CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-721

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

EDMS-USRA-8851688

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
21-721

NAME OF APPLICANT / NDA HOLDER
Ortho-McNeil Pharmaceutical, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
LEVAQUIN

ACTIVE INGREDIENT(S)
levofloxacin

STRENGTH(S)
25mg/ml

DOSAGE FORM
Oral Solution

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number
5,053,407

b. Issue Date of Patent
10/1/1991

c. Expiration Date of Patent
12/20/2010

d. Name of Patent Owner
Daiichi Pharmaceutical Co., Ltd.

Address *(of Patent Owner)*
14-10 Nihonbashi 3-Chome
Chuo-ku,

City/State
Tokyo

ZIP Code
Japan

FAX Number *(if available)*

Telephone Number

E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Philip S. Johnson

Address *(of agent or representative named in 1.e.)*
Johnson & Johnson
One Johnson & Johnson Plaza

City/State
New Brunswick, NJ

ZIP Code
08933-7003

FAX Number *(if available)*

Telephone Number
732-524-2368

E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3.**		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? *(Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)*	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* Claims 4 and 5	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* Method for treatment of mild, moderate and severe infections.	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*

Date Signed: 11/13/2003

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name: Joseph S. Kentoffio	
Address: Johnson & Johnson One Johnson & Johnson Plaza	City/State: New Brunswick, NJ
ZIP Code: 08933-7003	Telephone Number: 732-524-3711
FAX Number *(if available)*: 732-524-5008	E-Mail Address *(if available)*

EXCLUSIVITY SUMMARY FOR NDA # 21-721 SUPPL # N/A

Trade Name Levaquin® Generic Name levofloxacin

Applicant Name Ortho-McNeil(c/o J&JPRD) HFD-590

Approval Date If Known October 21, 2004

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?
YES /_x_/ NO /___/

b) If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

__505(b)(1)__

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /___/ NO /_X_/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

Bioavailability studies comparing the tablets, oral solution, and IV were submitted to obtain approval for the oral solution as a new formulation of levofloxacin. Clinical data was not submitted.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X_/

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Writen Request?

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X__/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-634 Levaquin(levofloxacin)Tablets

NDA# 20-635 Levaquin(levofloxacin)Injection

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES" GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than

bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /_X_/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

---

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support

the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50

percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ NO /___/ Explain: _____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

Signature Date
Rebecca D. Saville, Pharm.D.
Title: Regulatory Project Manager

Signature of Office/ Date
Division Director
Renata Albrecht, M.D.

Form OGD-011347 Revised 05/10/2004

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Rebecca Saville
10/21/04 03:00:50 PM

Renata Albrecht
10/21/04 03:22:24 PM

WAIVER REQUEST (PEDIATRIC)

In compliance with 21 CFR314.55(b), Johnson & Johnson Pharmaceutical Research and Development L.L.C (JJPRD) is submitting this statement to NDA 21-721 for Levaquin® Oral Solution. Levaquin® is a synthetic broad spectrum antibacterial agent for oral and intravenous use.

JJPRD requests a waiver of pediatric studies for this formulation.

This supplemental application provides data for the new oral solution formulation of Levaquin.

Manisha Padhye

Manisha Padhye

Regulatory Affairs

12·10·03

Date

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA : 21-721 **Supplement Type (e.g. SE5):** _____ **Supplement Number:**

Stamp Date: December 22, 2003 **Action Date:** October 22, 2004

HFD-590 **Trade and generic names/dosage form:** Levaquin® (levofloxacin) Oral Solution, 25 mg/mL

Applicant: Johnson & Johnson PRD on behalf of Ortho-McNeil Pharmaceutical, Inc. **Therapeutic Class:** 4030100

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application: 10

Indication #1: Acute Maxillary Sinusitis

Is there a full waiver for this indication (check one)?

☒ **Yes: Please proceed to Section A.**

☐ **No: Please check all that apply:** ☐ **Partial Waiver** ☐ **Deferred** ☐ **Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☒ **There are safety concerns**
- ☐ **Other:** _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____	kg_____	mo._____	yr._____	Tanner Stage_____
Max_____	kg_____	mo._____	yr._____	Tanner Stage_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ **kg**_____ **mo.**_____ **yr.** 0 **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.** 16 **Tanner Stage**_____

Reason(s) for deferral:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Adult studies ready for approval**
☐ **Formulation needed**
Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Attachment A
(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: Acute Bacterial Exacerbation of Chronic Bronchitis

Is there a full waiver for this indication (check one)?

X Yes: Please proceed to Section A.

☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☒ **Disease/condition does not exist in children**
☒ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for partial waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Adult studies ready for approval**
☐ **Formulation needed**
☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

Indication #3: Community Acquired Pneumonia

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**

X **No: Please check all that apply: ____Partial Waiver _X___Deferred ____Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:_____**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ **kg**_____ **mo.**_____ **yr.** 0 **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.** 16 **Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- X **There are safety concerns**
- X **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Comments:

Indication #4: Complicated Urinary Tract Infections

Is there a full waiver for this indication (check one)?

