CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-637/S-008, S-009
20-635/S-007, S-008

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

Patent Information

Provided by sponsor in cover letter for supplemental New Drug Application
March 31, 1999

Levofioxacin is protected by U.S. Patent Numbers 4,382,892 and 5,053,407. These patents cover the changed product as proposed in this supplemental application. Patent information required by 21 C.F.R. §314.53© has been previously filed to NDA 20-634 on 21 December 1995. This reference fulfills our patent reporting requirements pursuant to 21 C.F.R. §314.53(d)(2)(ii).

NDA 20-634/5 S-008/007 March 31, 1999
Treatment of Community Acquired Pneumonia due to Penicillin-Resistant
S. Pnuemoniae

NDA 20-634
ELEQUIN™(levofloxacin tablets) Tablets
Item 13
Patent Information

Levofloxacin is protected by the following:

U.S. Patent No.	Patent Type	Expiration Date	Owner	U.S. Agent
4,382,892	Drug Substance (Broad patent covers compound regardless of steriochemistry)	Sept. 2, 2001	Daiichi Seiyaku, Co., Ltd. Tokyo, Japan	Daiichi Pharmaceutical 1 Parker Plaza Fort Lee, NJ 07024
5,053,407	Drug Substance	Oct. 1, 2008	Daiichi Pharmaceutical Co., Ltd Tokyo, Japan	

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Exclusivity Checklist

NDA:	20-634/20-635, S-008/007
Trade Name:	Levaquin
Generic Name:	levofloxacin
Applicant Name:	R.W. Johnson Pharmaceutical Research Institute
Division:	HFD-590
Project Manager:	Jeff Fritsch
Approval Date:	February 2, 2000

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a. Is it an original NDA?	Yes		No	X
b. Is it an effectiveness supplement?	Yes	X	No	
c. If yes, what type? (SE1, SE2, etc.)	SE1			
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	X	No	

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.

Explanation:

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:

Explanation:

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?				

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

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?	Yes		No	X
If yes, NDA #				
Drug Name:				

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS.				
3. Is this drug product or indication a DESI upgrade?	Yes		No	X
IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS (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.	Yes		No	
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).				
Drug Product	Levaquin, Tablets			
NDA #	20-634			
Drug Product	Levaquin, I.V.			
NDA #	20-635			
Drug Product				
NDA #				
2. Combination product.	Yes		No	
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).				
Drug Product				
NDA #				
Drug Product				
NDA #				
Drug Product				

NDA #	

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS. 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	X	No	

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.

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. For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

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	X	No	

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCKS.**

Basis for conclusion:

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	X
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	X

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	X
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:				
Investigation #1, Study #:	LOFBIV-PCAP 001			
Investigation #2, Study #:	CAPSS-043			
Investigation #3, Study #:	CAPSS-018			
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	X
Investigation #2	Yes	X	No	
Investigation #3	Yes	X	No	
If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:				
Investigation #1 -- NDA Number				
Investigation #2 -- NDA Number	20-634 & 20-635			
Investigation #3 -- NDA Number	20-634 & 20-635			
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	X
Investigation #2	Yes		No	X
Investigation #3	Yes		No	X
If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:				
Investigation #1 -- NDA Number				
Investigation #2 -- NDA Number				
Investigation #3 -- NDA Number				

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"):					
Investigation #1					
Investigation #2					
Investigation #3					
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	Yes	x	No		
IND#: 36,627 & 38,368					
Explain:					
Investigation #2	Yes		No		
IND#:					
Explain:					
Investigation #3	Yes		No		
IND#:					
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		No		
IND#:					
Explain:					
Investigation #2	Yes		No		
IND#:					
Explain:					
Investigation #3	Yes		No		

IND#:				
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	X
If yes, explain:				

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Signature of PM/CSO /S/
Date: 8/7/00

Signature of Division Director /S/
Date: 8/7/00

cc:
Original NDA
Division File
HFD-93 Mary Ann Holovac

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PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA Number:	020634	**Trade Name:**	LEVAQUIN(LEVOFLOXACIN) TABS 250MG/500MG
Supplement Number:	008	**Generic Name:**	LEVOFLOXACIN TABS
Supplement Type:	SE1	**Dosage Form:**	
Regulatory Action:	AP	**COMIS Indication:**	ACUTE BACTERIAL SINUSITIS/ACUTE BACTERIAL EXACERBATION OF CHRONIC BRONCHITIS/COMMUNITYACQUIRED PNEUMONIA COMPLICATED URINARY TRACT INFECTIONS/ACUTE PYELONEPHRIS
Action Date:	12/20/96		

Indication # 1 Levaquin is approved for the treatment of levofloxacin susceptible strains of penicillin-resistant Streptococcus pneumoniae in patinets with community-acquired pneumonia.

