

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**020634Orig1s061, 020635Orig1s067,  
021721Orig1s028**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 020634	NDA Supplement # 061	If NDA, Efficacy Supplement Type: SE-1
Proprietary Name: Levaquin Tablets Established/Proper Name: levofloxacin Dosage Form: tablets, 250 mg, 500 mg, 750 mg		Applicant: Janssen Pharmaceuticals, Inc Agent for Applicant (if applicable):
RPM: Dean		Division: Division of Anti-Infective Products
<p><b><u>NDA and NDA Efficacy Supplements:</u></b></p> <p>NDA Application Type:   <input type="checkbox"/> 505(b)(1)   <input type="checkbox"/> 505(b)(2)            Efficacy Supplement:   <input checked="" type="checkbox"/> 505(b)(1)   <input type="checkbox"/> 505(b)(2)</p> <p>(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). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p><b><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></b></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug.  <input type="checkbox"/> This application relies on literature.  <input type="checkbox"/> This application relies on a final OTC monograph.  <input type="checkbox"/> This application relies on (explain)</p> <p><b><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></b></p> <p><b><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></b></p> <p><input type="checkbox"/> No changes   <input type="checkbox"/> Updated   Date of check:</p> <p><b>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</b></p>
<b>❖ Actions</b>		
<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is April 28, 2012</li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>• Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		<input checked="" type="checkbox"/> None

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a>). If not submitted, explain</p>	<p>No, because sponsor does not plan promotion of the product for this use in the next 120 days.</p>
<p>❖ Application Characteristics <sup>3</sup></p>	
<p>Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch  <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch  <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDA: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510)  <input type="checkbox"/> Restricted distribution (21 CFR 314.520)  Subpart I <input checked="" type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR  <input type="checkbox"/> Submitted in response to a PMC  <input type="checkbox"/> Submitted in response to a Pediatric Written Request</p> <p>BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41)  <input type="checkbox"/> Restricted distribution (21 CFR 601.42)  Subpart H <input type="checkbox"/> Approval based on animal studies</p> <p>REMS: <input type="checkbox"/> MedGuide  <input type="checkbox"/> Communication Plan  <input type="checkbox"/> ETASU  <input type="checkbox"/> MedGuide w/o REMS  <input type="checkbox"/> REMS not required</p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<p><input type="checkbox"/> Yes, dates</p>
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> <li>Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<ul style="list-style-type: none"> <li>Press Office notified of action (by OEP)</li> </ul>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<ul style="list-style-type: none"> <li>Indicate what types (if any) of information dissemination are anticipated</li> </ul>	<p><input type="checkbox"/> None  <input type="checkbox"/> HHS Press Release  <input type="checkbox"/> FDA Talk Paper  <input type="checkbox"/> CDER Q&amp;As  <input checked="" type="checkbox"/> Other - FDA Press Release</p>

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA #                      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #                      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #                      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #                      and date exclusivity expires:
<ul style="list-style-type: none"> <li>NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #                      and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> <li>Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>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.</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i></li> </ul>	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes     No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

*If "Yes," skip to question (4) below. If "No," continue with question (2).*

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes     No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

*If "No," continue with question (3).*

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes     No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

*If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes     No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).*

*If "No," continue with question (5).*

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
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**CONTENTS OF ACTION PACKAGE**

❖ Copy of this Action Package Checklist <sup>4</sup>	April 27, 2012
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
<b>Action Letters</b>	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Approval, April 27, 2012
<b>Labeling</b>	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	April 25, 2012
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	October 28, 2011
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	