☐ **Yes: Please proceed to Section A.**

X No: Please check all that apply: ____Partial Waiver _X_Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:_____**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**
Max_____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____	**kg_____**	**mo._____**	**yr._0___**	**Tanner Stage_____**
Max_____	**kg_____**	**mo._____**	**yr._16___**	**Tanner Stage_____**

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- X **There are safety concerns**
- X **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

Date studies are due (mm/dd/yy): ____February 2, 2009_____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Comments:

Indication #5: Acute Pyelonephritis

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**

X **No: Please check all that apply:** ____**Partial Waiver** _X_**Deferred** ____**Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____	**kg**_____	**mo.**_____	**yr.** 0	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.** 16	**Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- X **There are safety concerns**
- X **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

Date studies are due (mm/dd/yy): February 2, 2009

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Comments:

Indication #6: Uncomplicated Skin and Skin Structure Infections

Is there a full waiver for this indication (check one)?

☒ Yes: Please proceed to Section A.

☐ No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed
NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☒ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ **kg**_____ **mo.**_____ **yr.** 0 **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.** 16 **Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

Indication #7: Uncomplicated Urinary Tract Infections

Is there a full waiver for this indication (check one)?

☒ **Yes: Please proceed to Section A.**

☐ **No: Please check all that apply: ____Partial Waiver _____Deferred ____Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☒ **There are safety concerns**
- ☐ **Other:_____**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

❑ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____	**kg**_____	**mo.**_____	**yr.** 0	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.** 16	**Tanner Stage**_____

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:**_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Comments:

Indication #8: Complicted Skin and Skin Structure Infections

Is there a full waiver for this indication (check one)?

- ❑ **Yes: Please proceed to Section A.**

X **No: Please check all that apply: ____Partial Waiver _X___Deferred ____Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**

- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____	**kg**_____	**mo.**_____	**yr.** 0	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.** 16	**Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- X **There are safety concerns**
- X **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

Date studies are due (mm/dd/yy): February 2, 2009

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

Indication #9: Chronic Bacterial Prostatitis

Is there a full waiver for this indication (check one)?

X Yes: Please proceed to Section A.

☐ No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- X **Disease/condition does not exist in children**
- ☒ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:_____**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

Indication #10: Nosocomial Pneumonia

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**

- ☒ **No: Please check all that apply: ____Partial Waiver _X___Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:_____**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ **kg**_____ **mo.**_____ **yr.** 0 **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.** 16 **Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☒ **Too few children with disease to study**
- ☒ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

Date studies are due (mm/dd/yy): February 2, 2009

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no

other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Rebecca D. Saville
Regulatory Project Manager

cc: NDA 21-721
HFD-960/ Grace Carmouze
(revised 10-14-03)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Rebecca Saville
10/19/04 09:13:27 PM

DEBARMENT CERTIFICATION

Johnson &Johnson Pharmaceutical Research and Development, L.L.C certifies that we did not and will not use in any capacity the services of any person debarred under subsections 206 (a) or 306 (b) of the Federal Food and Drug and Cosmetic Act in connection with this new supplemental New Drug Application.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-721	Efficacy Supplement	Supplement Number N/A	
Drug: Levaquin® (levofloxacin) Oral Solution, 25 mg/mL		Applicant: Ortho McNeil Pharmaceutical, Inc., c/o Johnson & Johnson Pharmaceutical Research and Development	
RPM: R. Saville		HFD-590	Phone # 301-827-2127
Application Type: (X) 505(b)(1) ( ) 505(b)(2)		Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): N/A	

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	Type 3 New Formulation
• Other (e.g., orphan, OTC)	N/A
❖ User Fee Goal Dates	October 22, 2004
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information	
• User Fee	(X) Paid UF ID number 4678
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other (specify) _____
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) ( ) Other (specify)_____
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	N/A
• OC clearance for approval	N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(X) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	(X) Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ( ) Verified 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)

• Other	N/A
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	N/A
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	October 20, 2004
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	February 5, 2004
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	N/A
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	February 4, 2004 Updated October 19, 2004
❖ Demographic Worksheet *(NME approvals only)*	N/A
❖ Statistical review(s) *(indicate date for each review)*	N/A
❖ Biopharmaceutical review(s) *(indicate date for each review)*	October 21, 2004
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	August 25, 2004
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	October 13, 2004
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	N/A
• Review & FONSI *(indicate date of review)*	July 13, 2004
• Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	N/A
❖ Facilities inspection (provide EER report)	Date completed: September 13, 2004 **(X)** Acceptable **( )** Withhold recommendation
❖ Methods validation	**(X)** Completed **( )** Requested **( )** Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	October 19, 2004
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

MEMORANDUM

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

DATE: August 25, 2004

TO: Renata Albrecht, M.D.
Director, Division of Special Pathogen and Immunologic Drug Products (HFD-590)

FROM: Jacqueline A. O'Shaughnessy, Ph.D.
John A. Kadavil, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D.
Associate Director - Bioequivalence
Division of Scientific Investigations (HFD-48)

Michael Skelly for CTV 8/26/04

SUBJECT: Review of EIRs Covering NDA 21-721, Levaquin® (levofloxacin) Oral Solution, Sponsored by Johnson & Johnson Pharmaceutical Research & Development, L.L.C. (on behalf of Ortho McNeil Pharmaceutical, Inc.)