Label Adequacy: Inadequate

Forumulation Needed:

Comments (if any):

Lower Range	Upper Range	Status	Date

This page was completed based on information from Jeffrey Fritsch

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Date

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PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA Number:	020635	**Trade Name:**	LEVAQUIN(LEVOFLOXACIN INJ) IV 25MG/ML/5M
Supplement Number:	007	**Generic Name:**	LEVOFLOXACIN
Supplement Type:	SE1	**Dosage Form:**	
Regulatory Action:	AP	**COMIS Indication:**	ACUTE BACTERIAL SINUSITIS/ACUTE BACTERIAL EXACERBATION OF CHRONIC BRONCHITIS/COMMUNITY ACQUIRED PNEUMONIA/COMPLICATED URINARY TRACT INFECTIONS/ACUTE PYELONEPHRS
Action Date:	12/20/96		

Indication # 1 Levaquin is approved for the treatment of levofloxacin susceptible strains of penicillin-resistant Streptococcus pneumoniae in patients with ccommunity-acquired pneumonia

Label Adequacy: Inadequate

Forumulation Needed:

Comments (if any):

Lower Range	Upper Range	Status	Date

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Date

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LEVAQUIN (levofloxacin tablets) Tablets **NDA 20-634**

DEBARMENT CERTIFICATION

The R.W. Johnson Pharmaceutical Research Institute certifies that we did not and will not use in any capacity the services of any person debarred under subsections 306 (a) or 306 (b) of the Federal Food Drug and Cosmetic Act in connection with this supplemental New Drug Application.

Note:
Debarment certification was not part of the 20-635 package. Certification was referenced to 20-634 submission.

FINANCIAL DISCLOSURE CLASSIFICATION TABLE

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE
Route 202, P.O. Box 300
Raritan, New Jersey 08869

PROTOCOL NO.: LOFBIV-PCAP-001

PROTOCOL TITLE: NONCOMPARATIVE, MULTICENTER STUDY TO EVALUATE THE SAFETY AND EFFICACY OF LEVOFLOXACIN 500 mg ONCE-DAILY IN THE TREATMENT OF COMMUNITY-ACQUIRED PNEUMONIA IN ADULTS

Enter applicable information for all Investigators and Sub-Investigators participating in the covered clinical study.

NAME OF INVESTIGATOR	SITE NUMBER	DUE DIL.	SUPP. DOC. Vol. / Page	CERT.	SUPP. DOC. Vol. / Page	DISC.	SUPP. DOC. Vol. / Page	EMP.
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. XXXX-XXXX
Expiration Date: XX/XX/XX

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	Please refer to attached list.	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Kimberly Edwards-Swanson	Team Leader, Clinical Reports & Submissions
FIRM/ORGANIZATION	
The R.W. Johnson Pharmaceutical Research Institute	
SIGNATURE	**DATE**
Kimberly Edwards-Swanson	3-24-99

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

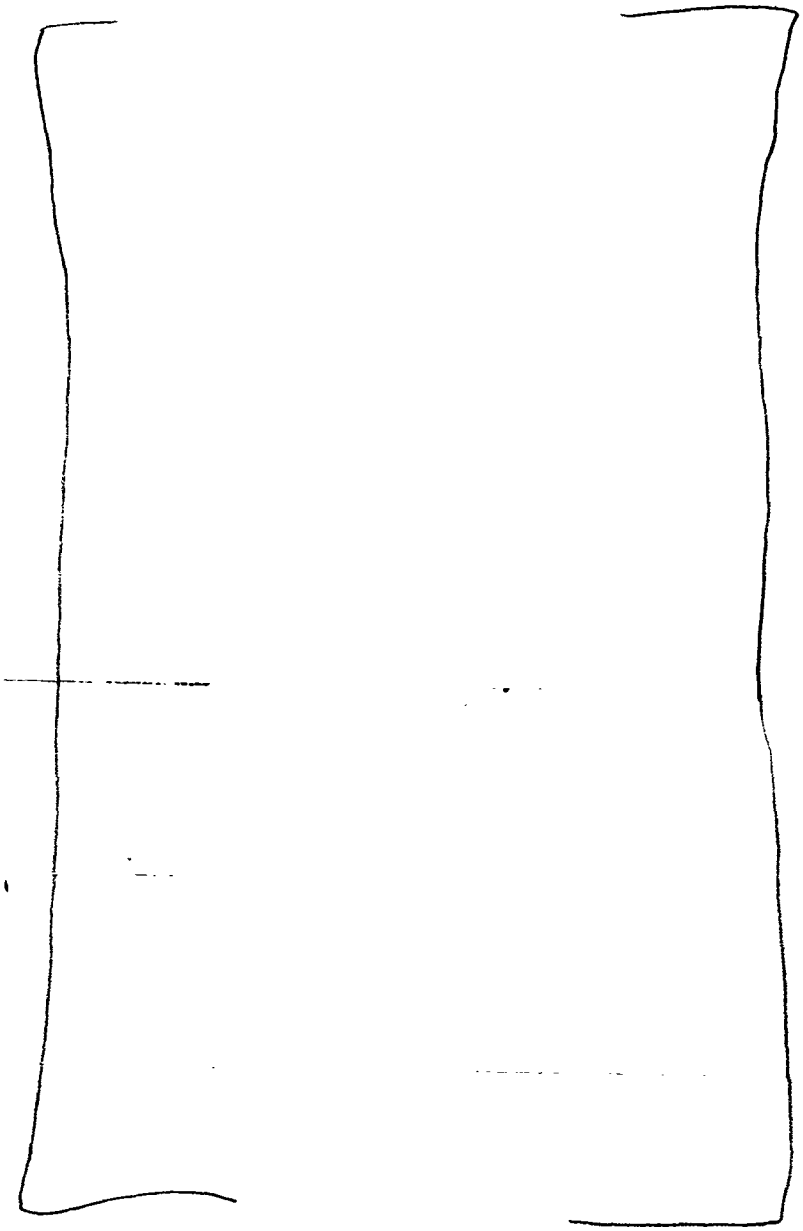
Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