<sup>4</sup> Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> <li>❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)</li> </ul>	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	April 25, 2012
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	See Original Sponsor Package Insert dated October 28, 2011
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	
<ul style="list-style-type: none"> <li>❖ Labels (<b>full color</b> carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	N/A
<ul style="list-style-type: none"> <li>❖ Proprietary Name             <ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>• Review(s) (<i>indicate date(s)</i>)</li> <li>• Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.</li> </ul> </li> </ul>	N/A
<ul style="list-style-type: none"> <li>❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)</li> </ul>	<input checked="" type="checkbox"/> RPM - April 24, 2012 <input type="checkbox"/> DMEPA <input checked="" type="checkbox"/> DMPP/PLT (DRISK) – April 16, 2012 <input checked="" type="checkbox"/> ODPD (DDMAC) - April 23, 2012 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
<b>Administrative / Regulatory Documents</b>	
<ul style="list-style-type: none"> <li>❖ Administrative Reviews (<i>e.g., RPM Filing Review<sup>5</sup>/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)</li> </ul>	RPM Filing Review: April 26, 2012
<ul style="list-style-type: none"> <li>❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte</li> <li>❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)</li> </ul>	RPM PLR Label Review: April 24, 2012 <input checked="" type="checkbox"/> Not a (b)(2) <input type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> <li>❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)</li> </ul>	<input type="checkbox"/> Included
<ul style="list-style-type: none"> <li>❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></li> </ul>	
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• This application is on the AIP             <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input type="checkbox"/> No  <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> <li>❖ Pediatrics (<i>approvals only</i>)             <ul style="list-style-type: none"> <li>• Date reviewed by PeRC: <u>March 14, 2012</u> If PeRC review not necessary, explain: _____</li> <li>• Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul> </li> </ul>	<input checked="" type="checkbox"/> Included

<sup>5</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent <i>(include certification)</i>	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications <i>(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)</i>	X
❖ Internal memoranda, telecons, etc.	X
❖ Minutes of Meetings	
• Regulatory Briefing <i>(indicate date of mtg)</i>	<input type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting <i>(indicate date of mtg)</i>	<input type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting <i>(indicate date of mtg)</i>	<input type="checkbox"/> No mtg
• EOP2 meeting <i>(indicate date of mtg)</i>	<input type="checkbox"/> No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) <i>(indicate dates of mtgs)</i>	Pre-supplement Submission Guidance Telecon – July 21, 2011
❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	April 4, 2012
• 48-hour alert or minutes, if available <i>(do not include transcript)</i>	N/A
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Division Director Summary Review <i>(indicate date for each review)</i>	April 27, 2012
Cross-Discipline Team Leader Review <i>(indicate date for each review)</i>	April 25, 2012
PMR/PMC Development Templates <i>(indicate total number)</i>	1
<b>Clinical Information<sup>6</sup></b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) <i>(indicate date for each review)</i>	See Cross-Discipline Team Leader Review, April 25, 2012
• Clinical review(s) <i>(indicate date for each review)</i>	April 10, 2012 (Clinical) April 20, 2012 (Animal Model Review)
• Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input checked="" type="checkbox"/> and include a review/memo explaining why not <i>(indicate date of review/memo)</i>	Clinical Review – April 10, 2012, page 14
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not applicable

<sup>6</sup> Filing reviews should be filed with the discipline reviews.

❖ Risk Management <ul style="list-style-type: none"> <li>REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>)</li> <li>REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul>	N/A <input type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )	<input checked="" type="checkbox"/> None requested
<b>Clinical Microbiology</b> <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	April 5, 2012
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	April 5, 2012
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	April 6, 2012
Statistical Review(s) ( <i>indicate date for each review</i> )	April 6, 2012
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )	April 13, 2012
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	April 13, 2012
❖ DSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of DSI letters</i> )	<input checked="" type="checkbox"/> None
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
• Supervisory Review(s) ( <i>indicate date for each review</i> )	April 13, 2012
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	April 13, 2012 Reference to IND 64429
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	January 25, 2012 March 27, 2012 March 29, 2012 April 3, 2012 April 5, 2012
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary ( <i>include copies of DSI letters</i> )	X

<b>Product Quality</b>		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> None
❖ Microbiology Reviews		
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>		<input checked="" type="checkbox"/> Not needed
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>		
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>		
		<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)		
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>		March 8, 2012
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>		N/A
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>		N/A
❖ Facilities Review/Inspection		
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>7</sup>)</i>		Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input checked="" type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>		Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>		
		<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

<sup>7</sup> I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

## Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy 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).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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/s/  
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JANE A DEAN  
04/27/2012

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**From:** Dean, Jane  
**Sent:** Wednesday, April 25, 2012 5:05 PM  
**To:** 'Gannon, Melissa [JRDUS]'  
**Subject:** NDA 20634, 20635, 21721 - division proposed label  
**Importance:** High

Hi Melissa, below are comments from the review team that explains the rationale behind the changes made to the label. Also, attached is another version of the label that incorporates updated changes made to the label since your email of 4/23/12. Please let me know via email if these changes are acceptable to you and if so, submit a letter stating such to the NDAs asap. Thanks. Jane

The following provides our rationale for the removal of references to MDRSP from the levofloxacin label:



We concur that leaving the methicillin susceptible isolates only in is appropriate because MSSA and MRSA have, among other things, different clinical courses, and there seems to be a relationship between decreased susceptibility of *Staphylococcus aureus* to methicillin and decreased susceptibility to fluoroquinolones.