At the request of HFD-590, the Division of Scientific Investigations conducted audits of the clinical and analytical portions of the following bioequivalence study:

> **Protocol LOFBO-PHI-116**: An Open-Label Randomized, 3-Way Crossover Study to Evaluate the Bioequivalence of an — Formulation, an Oral Solution Formulation, and the Marketed Tablet Formulation of Levofloxacin in Healthy Subjects.

The clinical portion of the study was conducted at — The analytical portion of the study was conducted at —

Following inspections at — (7/22/04 - 7/29/04) and at — (7/19/04 - 7/21/04), Forms FDA 483 were issued. The objectionable findings and our evaluations are as follows:

---

1. Failure to maintain accurate records.

According to the records on site, 504 tubes of blood samples from subjects in Group 1, Period 1 (this was a discontinued group) were stored on site. However, the samples could not be located, and the staff could not account for the whereabouts of the samples. Since this was a discontinued group, there is no consequence on the assessment of bioequivalence.

— agreed to implement procedures to prevent this error in the future.

---

1. The stability of L-ofloxacin in extracted samples was not demonstrated. Several study runs (e.g., 17, 18, 20, 21) were stored for at least 24 hours before injection.

— stability experiment compared stored quality control (QC) sample extracts against calibration standards held under identical conditions. This experimental design is not ideal since stored calibration curves are only reliable after analyte stability in an extracted sample has been demonstrated. In response to the Form 483 (Attachment 2), the firm repeated the stability study and compared stored QC extracts against freshly prepared calibration standards. No stability problems were found.

Conclusion:

Following our evaluation of the inspectional findings, DSI recommends that Study LOFBO-PHI-116 be accepted for review.

After you have reviewed this transmittal memo, please append it to the original NDA submissions.

Jacqueline A. O'Shaughnessy, Ph.D.

John A. Kadavil, Ph.D.

Final Classifications:
VAI - ——
VAI - —

cc:
HFD-45/RF
HFD-48/O'Shaughnessy(2)/Kadavil(2)/Himaya/CF
HFD-590/Albrecht/Peacock/NDA 21-721
HFD-880/Jang
HFR-PA2530/Shire
HFR-CE2545/Mandera
Draft: JAO/JAK 8/25/04
Edit: MKY 8/26/04
DSI: 5520; O:\BE\EIRCOVER\21721joh.lev.doc
FACTS: 519560

Atts:
FDA-483, ——
FDA-483, —
FDA-483 Response, ——

A

10 Page(s) Withheld

1 Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE IV

FACSIMILE TRANSMITTAL SHEET

DATE: March 30, 2004

To: Manisha Padhye	**From:** Susan Peacock
Company: J&JPRD	Division of Division of Special Pathogen and Immunologic Drug Products
Fax number: 908-704-1501	**Fax number:** 301-827-2475
Phone number: 908-218-6473	**Phone number:** (301) 827-2127

Subject: CMC Comments regarding NDA 21-721

Total no. of pages including cover: 3

Comments: This facsimile was reviewed by Gene Holbert and Norman Schmuff

Document to be mailed: • YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

INFORMATION REQUEST LETTER

Dear Dr. Padhye:

Please refer to your December 19, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for LEVAQUIN® (levofloxacin) Oral Solution, 25 mg/ml.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Concerning the method of manufacture:

   - Section 3.2.P.2.2.1.1.1 refers to a trace impurity which [redacted] Please identify that impurity if possible.

   - Please specify the target fill volume and fill weight for each size container. [redacted]

2. Concerning Microbiological Attributes (Section 3.2.P.2.5):

   - Please identify the method used for [redacted] esting.

   - Please comment on the reasons for the [redacted] of the placebo formulation.

3. Concerning the Drug Product Specification:

   - The current acceptance criteria for the specified impurities in levofloxacin tablets are [redacted] and no other unknown impurity to exceed [redacted]. The liquid formulations have a limit for [redacted] content, and the acceptance criterion for the specified impurities is [redacted] We suggest adding a limit for the [redacted] and setting the acceptance criteria for impurities to correspond to those in the [redacted] formulations. We also recommend that you re-examine the impurity limits in all levofloxacin formulations with the goal of reducing those limits where possible.

4. Concerning HPLC Method [redacted]

- Please explain precisely what is meant by — (Section 1.2.3 of the method)

5. Concerning the HPLC Method validation:

   - Please provide data, such as chromatograms, to support the claim — — Section 2.1.4 Forced Degradation Study).

   - Please describe in greater detail how the Limits of Quantitation and Detection were calculated using the — method.