Please DO NOT RETURN this form to this address.

LOFBIV-PCAP-001

Certification: Financial Interests and Arrangements of Clinical Investigators

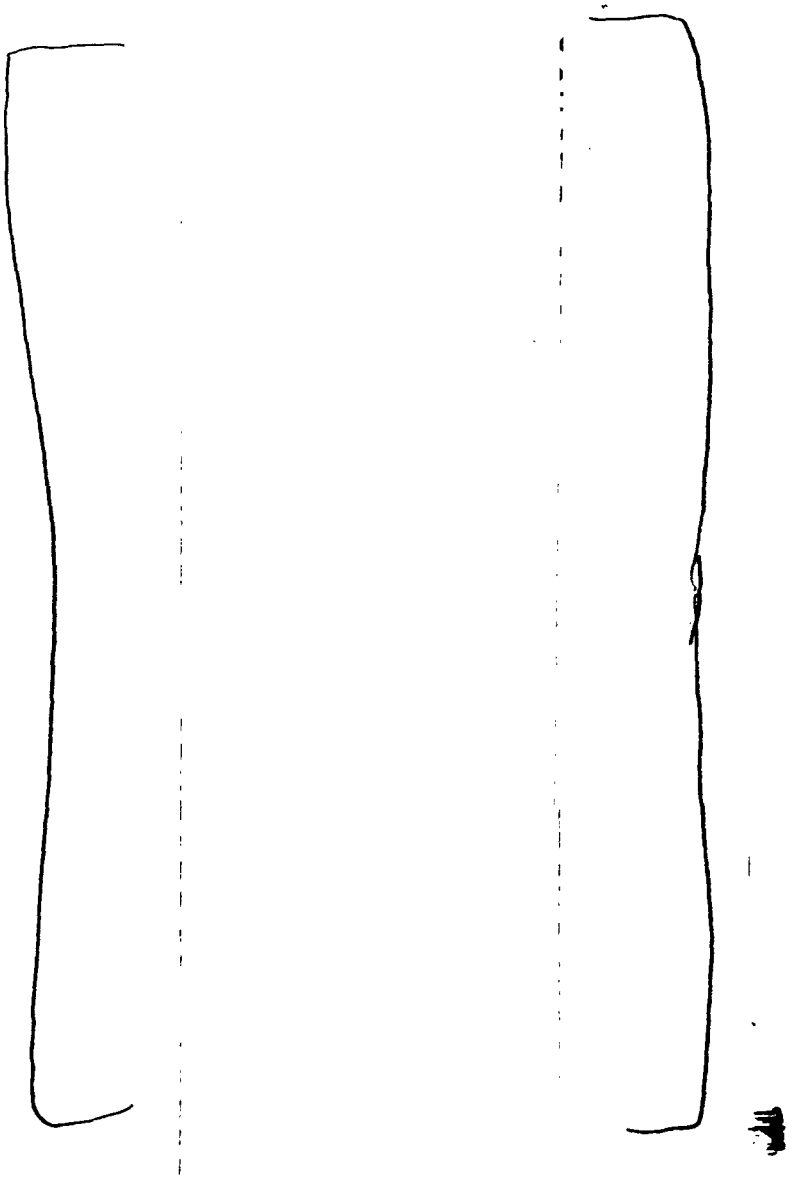
List of Investigators Applicable to #1 on preceding form:



Study LOFBIV-PCAP-001

Statement of Due Diligence

The R.W. Johnson Pharmaceutical Research Institute (RWJPRI), sponsor of study LOFBIV-PCAP-001, acted with due diligence to obtain financial disclosure information from the following list of investigators. RWJPRI made two written attempts to obtain this information from each principal investigator and subinvestigators as listed on the Form FDA 1572. Since this study was initiated in October 1996 and financial disclosure information was not obtained at initiation or at study close, many investigators have not responded to these requests.