NDA 20634  
5 and 21721 (

Jane

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Jane A. Dean, RN, MSN  
Regulatory Health Project Manager  
Division of Anti-Infective Products  
Office of Antimicrobial Products  
FDA/CDER

Office: 301-796-1202  
Fax: 301-796-9881  
Rm. 6397, Bdg. 22

Email address: [jane.dean@fda.hhs.gov](mailto:jane.dean@fda.hhs.gov)

69 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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JANE A DEAN  
04/25/2012

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**From:** Dean, Jane  
**Sent:** Tuesday, April 24, 2012 4:24 PM  
**To:** 'Gannon, Melissa [JRDUS]'  
**Subject:** Wording for PMR

Melissa, here is the Agency's request for the Post Marketing Requirement (PMR). We are asking for a letter of commitment to the PMR by COB tomorrow (April 25, 2012). You can email the letter to me and send it through the Gateway as a formal submission at the same time. Please confirm that your team can turn this around by tomorrow afternoon. Thanks.

Also, I will not be able to send you our suggested revisions to the USPI or Med Guide today. Most likely it will come to you tomorrow.

1. *Postmarketing Studies.* This subsection requires you to conduct postmarketing studies, such as field studies, to verify and describe the drug's clinical benefit and to assess its safety when used as indicated when such studies are feasible and ethical. Please submit a letter prior to April 25, 2012, stating that you agree to conduct a field study to evaluate the efficacy and safety of LEVAQUIN in the event of an attack with intentional release of *Yersinia pestis* in the United States and to submit a protocol for the field study on or before April 30, 2013.
2. *Approval with restrictions to ensure safe use.* This subsection permits the Agency to require postmarketing restrictions as are needed to ensure safe use of the drug product, commensurate with the specific safety concerns presented by the drug product. We conclude that levofloxacin can be safely used without restrictions on distribution or use.
3. *Information to be provided to patient recipients.* This subsection requires applicants to prepare labeling to be provided to patient recipients for drug products approved under this subpart. We conclude that the FDA-approved Medication Guide for LEVAQUIN meets the requirements of this subsection.

*Information to be provided to patient recipients.* This subsection requires applicants to prepare labeling to be provided to patient recipients for drug products approved under this subpart. We conclude that the FDA-approved Medication Guide for LEVAQUIN meets the requirements of this subsection.

Jane

-----  
Jane A. Dean, RN, MSN  
Regulatory Health Project Manager  
Division of Anti-Infective Products  
Office of Antimicrobial Products

FDA/CDER

Office: 301-796-1202

Fax: 301-796-9881

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Email address: [jane.dean@fda.hhs.gov](mailto:jane.dean@fda.hhs.gov)



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/s/  
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JANE A DEAN  
04/24/2012

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**From:** Dean, Jane  
**Sent:** Monday, March 05, 2012 12:23 PM  
**To:** 'Gannon, Melissa [JRDUS]'  
**Subject:** RE: Levaquin sNDAs for Plague - Ad Com Rehearsal Feedback  
**Importance:** High

Hi, Melissa, here is the response to your question.

The animal model is designed to evaluate antibacterial treatment of symptomatic disease, so we would want the committee to focus on whether the animal model provides adequate evidence of efficacy for treatment of human patients with pneumonic plague. At the same time, we understand the issues raised at your mock rehearsal, and suggest you be prepared to address whether you think the risk/benefit profile for Levaquin would also be favorable for "prophylactic use". We are having internal discussions about this issue and expect we would address the specific claim with you at the time of labeling discussions. We expect that the advisory committee will have considered this treatment use vs post-exposure prophylaxis prior to discussion of your product, but if questions about the scope of the intended claims arise, you can direct them to the Division representatives for a response.

Jane

-----  
Jane A. Dean, RN, MSN  
Regulatory Health Project Manager  
Division of Anti-Infective Products  
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**From:** Gannon, Melissa [JRDUS] [<mailto:MGannon2@its.jnj.com>]  
**Sent:** Tuesday, February 28, 2012 3:47 PM  
**To:** Dean, Jane  
**Subject:** Levaquin sNDAs for Plague - Ad Com Rehearsal Feedback

Dear Jane,

As a follow-up to our discussion on Friday, I was hoping to share and get some feedback from the Division on an issue that was raised in a mock rehearsal we had in preparation for the Ad Com. In our submission, we proposed the following indication: LEVAQUIN® is

indicated for pneumonic plague following exposure to *Yersinia pestis* (*Y. pestis*) in adults and pediatric patients  $\geq 6$  months of age.