6. Concerning the Container/Closure System:

   - Although not required by regulations subject to FDA enforcement, we would prefer to see

7. Concerning the Stability Studies:

   -

8. Concerning the Proposed Expiry Period:

   - The data available do not support the proposed expiration dating for the product packaged in 16-oz bottles. Please submit updated stability data.

9. Concerning the draft labeling:

   - Please submit draft container labeling for the — bottle.

If you have any questions, call Susan Peacock, Regulatory Project Manager, at (301) 827-2127.

Susan Peacock, Regulatory Project Manager
Division of Special Pathogen and Immunologic Drug Products

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/s/

Susan Peacock
3/30/04 11:55:22 AM

Peacock

MEMORANDUM

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

DATE: March 26, 2004

TO: Directors, Investigations Branch

Los Angeles District Office
19900 MacArthur Blvd
Suite 300
Irvine, CA 92612-2445

Baltimore District Office
6000 Metro Drive, Suite 101
Baltimore, MD 21215

FROM: C.T. Viswanathan, Ph.D. CTV 3/30/04
Associate Director (Bioequivalence)
Division of Scientific Investigations (HFD-48)

SUBJECT: FY 2004, **High Priority CDER User Fee NDA,** Pre-Approval Data Validation Inspection, Bioresearch Monitoring, Human Drugs, CP 7348.001

RE: NDA 21-721
DRUG: Levaquin® (levofloxacin) Oral Solution
SPONSOR: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. (on behalf of Ortho McNeil Pharmaceutical, Inc.)
CONTACT: Manisha Padhye, Ph.D.
920 U.S. Highway 202
P.O. Box 300
Raritan,NJ 08869
TEL: (908) 218-6473
FAX: (908) 704-1501

This memo requests that you arrange for inspection of the relevant portion of the following bioequivalence study located in your district. **Due to the User Fee deadline, the inspection should be completed by August 1, 2004.**

Study: Protocol LOFBO-PHI-116 - An Open-Label Randomized, 3-Way Crossover Study to Evaluate the Bioequivalence of an Oral — Formulation, an Oral Solution Formulation, and the Marketed Tablet Formulation of Levofloxacin in Healthy Subjects.

Clinical Site: /

Clinical Investigator: /

This was a randomized, open-label, single-dose, 3-way crossover bioequivalence study of three oral levofloxacin formulations in 36 healthy men and women. Please check the batch numbers of both the test and the reference drug formulations used in the study with descriptions in the documents submitted to the Agency. Samples of both the test and reference drug formulations should be collected and mailed to the Division of Pharmaceutical Analysis, St. Louis, MO, for screening. **Please confirm whether reserve samples were retained as required by 21 CFR Parts 320.38 and 320.63.**

Please have the records of all study subjects audited. Please determine if the patients met the protocol inclusion/exclusion criteria. The subject records in the NDA submission should be compared to the original documents at the firm. In addition to the standard investigation involving the source documents, case report forms, adverse events, concomitant medications, number of evaluable subjects, drug accountability, etc., the files of communication between the clinical site and the sponsor should be examined for their content. Dosing logs must be checked to confirm that correct drug products were administered to the subjects. Please confirm the presence of 100% of the signed and dated consent forms, and comment on this informed consent check in the EIR.

Analytical Site: /

Analytical Investigator: To be provided at a later date

Analytical Method: HPLC

All pertinent items related to the analytical method should be examined and the sponsor's data should be audited. The analytical data provided in the NDA submission should be compared with the original documents at the firm. The method validation and the actual assay of the subject plasma samples, as well as the variability between and within runs, QC, stability, the number of repeat assays of the subject plasma samples, and the reason for such repetitions, if any, should be examined. The SOPs for various procedures must also be scrutinized. In addition to the standard investigation involving the source documents, the files of communication between the analytical site and the sponsor should be examined for their content.

Following the identification of the investigator, background materials will be forwarded directly. **A member of the Bioequivalence Team from the Division of Scientific Investigations may participate in the inspection.**

Headquarters Contact Person: John A. Kadavil, Ph.D.
(301) 594-1048

cc:
HFD-45/RF ACH
HFD-48/Kadavil(2)/Himaya/CF
HFD-590/Peacock
HFD-880/Jang
HFR-PA2565/Koller (BIMO, please fax cc copy)
HFR-CE250/Salisbury (BIMO, please fax cc copy)
Draft: JAK 3/25/04
Edit: MKY 3/26/04
DSI: 5520 O:\BE\assigns\bio21721.doc
FACTS 519560

Wednesday, March 10, 2004
T-Con with Ms. Padhye and Edward Nowak (J&J)

Reference: NDA 21-721, EA dated Oct 15, 2003, Section 6
Levaquin (levofloxacin) Oral Solution

J&J states "The no observed effect concentration (NOEC) for Daphnia Magna was —; and the NOEC for bluegill sunfish was —.

The definition of NOEC (Guidance for Industry, Environmental Assessment of Human Drug and Biologics Applications, July 1998, page 38) is.... "The highest concentration of a material used in a toxicity test that has no statistically significant adverse effect on the exposed population of test organisms as compared with the controls."