FINANCIAL DISCLOSURE CLASSIFICATION TABLE

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE
Route 202, P.O. Box 300
Raritan, New Jersey 08869

PROTOCOL NO.: CAPSS-043

PROTOCOL TITLE: Multicenter Study to Evaluate the Safety and Efficacy of Levofloxacin 500 mg, Once Daily, in the Treatment of Community-Acquired Pneumonia in Adults

Enter applicable information for all investigators and Sub-investigators participating in the covered clinical study.

NAME OF INVESTIGATOR	SITE NUMBER	DUE DIL.	SUPP. DOC. Vol. Page	CERT.	SUPP. DOC. Vol. Page	DISC.	SUPP. DOC. Vol. Page	EMP.
[redacted]				x	Vol. 1/ Page 14			
				x	Vol. 1/ Page 14			
				x	Vol. 1/ Page 14			
				x	Vol. 1/ Page 14			
				x	Vol. 1/ Page 14			
				x	Vol. 1/ Page 14			
				x	Vol. 1/ Page 14			

PROTOCOL NO.: CAPSS-056

PROTOCOL TITLE: Multicenter, Open-Label, Randomized Study to Compare the Safety and Efficacy of Levofloxacin vs Azithromycin in the Treatment of Moderate to Severe Community-Acquired Pneumonia in Adults

Enter applicable information for all investigators and Sub-investigators participating in the covered clinical study.

NAME OF INVESTIGATOR	SITE NUMBER	DUE DIL.	SUPP. DOC. Vol. Page	CERT.	SUPP. DOC. Vol. Page	DISC.	SUPP. DOC. Vol. Page	EMP.
[redacted]				X	Vol. 1/ Page 14			
		X	Vol. 1/ Page 15					

Due Dil.: Due Diligence, Cert.: Certification, Disc.: Disclosure, Emp.: Employee

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. XXXX-XXXX
Expiration Date: XX/XX/XX

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☑ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators [ ]

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Michael E. Kafrissen, MD	Vice President, Clinical Affairs
FIRM/ORGANIZATION: Ortho-McNeil Pharmaceutical	
SIGNATURE	DATE: 2(-3-99

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

Please DO NOT RETURN this form to this address.

Study CAPSS-056

Statement of Due Diligence

Ortho-McNeil Pharmaceutical Inc. (OMP), sponsor of study CAPSS-056, acted with due diligence to obtain financial disclosure information from investigator _____. Several attempts to obtain this information were made by letter and telephone; however, at the time of this filing, no response was received.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Memorandum

Date: August 4, 2000

From: Edward Cox, MD
Medical Officer
Division of Special Pathogen and Immunologic Drug Products (HFD-590)

Through: Rigoberto Roca, MD
Medical Team Leader
Division of Special Pathogen and Immunologic Drug Products (HFD-590)

To: Renata Albrecht, MD
Acting Division Director
Division of Special Pathogen and Immunologic Drug Products (HFD-590)

Subject: Financial Disclosure for NDA 20-634 SE1-008 and NDA 20-635 SE1-007

The Applicant certified (or exercised due diligence in certifying) that none of the investigators involved with studies submitted in NDA 20-634 SE1-008 and NDA 20-635 SE1-007 had or received any of the following:

1. A proprietary interest in the test product or significant equity interest in the Sponsor
2. Compensation affected by the outcome of clinical studies
3. Significant payments of other sorts as defined in 21 CFR 54.2(f)

We did not conduct any additional analyses because there was no evidence of financial interests that might result in potential bias.

APPEARS THIS WAY
ON ORIGINAL

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE
ROUTE 202 P.O. BOX 300 RARITAN NEW JERSEY 08869-0602

SEP - 7 1999

NDA SUPPL AMENDMENT

Food and Drug Administration
Center For Drug Evaluation and Research
Office of Drug Evaluation IV
Division of Special Pathogens and Immunologic
Drug Products (HFD-590)
Attn.: Document Control Room
9201 Corporate Blvd.
Rockville, Maryland 20850

NDA 20-634
LEVAQUIN® Tablets
(levofloxacin tablets)

NDA 20-635
LEVAQUIN® Injection
(levofloxacin injection)

GENERAL CORRESPONDENCE
Supplement S-008 NDA 20-634
Supplement S-007 NDA 20-635

Dear Sir/Madam:

Reference is made to our approved New Drug Applications 20-634 and 20-635 for LEVAQUIN® Tablets and LEVAQUIN® Injection, respectively. Reference is specifically made to our pending supplements (S-008 NDA 20-634 and S-007 NDA 20-635) for the addition of penicillin-resistant/intermediate ——— strains of *S. pneumoniae* in community-acquired pneumonia.

At this time, and accordance with 21 CFR § 314.65, we are voluntarily withdrawing our proposed claim for ——— without prejudice to refiling this data in the future. We are, however, continuing to pursue our claim for penicillin-resistant/intermediate strains of *S. pneumoniae* in community-acquired pneumonia.