The intention is that Levaquin will be used in a mass casualty setting as post-exposure prophylaxis (i.e., administered to patients with known or suspected exposure). We do not expect that physicians will confirm patient exposure to *Y. pestis* or wait for them to exhibit initial signs (e.g., fever).

The efficacy study in AGMs was a treatment model (animals were exposed, exhibited signs of disease and were then treated).

The discussion at our mock rehearsal focused on these differences in prophylactic use vs. treatment and we anticipate this may come up in the actual Ad Com. We would like to get alignment with FDA on this topic. Do you agree that the intention would be to use Levaquin in a prophylactic post-exposure setting? The only model that could be tested is a treatment model, but in real world use, we do not expect that one would wait for "treatment".

Kind regards,

*Melissa*

**Melissa L. Gannon**  
**Director, Global Regulatory Leader for**  
**Women's Health/Urology/Anti-Infectives/Anti-Fungals**  
**Established Products**  
**Janssen R&D**  
**920 Route 202 South**  
**Raritan, NJ 08869**  
**Phone: (908) 927-2382**  
**(b) (6)**  
**Fax: (908) 722-5113**  
**e-mail: [mgannon2@its.jnj.com](mailto:mgannon2@its.jnj.com)**



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/s/  
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JANE A DEAN  
03/05/2012

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**From:** Dean, Jane  
**Sent:** Thursday, February 23, 2012 2:24 PM  
**To:** 'Gannon, Melissa [JRDUS]'  
**Subject:** NDA 20634/S-061, 20635/S-067 and 21721/S-028 (levofloxacin) - IR  
**Importance:** High

Hi, Melissa, I have an information request from the clinical micro reviewer. Can you please let me know when you can either respond to it or send the information requested? Thanks!

In the levofloxacin efficacy study FY06-126, you reported that 3 animals (X523, X663, X648) were positive for *Y. pestis* in terminal blood and tissue cultures on day 28. Was levofloxacin minimum inhibitory concentration (MIC) determined for these *Y. pestis* isolates? Kindly provide this information to the NDA submission. If MICs were not determined, please determine the levofloxacin MICs for these isolates. If possible, it would also be informative if the susceptibility of these isolates to other fluoroquinolones (e.g. ciprofloxacin) were determined. We suggest that the *Y. pestis* used for the initial aerosol challenge be tested at the same time as the isolates obtained from these animals to reduce the variability in test results when MICs are determined at different times.

Jane

-----  
Jane A. Dean, RN, MSN  
Regulatory Health Project Manager  
Division of Anti-Infective Products  
Office of Antimicrobial Products  
FDA/CDER

Office: 301-796-1202  
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/s/  
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JANE A DEAN  
02/23/2012

**From:** Dean, Jane  
**Sent:** Wednesday, February 08, 2012 11:11 AM  
**To:** 'Gannon, Melissa [JRDUS]'  
**Subject:** NDA 20634/S-061, 20635/S-067 and 21721/S-028 (levofloxacin - information request)

Melissa, our stats reviewer has the following information request. Please let me know what the turn around time could be – thanks!

1. Provide any available data, such as baseline data, randomization information, for the animal that died prior to being challenged.
2. Provide any available data, such as, baseline, treatment, follow-up, and outcome data for animal X779 who was infused with test article prior to the onset of fever.
3. Provide more detail on how animals were randomized to treatment groups.
4. Provide the rationale for adding Cohort 3 and for the choice of a 4:1 ratio for randomization.

Jane

-----  
Jane A. Dean, RN, MSN  
Regulatory Health Project Manager  
Division of Anti-Infective Products  
Office of Antimicrobial Products  
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/s/  
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JANE A DEAN  
02/08/2012



NDA 020635/S-067  
NDA 021721/S-028

## FILING COMMUNICATION

Janssen Pharmaceuticals, Inc.  
c/o Johnson & Johnson Pharmaceutical Research and Development, LLC  
Attention: Melissa L. Gannon  
Director, Regulatory Affairs  
920 Route 202 South, PO Box 300  
Raritan, NJ 08869-0602

Dear Ms. Gannon:

Please refer to your Supplemental New Drug Applications (sNDA) dated November 4, 2011, received November 7, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Levaquin (levofloxacin) Injection (NDA 020635) and Levaquin (levofloxacin) Oral Solution (NDA 021721).