In the T-con today between Manisha Padhye (J&J, 908 218-6473), Edward Nowak (J&J, 908 927-3235) and Florian Zielinski (FDA, 301 443-5186), J&J confirms that the NOEC reported for Daphnia Magna, namely — is quoted accurately from the — report. — reports that no effect was observed in the range-finding study at — but erratic swimming was observed at — the lowest concentration tested in the definitive study.

J&J will modify the EA to show that based on the ratio between EC_{50} and EIC, no significant adverse environmental effects are expected. (Reference: Guidance, page 14)

The fifth year production estimate reported in Confidential Appendix 1 pertains to all current dosage forms of levofloxacin, namely the sum of requirements for oral solution, tablets and injectable formulations for currently known indications.

J&J will submit the EA amendment electronically to NDA 21-721 (oral solution) before March 22, 2003.

J&J will state that the EA amendment applies to —

After receipt of the amendment(s), review of the amended EA and preparation of associated FONSIs will be completed expeditiously, probably on March 23, 2004.

Distribution:
Gene Holbert
Susan Peacock
Norman Schmuff
NDA 21-721
NDA 20-634 / S-030
NDA 20-635 / S-030

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/s/

Susan Peacock
3/12/04 01:53:34 PM

Request for Pharmacology and Biopharmaceutics Inspection

Date: February 6, 2004

To: CT Viswanathan, Ph.D., Division of Scientific Investigations, HFD-48

From: Susan Peacock, M.S., Regulatory Project Manager, Division of Special Pathogen and Immunologic Drug Products, HFD-590

Subject: **Request for Clinical Pharmacology and Biopharmaceutics Inspection**
Application: NDA 21-721
Sponsor: J&JPRD on behalf of OMP
Drug Trade Name (Generic Name): Levaquin® (levofloxacin) Oral Solution.

Protocol/Site Identification:

The following protocol/site essential for approval has been identified for inspection.

Indication(s)	Protocol #	Site (Name and Address)	Subject # (if applicable)
Acute Maxillary Sinusitis, Acute Bacterial Exacerbation of Chronic Bronchitis, Community Acquired Pneumonia, Complicated Urinary Tract Infections, Acute Pyelonephritis, Uncomplicted Skin and Skin Structure Infections, Uncomplicated Urinary Tract Infections, Complicated Skin and Skin Structure Infections.	**LOFBO-PHI-116**: Phase I An Open-Label Randomized, 3-Way Crossover Study to Evaluate the Bioequivalence of an Oral — Formulation, an Oral Solution Formulation, and the Marketed Tablet Formulation of Levofloxacin in Healthy Subjects		Planned: 36; Analyzed for safety: 72; Analyzed for Pharmacokinetics: 34

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by **September 1, 2004** (inspection summary goal date).
We intend to issue an action letter on this application by **October 22, 2004** (action goal date).

This NDA was submitted electronically and the network path location is:
\\CDSESUB1\N21721\N_000\2003-12-19
Should you require any additional information, please contact:
Susan Peacock, M.S., Regulatory Project Manager at (301) 827-2173.

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/s/

Susan Peacock
2/6/04 01:46:15 PM

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # **21-721** Supplement # SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8

Trade Name: **LEVAQUIN® Oral Solution**
Generic Name: **levofloxacin oral solution**
Strengths: **25 mg/ml, oral**

Applicant: Ortho McNeil Pharmaceutical, Inc., C/o Johnson & Johnson Pharmaceutical Research &Dev.

Date of Application: **December 19, 2003**
Date of Receipt: **December 22, 2003**
Date clock started after UN:
Date of Filing Meeting: **February 2, 2004**
Filing Date: **February 20, 2004**
Action Goal Date (optional): User Fee Goal Date: **October 22, 2004**

Indication(s) requested: **Acute Maxillary Sinusitis, Acute Bacterial Exacerbation of Chronic Bronchitis, Community Acquired Pneumonia, Complicated Urinary Tract Infections, Acute Pyelonephritis, Uncomplicted Skin and Skin Structure Infections, Uncomplicated Urinary Tract Infections, Complicated Skin and Skin Structure Infections.**

Type of Original NDA: (b)(1) ____X_____ (b)(2) _____
OR
Type of Supplement: (b)(1) _____ (b)(2) _____
NOTE: A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2) application, complete the (b)(2) section at the end of this review.

Therapeutic Classification: S ___X_____ P _____
Resubmission after withdrawal? _____ Resubmission after refuse to file? _____
Chemical Classification: (1,2,3 etc.) ___**Type 3 (New Formulation)**_____
Other (orphan, OTC, etc.) _____

User Fee Status: Paid ____X_____ Exempt (orphan, government) _____
Waived (e.g., small business, public health) _____

Form 3397 (User Fee Cover Sheet) submitted: **YES** NO
User Fee ID # __**4678**_____
Clinical data? YES **NO**, Referenced to NDA # ___**20-634 and 20-635**_____

Is there any 5-year or 3-year exclusivity on this active moiety in either a (b)(1) or a (b)(2) application?