In support of this change, we have attached a copy of the revised package inserts for both LEVAQUIN Tablets and Injection, incorporating the deletion of ——— (please refer to pages 7 and 12 of revised inserts).

Should you have any questions and/or comments, please contact me directly at (908) 704-4198 or call our telephone line dedicated for FDA use at (908) 704-4600.

Sincerely,

The R.W. Johnson
Pharmaceutical Research Institute

Mary Ellen Zamstein

Mary Ellen Zamstein
Principal Regulatory Scientist
Regulatory Affairs

Desk Copy: Mr. Jeff Fritsch (S357)
Ms. Robin Anderson (S438)

APPEARS THIS WAY
ON ORIGINAL

RECORD OF A 45 DAY FILING MEETING

DATE: May 17, 1999

SUBJECT: Levaquin (levofloxacin) Tablets, 250 and 500 mg
Levaquin (levofloxacin) Injection, 25 mg/ml and 5 mg/ml

OBJECTIVE: To determine the fileability of NDA 20-634, S008 and NDA 20-635, S007

PARTICIPANTS FROM FDA/CDER/HFD-590:
Leonard Sacks, Medical Officer
Nancy Silliman, Team Leader, Biostatistics
Cheryl Dixon, Biostatistics Reviewer
Peter Dionne, Microbiology Reviewer
Gene Holbert, Chemistry Reviewer
Ellen Frank, Supervisory Project Manager
Robin Anderson, Project Manager
Valerie Jensen, Project Manager

The meeting was convened to determine the adequacy of NDA 20-634, S008 and NDA 20-635, S007 for filing. All sections of the New Drug Applications (NDA) were evaluated in terms of the general content and format requirements.

From a preliminary evaluation of the general content and format, as well as the chemistry, manufacturing, and controls, microbiology, clinical data, and statistical sections of the application, it was recommended that NDA —— be filed. There was no non-clinical pharmacology and toxicology or human pharmacokinetics and bioavailability data submitted or required.

It was concluded that the application was generally complete and was therefore acceptable for filing. It was also concluded that there were no reviewer comments to be conveyed to the applicant.

/S/

Robin Anderson, RN, MBA
Project Manager, HFD-590

Attachments:
Checklists

cc:
Orig NDA 20-634 and NDA 20-635
HFD-590/Division File

45 DAY FILING MEETING PROJECT MANAGEMENT CHECKLIST

May 17, 1999

NDA #:	20-634, S008 and 20-635, S007
Drug name and Dosage:	Levaquin Tablets, 250 and 500 mg Levaquin Injection, 25 mg/ml and 5 mg/ml
Indication:	Community Acquired Pneumonia (penicillin- and strains of *S. pneumoniae*
Type:	SE1
Applicant:	RW Johnson PRI
Stamp Date:	4/1/99
Filing Date:	5/31/99
ODEIV Goal Date:	
PDUFA Goal Date:	2/1/00

FILEABILITY:

On initial overview of the NDA application:

(1) Do any of the following apply to this application (i.e., if YES , the application MUST BE REFUSED TO FILE under 314.101 (e) and there is no filing over protest):

(a) Is the drug product already covered by an approved application?
No.

(b) Does the submission purport to be an abbreviated application under 314.55; however the drug product is not one for which FDA has made a finding that an abbreviated application is acceptable under 314.55(b)?
No

c) Is the drug product subject to licensing by FDA under the Public Service Act and Subchapter F of Chapter I of Title 21 of the CFR?
No

(2) Do any of the following apply to this application (i.e., if NO, the application MAY BE REFUSED TO FILE under 314.101(d) and there is the potential for filing over protest):

(a) Does the application contain a completed application form as required under 314.50 or 314.55?
Yes.

(b) On its face, does the application contain the sections of an application required by regulation and Center guidelines?

Yes. No pharm/tox or biopharm data was included or required for this application.

c) Has the applicant submitted a complete environmental assessment which addresses each of the items specified in the applicable format under 25.31 or has the applicant submitted evidence to establish that the product is under 25.24 of the CFR?
A statement of categorical exclusion was submitted in the cover letter.

(d) On its face, is the NDA formatted in compliance with Center guidelines including integrated efficacy (ISE) and safety (ISS) summaries?
Yes, ISE is located in vol. 24. ISS was not submitted per agreement with FDA during a telecon on 7/27/98. ISS will be submitted with the next efficacy supplement submitted.

(e)Is the NDA indexed and paginated?
Yes.

(f) On its face, is the NDA legible?
Yes.

(g) Has the applicant submitted all required copies of the submission and various sections of the submission?
Yes.

