microorganisms, the total count of yeasts and molds, and the absence of specific objectionable bacteria (e.g., Staphylococcus aureus, Escherichia coli, Salmonella, Pseudomonas aeruginosa). These should be determined by suitable procedures, using pharmacopeial procedures, and at a sampling frequency or time point in manufacture that is justified by data and experience. The type of microbial test(s) and acceptance criteria should be based on the nature of the drug substance, method of manufacture, and the intended use of the drug product. With acceptable scientific justification, it should be possible to propose no microbial limit testing for solid oral dosage forms."

It is this last section that has not been addressed in this submission.

Deficiency for the applicant:

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.

END

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/s/

JAMES L MCVEY

10/05/2010

Still need a microbial limits test or reasonable evidence of microbial control.

STEPHEN E LANGILLE

10/05/2010



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FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF PHARMACEUTICAL SCIENCES
NEW DRUG MICROBIOLOGY

MEMORANDUM

Date: 19 August 2010
TO: Craig Bertha, DARRTS
FROM: James L. McVey, Team Leader, New Drug Microbiology
Cc: David Hussong, Ph.D., Associate Director, New Drug Microbiology
SUBJECT: NDA 201655 Oxyorphone HCl (b)(4) extended-release tablets

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.

(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

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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 [REDACTED] (b) (4)

Reviewer comments:

[REDACTED] (b) (4)
[REDACTED] (b) (4) No bioburden information is provided for the excipients used. Although the data summary provided demonstrates that the compendial organisms do not grow in the product, there is no evidence of the extent of microbiological contamination before or after manufacturing. The growth capabilities of the indigenous microorganisms may be more significant than the compendial testing demonstrates.

Recommended Comment to Applicant.

Include a test for microbial limits (USP<61>, <62>) in the release specifications for this product. USP <1111> provides recommendations for acceptable limits. The information provided does not address the microbiological load or in-process control. It is recommended that the appropriate ingredients also be tested for bioburden as part of the microbiological control of this manufacturing process.

Over time it is possible that the product may take on water and support growth. This issue should be addressed in the stability plan. Annual testing is recommended.

Memoranda

END

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201655	ORIG-1	ENDO PHARMACEUTICA LS INC	Oxymorphone HCl (b) (4) extended-release tablet

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/s/

JAMES L MCVEY
08/19/2010
Needs a microbil limits release test.

STEPHEN E LANGILLE
08/19/2010