YES **NO**

If yes, explain:

Does another drug have orphan drug exclusivity for the same indication? YES **NO**

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

YES NO

Is the application affected by the Application Integrity Policy (AIP)? YES **NO**
If yes, explain.

If yes, has OC/DMPQ been notified of the submission? YES NO

- Does the submission contain an accurate comprehensive index? **YES** NO
- Was form 356h included with an authorized signature? **YES** NO
  If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? **YES** NO
  If no, explain:
- If an electronic NDA, does it follow the Guidance? N/A **YES** NO
  If an electronic NDA, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:
- If in Common Technical Document format, does it follow the guidance? **N/A** YES NO
- Is it an electronic CTD? N/A YES **NO**
  If an electronic CTD, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:
- Patent information submitted on form FDA 3542a? **YES** NO
- Exclusivity requested? YES, _____years **NO**
  Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? **YES** NO
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e.,

"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."

- Financial Disclosure forms included with authorized signature? **YES** NO
  (Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)

- Field Copy Certification (that it is a true copy of the CMC technical section)? **YES** NO

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? **YES** NO
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.

- List referenced IND numbers: **IND 36,627 and IND 38,368**

- End-of-Phase 2 Meeting(s)? Date(s) _____ **NO**
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) _____ **NO**
  If yes, distribute minutes before filing meeting.

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
  YES **NO**

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? YES **NO**

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? **N/A** YES NO

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS?
  N/A YES NO

- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  N/A YES NO

Chemistry

• Did applicant request categorical exclusion for environmental assessment?	YES	**NO**
If no, did applicant submit a complete environmental assessment?	**YES**	NO
If EA submitted, consulted to Nancy Sager (HFD-357)?	**YES**	NO
• Establishment Evaluation Request (EER) submitted to DMPQ?	**YES**	NO
• If a parenteral product, consulted to Microbiology Team (HFD-805)?	YES	**NO**

If 505(b)(2) application, complete the following section: N/A

- Name of listed drug(s) and NDA/ANDA #:

- Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.)

  YES NO

- Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 314.101(d)(9).

  YES NO

- Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9).

  YES NO

- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

  ____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

  ____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

  ____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

  ____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

  IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

____ 21 CFR 314.50(i)(1)(ii): No relevant patents.

____ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.

____ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above.)
____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

- Did the applicant:

  - Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

    YES NO

  - Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

    YES NO

  - Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

    N/A YES NO

  - Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

    N/A YES NO

- If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

  - Certification that each of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

    YES NO

  - A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

    YES NO

  - EITHER
    The number of the applicant's IND under which the studies essential to approval were conducted.

    IND # _____ NO

    OR

    A certification that it provided substantial support of the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

    N/A YES NO

- Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

YES NO

APPEARS THIS WAY
ON ORIGINAL

ATTACHMENT

MEMO OF FILING MEETING

DATE: February 2, 2004

BACKGROUND:

Levaquin® Tablet (NDA 20-634) and Levaquin® Injections (NDA 20-635) were approved December 20, 1996. The following indications are approved: Acute Maxillary Sinusitis, Acute Bacterial Exacerbation of Chronic Bronchitis, Nosocomial Pneumonia, Community-Acquired Pneumonia, Complicated Skin and Skin Structure Infections, Uncomplicated Skin and Skin Structure Infections, Chronic Bacterial Prostatitis, Complicated Urinary Tract Infections, Acute Pyelonephritis, Uncomplicated Urinary Tract Infections. This NDA provides for a new oral solution dosage form of Levaquin®. This oral solution has been developed for use in the treatment of all approved indications for the Levaquin® Tablets and Injections.

ATTENDEES: Carl Kraus, Renata Albrecht, Seong Jang, Stephen Hundley, LaRee Tracy, Peter Dionne, Shukal Bala, Gene Holbert, Philip Colangelo, Diana Willard and Ellen Molinaro.

ASSIGNED REVIEWERS:

Discipline	**Primary Reviewer/TL**
Medical:	Carl Kraus/Leonard Sacks
Statistical:	LaRee Tracy/Karen Higgins
Pharmacology:	Stephen Hundley
Chemistry:	Gene Holbert/Norman Schmuff
Environmental Assessment (if needed):	Nancy Sager
Biopharmaceutical:	Seong Jang/Philip Colangelo
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	Peter Dionne/Shukal Bala
DSI:	
Regulatory Project Management:	Susan Peacock/Ellen Molinaro
Other Consults:	

Per reviewers, are all parts in English or English translation? **YES** NO
If no, explain:

CLINICAL FILE __X_____ REFUSE TO FILE _____

- Clinical site inspection needed: YES **NO**
- Advisory Committee Meeting needed? YES, date if known _____ **NO**
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A YES NO

CLINICAL MICROBIOLOGY	NA _____	FILE __X____	REFUSE TO FILE _____
STATISTICS		FILE ___X___	REFUSE TO FILE _____
BIOPHARMACEUTICS		FILE ___X___	REFUSE TO FILE _____
• Biopharm. inspection needed:			**YES** NO
PHARMACOLOGY	NA _____	FILE _X____	REFUSE TO FILE _____
• GLP inspection needed:			YES **NO**
CHEMISTRY		FILE ___X___	REFUSE TO FILE _____
• Establishment(s) ready for inspection?			**YES** NO
• Microbiology			YES **NO**

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ The application is unsuitable for filing. Explain why:

___X____ The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

__X_____ No filing issues have been identified.

_____ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. If RTF, notify everybody who already received a consult request of the RTF action. Cancel the EER.
2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. Document filing issues/no filing issues conveyed to applicant by Day 74.