(h) Has the sponsor submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor?
N/A

(i) Does the application contain a statement that all nonclinical laboratory studies were conducted in compliance with the requirements set forth in Part 58 or a statement why a study was not conducted in compliance with those requirements?
N/A

(j) If required, has the applicant submitted carcinogenicity studies?
N/A

(k) On its face, does the application contain at least two adequate and well-controlled clinical trials?
Yes.

(l) Does the application contain a statement that all clinical trials were conducted in accord with the IRB/Declaration of Helsinki provisions of the CFR?
Yes, located in vol. 3, pg. 119.

20-634, S008 and 20-635, S007

(m) Have all articles/study reports been submitted whether in English or translated into English?
N/A

(n) Has the applicant submitted draft labeling in compliance with 210.56 and 210.57 of the CFR?
Yes.

(o) Has the applicant submitted the required FRAUD POLICY notice?
Yes.

(p) Has the applicant submitted copies of all package inserts (or their equivalent) from all countries in which this product has been previously approved for marketing? Have all non-English package inserts been translated?
The PI from Ireland was submitted and that was representative of all the European labels. This is discussed in the marketing history section of the application.

(q) Has the applicant stated that the integrated summary of safety includes all safety data for this product of which they are aware from all sources, domestic and foreign? What is the cut-off date for the preparation of the ISS?
ISS was not submitted per agreement with FDA during a telecon on 7/27/98. ISS will be submitted with the next efficacy supplement submitted.

(r) If this is a CANDA submission, has the applicant submitted a statement to the archival NDA that the text, tables, and data in the CANDA and the archival hard copy NDA are identical? If they are not identical, is there a letter to the archival NDA that specifies distinctly ALL of the differences in the two submissions?
N/A

(3) From a project management perspective, is this NDA fileable? If "no". please state on the reverse why it is not.
Yes

/S/

Project Manager

/S/

Supervisory Project Manager

APPEARS THIS WAY
ON ORIGINAL

cc: 20-634 and 20-635
HFD-590 Division Files

STATISTICAL REVIEW AND EVALUATION: 45 DAY MEETING REVIEW
(COMPLETED REVIEW FOR INTERNAL DISTRIBUTION ONLY)

NDA: 20-634
Name Of Drug: Levaquin® Tablets (levofloxacin tablets)
Applicant: R. W. Johnson Pharmaceutical Research Institute
Submission Date: April 1, 1999

MAY 17 1999

Indication(s): Penicillin and [redacted] *S. pneumonia* in community acquired pneumonia

Number And Type Of Controlled Clinical Studies (By Indication): Seven studies support the proposed indication. Three studies were open-label noncomparative studies. Two studies, one of which was double-blind and the other open-label, were randomized, active-controlled, and comparative in design. Two non-IND studies sponsored by Ortho-McNeil Pharmaceutical are currently ongoing, one of which was an open-label, comparative trial and one which was an open-label, noncomparative trial.

Statistical Reviewer: Cheryl Dixon
Clinical Reviewer: Leonard Sacks
Project Manager: Robin Anderson

APPEARS THIS WAY
ON ORIGINAL

45 Day Meeting Date: May 17, 1999
Date Draft Review Expected: 12/31/99
ODE IV Goal Date: 12/31/99
User Fee Date: 2/1/00

A. ORGANIZATION AND DATA PRESENTATION	YES	NO	N/A
I. Is there a comprehensive table of contents with adequate indexing and pagination?	✓		
II. Are the original protocols, protocol amendments and proposed label provided?	✓		
III. Are patient profile listings (for all enrolled patients) provided in each study report?	✓		
IV. Are adverse event listings by center and time of occurrence relative to enrollment date included?	✓		
V. Have the data been submitted electronically?	✓		[redacted]
a. If so, has adequate documentation of the data sets been provided?	✓		
b. Do the electronic data appear to accurately represent			

the data described in the study reports?	✓		
c. Can the data be easily merged across studies and indications?			✓
d. Are inclusion/exclusion and evaluability criteria adequately coded and described?	✓		

B. STATISTICAL METHODOLOGY	**YES**	**NO**	**N/A**
I. Are all primary efficacy studies of appropriate design to meet basic approvability requirements, within current Divisional policy statements or to the extent agreed upon previously with the sponsor by the Division?	✓		
II. For each study, is there a comprehensive statistical summary of the efficacy analyses which covers the intent-to-treat population, evaluable subject population and other applicable subgroups (age, gender, race, etc.)?	✓		
III. Based on the summary analyses of each study, do you believe:			
a. The analyses are appropriate for the type of data collected, the study design, and the study objectives (based on protocol objectives and proposed labeling claims)?	✓		
b. Intent-to-treat and evaluable patient analyses are properly performed?	✓		
c. Missing data has been appropriately handled?	✓		
d. Any multiplicity issues (e.g., regarding endpoints, timepoints, or multiple dose groups) have been adequately addressed?			✓
e. If interim analyses were performed, were they planned in the protocol and were appropriate significance level adjustments made?			✓
IV. Were sufficient and appropriate references included for novel statistical approaches?			✓
V. Are all of the pivotal studies complete?		✓	
The two non-IND studies are still ongoing. Data from subjects enrolled on or before 12 June 1998 are included in the submission.			
VI. Have safety data been comprehensively and adequately summarized?	✓		

C. FILEABILITY CONCLUSIONS

From a statistical perspective this submission, or indications therein, is reviewable with only minor further input from the sponsor.