We also refer to your submissions dated November 23, and December 21, 22 and 23, 2011.

These supplemental applications propose the following change: to add the indication for use of Levaquin in the treatment of pneumonic plague following exposure to *Yersinia pestis* in adults and pediatric patients  $\geq 6$  months of age.

We have completed our filing review and have determined that your applications are sufficiently complete to permit a substantive review. Therefore, these applications are considered filed 60 days after the date we received your applications in accordance with 21 CFR 314.101(a). The review classification for these applications is **Priority**. Therefore, the user fee goal date is May 7, 2012.

We are reviewing your applications according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed

labeling and, if necessary, any postmarketing requirement/commitment requests by April 7, 2012.

During our filing review of your supplemental applications, we identified the following potential review issues with the datasets for Study FY07-070:

1. Infusion dataset: The parameter "Study Day" was provided in the other study datasets. Provide the "Study Day" in the infusion dataset. Provide the "Date and Time" as separate variables.
2. Animal ID dataset: Verify if the study start date is the "end of nebulization date." Provide the "Date and Time" as separate variables and the "Study Day" for death and fever onset.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the supplemental applications and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the supplemental applications. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your applications.

We will review these applications under the provisions of 21 CFR 314 Subpart I – *Approval of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible*. Unless we otherwise inform you, as required by 21 CFR 314.640, you must submit during the preapproval review period copies of all promotional materials, including promotional labeling and advertisements, intended for dissemination or publication within 120 days following marketing approval (i.e., your launch campaign). We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and proposed package insert (PI)/Medication Guide/patient PI (as applicable). Send each submission directly to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

If you have any questions, call OPDP at 301-796-1200.

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We note that you have not addressed how you plan to fulfill this requirement. Within 30 days of the date of this letter, please submit (1) a full waiver request, (2) a partial waiver request and a pediatric development plan for the pediatric age groups not covered by the partial waiver request, or (3) a pediatric drug development plan covering the full pediatric age range. All waiver requests must include supporting information and documentation. A pediatric drug development plan must address the indication(s) proposed in this supplemental application.

If you have any questions, call Jane A. Dean, RN, MSN, Regulatory Health Project Manager, at (301) 796-1202.

Sincerely,

*{See appended electronic signature page}*

John Farley, MD, MPH  
Acting Director  
Division of Anti-Infective Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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/s/  
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JANE A DEAN  
12/29/2011

JOHN J FARLEY  
12/29/2011



NDA 020634/S-061

**FILING COMMUNICATION**

Janssen Pharmaceuticals, Inc.  
c/o Johnson & Johnson Pharmaceutical Research and Development, LLC  
Attention: Melissa L. Gannon  
Director, Regulatory Affairs  
920 Route 202 South, PO Box 300  
Raritan, NJ 08869-0602

Dear Ms. Gannon:

Please refer to your Supplemental New Drug Application (sNDA) dated October 27, 2011, received October 28, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Levaquin (levofloxacin) Tablets, 250 mg, 500 mg and 750 mg.

We also refer to your submissions dated November 23, and December 21, 22 and 23, 2011.

This supplemental application proposes the following change: to add the indication for use of Levaquin in the treatment of pneumonic plague following exposure to *Yersinia pestis* in adults and pediatric patients  $\geq$  6 months of age.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is April 28, 2012.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by April 7, 2012.

During our filing review of your supplemental application, we identified the following potential review issues with the datasets for Study FY07-070:

1. Infusion dataset: The parameter "Study Day" was provided in the other study datasets. Provide the "Study Day" in the infusion dataset. Provide the "Date and Time" as separate variables.
2. Animal ID dataset: Verify if the study start date is the "end of nebulization date." Provide the "Date and Time" as separate variables and the "Study Day" for death and fever onset.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the supplemental application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the supplemental application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We will review this application under the provisions of 21 CFR 314 Subpart I – *Approval of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible*. Unless we otherwise inform you, as required by 21 CFR 314.640, you must submit during the preapproval review period copies of all promotional materials, including promotional labeling and advertisements, intended for dissemination or publication within 120 days following marketing approval (i.e., your launch campaign). We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and proposed package insert (PI)/Medication Guide/patient PI (as applicable). Send each submission directly to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

If you have any questions, call OPDP at 301-796-1200.