Susan Peacock
Regulatory Project Manager, HFD-590

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/s/

Susan Peacock
2/3/04 11:11:22 AM
CSO

Susan Peacock
2/3/04 11:13:16 AM
CSO

Ellen Molinaro
2/3/04 03:45:25 PM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: OPS/Quality Implementation Staff (HFD-357)

FROM: Gene W. Holbert

DATE:	IND NO.	NDA NO.	TYPE OF DOCUMENT:	DATE OF DOCUMENT:
07-JAN-2004		21-721	Original	19-DEC-2003

NAME OF DRUG:	PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE:
Levaquin (levofloxacin) Oral Solution	Prior Approval	Antibacterial (Synthetic)	15-AUG-2004

NAME OF FIRM: Ortho McNeil Pharmaceutical, Inc.

REASON FOR REQUEST

I. GENERAL

- ▯ NEW PROTOCOL
- ▯ PROGRESS REPORT
- ▯ NEW CORRESPONDENCE
- ▯ DRUG ADVERTISING
- ▯ ADVERSE REACTION REPORT
- ▯ MANUFACTURING CHANGE/ADDITION
- ▯ MEETING PLANNED BY
- ▯ PRE--NDA MEETING
- ▯ END OF PHASE II MEETING
- ▯ RESUBMISSION
- ▯ SAFETY/EFFICACY
- ▯ PAPER NDA
- ▯ CONTROL SUPPLEMENT
- ▯ RESPONSE TO DEFICIENCY LETTER
- ▯ FINAL PRINTED LABELING
- ▯ LABELING REVISION
- ▯ ORIGINAL NEW CORRESPONDENCE
- ▯ FORMULATIVE REVIEW
- X OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
▯ TYPE A OR B NDA REVIEW ▯ END OF PHASE II MEETING ▯ CONTROLLED STUDIES ▯ PROTOCOL REVIEW ▯ OTHER (SPECIFY BELOW):	▯ CHEMISTRY REVIEW ▯ PHARMACOLOGY ▯ BIOPHARMACEUTICS ▯ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ▯ DISSOLUTION
- ▯ BIOAVAILABILTY STUDIES
- ▯ PHASE IV STUDIES
- ▯ DEFICIENCY LETTER RESPONSE
- ▯ PROTOCOL-BIOPHARMACEUTICS
- ▯ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ▯ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ▯ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ▯ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ▯ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ▯ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ▯ SUMMARY OF ADVERSE EXPERIENCE
- ▯ POISION RICK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ▯ CLINICAL
- ▯ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: This NDA provides for a new levofloxacin formulation. Please review the EA information provided by the applicant. The document is in the CTD format and may be found in the EDR at \\Cdsesub1\N21721. Thank you.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) X MAIL ▯ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Susan Peacock
1/8/04 09:23:20 AM

EDMS-USRA-8863713

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

Johnson & Johnson Pharmaceutical Research & Development, LLC
920 Route 202 South
P.O. Box 300
Raritan, NJ 08869-0602
on behalf of
Ortho-McNeil Pharmaceutical , Inc
1000 Route 202 South
Raritan, NJ 08869-0602

2. TELEPHONE NUMBER *(Include Area Code)*

(908) 218-6473

3. PRODUCT NAME

LEVAQUIN (levofloxacin) Oral Solution

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

NDA 21-721

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☐ YES ☒ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☐ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

4678

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE **EXCLUSIONS**? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

☐ YES ☒ NO

(See item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

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SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Manisha Padhye MPadhye	Manager, Regulatory Affairs	12·10·03

FORM FDA 3397 (3/01)

Created by: PSC Media Arts (301) 443-2454 EF

NDA 20-634
NDA 20-635
Facsimile

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: July 14, 2003

To: Jerry Klimek	**From:** Susan Peacock
Company: Johnson & Johnson Pharmaceutical Research and Development, L.L.C.	Division of Special Pathogen and Immunologic Drug Products
Fax number: 908-704-1501	**Fax number:** (301) 827-2475
Phone number: (908) 704-4587	**Phone number:** (301) 827-2173

Subject: Comments regarding Questions about submission of CTD for Levaquin Oral Solution

Total no. of pages including cover: 4

Document to be mailed: ☐ YES ☑ NO

Date: July 14, 2003

To: Jerry Klimek
J&J Pharmaceutical Research and Development, L.L.C.
920 U.S. Highway 202
P.O. box 300
Raritan, NJ 08869