/S/ 5/17/99

Cheryl Dixon, Ph.D.
Mathematical Statistician, DB III

/S/ 5/17/99

Concur: Nancy Silliman, Ph.D.
Statistics Team Leader, DB III

cc:
Archival: NDA #20-634
HFD-590
HFD-590/Dr. Goldberger
HFD-590/Dr. Hopkins
HFD-590/Dr. Sacks
HFD-590/Ms. R. Anderson
HFD-725/Dr. Huque
HFD-725/Dr. Silliman
HFD-725/Dr. Dixon
HFD-725/Ms. Shores

APPEARS THIS WAY
ON ORIGINAL

NDA 20-634/SEI-008
Levofloxacin Tablets
Penicillin and ——— *S. pneumoniae*

45 DAY MEETING CHECKLIST

FILEABILITY:

On initial overview of the NDA application:	YES	NO

MICROBIOLOGY:

(1) On its face, is the microbiologic section of the NDA organized in a manner to allow substantive review to begin?	X	
(2) Is the microbiologic section of the NDA indexed and paginated in a manner to allow substantive review to begin?	X	
(3) On its face, is the microbiologic section of the NDA legible so that substantive review can begin?	X	
(4) On its face, has the applicant submitted *in vitro* data in necessary quantity, using necessary clinical and non-clinical strains, and using necessary numbers of approved current divisional standard of approvability of the submitted draft labeling?	X (same as submitted in supplement 006)	
(5) Has the applicant submitted any required animal model studies necessary for approvability of the product based on the submitted draft labeling?	None needed	

APPEARS THIS WAY
ON ORIGINAL

FILEABILITY (cont):

On initial overview of the NDA application:	YES	NO

MICROBIOLOGY:

(6) Has the applicant submitted draft breakpoint and interpretive criteria in a manner consistent with contemporary standards, in a manner which attempts to correlate criteria with clinical results of NDA studies, and in a manner to allow substantive review to begin?	Breakpoints previously set	
(7) Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	Not needed	
(8) Has the applicant submitted draft labeling consistent with §201.56 and §201.57, current divisional policy, and the design of the development package?	X	
(9) If necessary for this product, has the applicant submitted the sterilization procedures and documentation required for the approval of the manufacturing and controls elements for this NDA?	Not a sterile product	
(10) From a microbiology perspective, is this NDA If "no", please state on reverse why it is not.	X--fileable	

APPEARS THIS WAY
ON ORIGINAL

Comment:

All of the pre-clinical microbiology information submitted in this supplement was previously submitted in supplement 006 dated December 17, 1998. The sponsor has performed one new study LOFBIV-PCAP-001 and looks at other Phase 3 Community-acquired Pneumonia (CAP) studies in which levofloxacin was dosed at 500 mg qd for 7 to 14 days. The sponsor is trying to find enough

APPEARS THIS WAY
ON ORIGINAL

/S/ 5-5-99
Peter A. Dionne
Reviewing Microbiologist

/S/ 5/12/99
Sheryl Lard Whiteford
Group Leader Microbiology

NDA 20-635/SEI-007
Levofloxacin IV
Penicillin and [redacted] *S. pneumoniae*

45 DAY MEETING CHECKLIST

FILEABILITY:

On initial overview of the NDA application:	YES	NO

MICROBIOLOGY:

(1) On its face, is the microbiologic section of the NDA organized in a manner to allow substantive review to begin?	X	
(2) Is the microbiologic section of the NDA indexed and paginated in a manner to allow substantive review to begin?	X	
(3) On its face, is the microbiologic section of the NDA legible so that substantive review can begin?	X	
(4) On its face, has the applicant submitted *in vitro* data in necessary quantity, using necessary clinical and non-clinical strains, and using necessary numbers of approved current divisional standard of approvability of the submitted draft labeling?	X (same as submitted in supplement 006)	
(5) Has the applicant submitted any required animal model studies necessary for approvability of the product based on the submitted draft labeling?	None needed	

FILEABILITY (cont):

On initial overview of the NDA application:	YES	NO
MICROBIOLOGY:		
(6) Has the applicant submitted draft breakpoint and interpretive criteria in a manner consistent with contemporary standards, in a manner which attempts to correlate criteria with clinical results of NDA studies, and in a manner to allow substantive review to begin?	Breakpoints previously set	
(7) Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	Not needed	
(8) Has the applicant submitted draft labeling consistent with §201.56 and §201.57, current divisional policy, and the design of the development package?	X	
(9) If necessary for this product, has the applicant submitted the sterilization procedures and documentation required for the approval of the manufacturing and controls elements for this NDA?	(Not Needed) Submitted in Original NDA	
(10) From a microbiology perspective, is this NDA If "no", please state on reverse why it is not.	X--fileable	

Comment:

All of the pre-clinical microbiology information submitted in this supplement was previously submitted in supplement 006 dated December 17, 1998. The sponsor has performed one new study LOFBIV-PCAP-001 and looks at other Phase 3 Community-acquired Pneumonia (CAP) studies in which levofloxacin was dosed at 500 mg qd for 7 to 14 days. The sponsor is trying to find enough

[redacted]

APPEARS THIS WAY
ON ORIGINAL

/S/ 5-5-99
Peter A. Dionne
Reviewing Microbiologist

/S/ 5/12/99
Sheryl Lard Whiteford
Group Leader Microbiology

HFD-590 Anderson

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-635/S-008

The R. W. Johnson Pharmaceutical Reseacrh Institute
920 Route 202 South
P.O. Box 300
Raritan, NJ 08869-0602

APR 12 1999

Attention: William R. Sisco
Associate Director, Regulatory Affairs

Dear Mr. Sisco:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Levaquin® Injection

NDA Number: 20-635

Supplement Number: S-008

Date of Supplement: April 1, 1999

Date of Receipt: April 2, 1999

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on June 1, 1999 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Food and Drug Administration
Division of Special Pathogen and
Immunologic Drug Products, HFD-590
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

/S/

Ellen C. Frank, R.Ph.
Chief, Project Management Staff
Division of Special Pathogen and
Immunologic Drug Products, HFD-590
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

cc:
Original NDA 20-635/S-008
HFD-590/Div. Files
HFD-590/CSO/Anderson, R.

SUPPLEMENT ACKNOWLEDGEMENT

APPEARS THIS WAY
ON ORIGINAL

HFD-590 Anderson

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-635/S-007

R.W. Johnson Pharmaceutical Institute
920 Route 202 South
P.O. Box 300
Raritan, New Jersey 08869-0602

APR 12 1999

Attention: Mary Ellen Zamstein
Principal Regulatory Scientist

Dear Ms. Zamstein:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Levaquin (levofloxacin) Injection

NDA Number: 20-635

Supplement Number: S-007

Date of Supplement: March 31, 1999

Date of Receipt: April 01, 1999

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on May 31, 1999 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Food and Drug Administration
Division of Special Pathogen and
Immunologic Drug Products, HFD-590
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

/S/

Ellen C. Frank, R.Ph.
Chief, Project Management Staff
Division of Special Pathogen and
Immunologic Drug Products, HFD-590
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

cc:
Original NDA 20-635/S-007
HFD-590/Div. Files
HFD-590/CSO/Anderson, R.

SUPPLEMENT ACKNOWLEDGEMENT

HFD-590 Anderson

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-634/S-009

The R.W. Johnson Pharmaceutical Research Institute
920 Route 202 South
P. O. Box 300
Raritan, NJ 08869-0602

APR 12 1999

Attention: William R. Sisco
Associate Director, Regulatory Affairs

Dear Mr. Sisco:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Levaquin® (levofloxacin tablets) Tablets

NDA Number: 20-634

Supplement Number: S-009

Date of Supplement: April 1, 1999

Date of Receipt: April 2, 1999

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on June 1, 1999 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Food and Drug Administration
Division of Special Pathogen and
Immunologic Drug Products, HFD-590
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

/S/

Ellen C. Frank, R.Ph.
Chief, Project Management Staff
Division of Special Pathogen and
Immunologic Drug Products, HFD-590
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

cc:
Original NDA 20-634/S-009
HFD-590/Div. Files
HFD-590/CSO/Anderson, R.

SUPPLEMENT ACKNOWLEDGEMENT

APPEARS THIS WAY
ON ORIGINAL

HFD-590 Rotter 2

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-634/S-008

APR 12 1999

The R.W. Johnson Pharmaceutical Research Institute
920 Route 202 South
P.O. Box 300
Raritan, NJ 08869-0602

Attention: Mary Ellen Zamstein
Principal Regulatory Scientist

Dear Ms. Zamstein:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Levaquin® (levofloxacin tablets) Tablets

NDA Number: 20-634

Supplement Number: S-008

Date of Supplement: March 31, 1999

Date of Receipt: April 1, 1999

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on May 31, 1999 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Food and Drug Administration
Division of Special Pathogen and
Immunologic Drug Products, HFD-590
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

/S/

Ellen C. Frank, R.Ph.
Chief, Project Management Staff
Division of Special Pathogen and
Immunologic Drug Products, HFD-590
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

cc:
Original NDA 20-634/S-008
HFD-590/Div. Files
HFD-590/CSO/Anderson, R.

SUPPLEMENT ACKNOWLEDGEMENT

APPEARS THIS WAY
ON ORIGINAL