From: Susan Peacock
Regulatory Project Manager, HFD-590

Through: Rigoberto Roca, M.D., Medical Team Leader
Leonard Sacks, M.D., Medical Reviewer
Philip Colangelo, Pharm.D., Ph.D., Clinical Pharmacology/Biopharmaceutics Team Leader
Gene Holbert, Ph.D., Chemistry Reviewer
Norman Schmuff, Ph.D., Chemistry Team Leader

Subject: Comments regarding Questions about submission of CTD for Levaquin Oral solution

Dear Mr. Klimek,

I received your email containing the following questions regarding the Common Technical Document table of contents for the Oral Solution NDA for Levaquin. Please find our responses below in italics:

1. Page 2: In Module 2: Common Technical Document Summaries, **2.3.S Drug Substance** there is very limited new information for this section so we want to make sure that it would be allowable to cross reference previously submitted data for this section that has been submitted under the original NDA and supplements made to it. Is this acceptable?

   Yes, as far as possible, no redundant CMC data should be submitted. There should just be a cross reference to the approved NDA, and possibly to any pertinent approved supplements.

2. Page 3: In section **2.4 Non-clinical Overview** again this Oral Solution NDA will not have any of this type of data so we expect to cross reference here to our original NDA 20-634 for Levaquin in regard to previously submitted data, this is anticipated where ever we have no additional information to provide other than what has already been provided for under the original NDA 20-634 and supplements made to it. Is this acceptable?

   Yes, it is acceptable to cross-reference the Non-clinical overview.

3. Page 3: Section **2.5 Clinical Overview** Does the Division feel that an Clinical Overview is necessary since we will be providing for under section **2.7 Clinical Summary** (includes sections 2.7.1 to 2.7.6) all information in summary form for the studies conducted for this Oral Solution NDA. Namely summary information from the Bioequivalency Study PHI-116 and Bioavailability Study (food effect) PHI-117. The full reports for these studies will be located in (see page 6) Module 5: Clinical Study Reports, 5.3.1.1 Bioavailability (BA) Study Reports (Study PHI-117 food effect) and 5.3.1.2 Comparative BA and Bioequivalence (BE) Study Reports (Study PHI-116 bioequivalence). Is this acceptable?

   Yes, a clinical overview will not be necessary since this would only duplicate the clinical summary.

4. Page 7: There are two studies that we intend to place in Section **5.3.5.4 Other Clinical Study Reports.** These studies are taste test studies where the oral solution was tested to determine the best tasting solution. They are Studies LSTT-002 and LSTT-003. Does the Division accept the placement of these studies under this section of the CTD?

   Yes, we agree with the placement of 002 and 003 in the clinical study reports section.

Please contact me at (301) 827-2173, if you have any questions regarding this facsimile transmission.

Thank you.

Susan Peacock
Project Manager
Division of Special Pathogen and Immunologic Drug Products

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/s/

Susan Peacock
7/14/03 08:44:45 AM
CSO

Susan Peacock
7/14/03 08:47:45 AM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: March 18, 2003

To: Lillian Malahias	**From:** Susan Peacock
Company: J&J Pharmaceutical Research and Development, LLC	Division of Division of Special Pathogen and Immunologic Drug Products
Fax number: (908) 231-0056	**Fax number:** (301) 827-2475
Phone number: 908-704-4377	**Phone number:** (301) 827-2155
Subject: IND 36,627	
Total no. of pages including cover: 2	

Comments: Levofloxacin – Oral Solution-New Formulation

Document to be mailed: ☐ YES ☑ NO

Date: March 18, 2003

To: Lillian Malahias
Associate Director, Chem-Pharm Regulatory Affairs
Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
920 Route 202 South, P.O. Box 300
Raritan, New Jersey 08869-0602

From: Susan Peacock
Regulatory Project Manager, HFD-590

Through: Norm Schmuff, Ph.D., Chemistry Team Leader
Gene Holbert, Ph.D., Chemistry Reviewer

Subject: Response to your query submitted on March 12, 2003, via email.

Dear Ms. Malahias:

Please refer to your email sent on March 12, 2003, which included the following query:

We will be providing batch documentation for Levofloxacin Solution, 125 mg/5 mL , in accordance to 21CFR314.50(d)(1)(ii)(b). Our plan is to provide one executed batch record on a batch that was used to conduct both the pivotal bioequivalence study, as well as a primary stability study. Is the agency in agreement with our proposed plan?

Division Response: *Submission of the one executed batch record as described is acceptable if the batch was manufactured on at least a pilot scale.*

Please contact me at (301) 827-2173, if you have any questions regarding this facsimile transmission.

Thank you.

Susan Peacock
Project Manager
Division of Special Pathogen and Immunologic Drug Products

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/s/

Susan Peacock
3/18/03 12:33:31 PM
CSO

Susan Peacock
3/18/03 12:36:15 PM
CSO

B

6 Page(s) Withheld

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