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We note that you have not addressed how you plan to fulfill this requirement. Within 30 days of the date of this letter, please submit (1) a full waiver request, (2) a partial waiver request and a pediatric development plan for the pediatric age groups not covered by the partial waiver request,

or (3) a pediatric drug development plan covering the full pediatric age range. All waiver requests must include supporting information and documentation. A pediatric drug development plan must address the indication(s) proposed in this supplemental application.

If you have any questions, call Jane A. Dean, RN, MSN, Regulatory Health Project Manager, at (301) 796-1202.

Sincerely,

*{See appended electronic signature page}*

John Farley, MD, MPH  
Acting Director  
Division of Anti-Infective Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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JOHN J FARLEY  
12/27/2011

**From:** [Dean, Jane](#)  
**To:** "[Gannon, Melissa \[JRDUS\]](#)"  
**Subject:** NDA 20634/S-061, NDA 020635/S-067 and NDA 021721/S-028 (levofloxacin) - information request re datasets  
**Date:** Tuesday, December 27, 2011 3:43:39 PM

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Hi Melissa, we have the following information request.

The following is missing from the submissions NDA 20634/S-061, NDA 020635/S-067 and NDA 021721/S-028 (levofloxacin) and needs to be resolved:

1. Microbiology dataset:

a) missing for study 617 (Battelle)

b) timing of blood collection for culture is not specified (no variable) for studies 875 (Battelle), F03-09G (USAMRIID)

2. Telemetry dataset for study FY06-126 (LRRI) contains possibly erroneous temperature data, as animals 532, 538, 666, 705 and 756 appear to have been afebrile for the duration of the study. Animal 705 telemetry data do not support the conclusions presented in the study report on the onset of fever, tachypnea or tachycardia.

3. CRF post challenge are not available for studies: 617, 875, and FY06-126 (LRRI)

4. Individual animal pathology data (datasets and study report) are not available for study F03-09G

5. All natural history studies datasets are data listings. No analysis datasets were provided. Some analysis data were found in study reports, some were derived from listings datasets. In order to expedite review of the submitted application, for the (b) (4) efficacy study please provide an analysis dataset that will have data for each animal (Animal ID) that include baseline average temperature by the hour, target temperature value for the fever onset by the hour, date and time of challenge, date and time of fever onset, time in hours post challenge, date and time of first positive blood culture, date and time of animal death.

Also, please, could you give me an idea of your turn around time on this?

Thanks!

Jane

-----  
Jane A. Dean, RN, MSN  
Regulatory Health Project Manager  
Division of Anti-Infective Products

Office of Antimicrobial Products

FDA/CDER

Office: 301-796-1202

Fax: 301-796-9881

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Email address: [jane.dean@fda.hhs.gov](mailto:jane.dean@fda.hhs.gov)



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JANE A DEAN  
12/27/2011

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**From:** Dean, Jane  
**Sent:** Monday, December 05, 2011 4:08 PM  
**To:** 'Gannon, Melissa [JRDUS]'  
**Subject:** RE: sNDA020634/S-061 (Levaquin) - information request  
**Importance:** High

Hi, Melissa – see responses embedded in your email below in black . . .

Jane

-----  
Jane A. Dean, RN, MSN  
Regulatory Health Project Manager  
Division of Anti-Infective Products  
Office of Antimicrobial Products  
FDA/CDER

Office: 301-796-1202  
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Email address: [jane.dean@fda.hhs.gov](mailto:jane.dean@fda.hhs.gov)



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**From:** Gannon, Melissa [JRDUS] [<mailto:MGannon2@its.jnj.com>]  
**Sent:** Friday, December 02, 2011 6:01 PM  
**To:** Dean, Jane  
**Subject:** RE: sNDA020634/S-061 (Levaquin) - information request

Hello Jane,

It was nice talking with you. As indicated, I just finished a call with the team to discuss the request. We have some additional questions.

We have all the data requested. The team indicated they would be able to add the information identified in Item #2 to the Animal ID file we submitted on 23<sup>rd</sup> November with the exception of the infusion data and blood culture data. For these two parameters, the team would like to know if they are supposed to merge these data into the original file for each relevant data type or if it would be acceptable for these data to be provided as separate data files? We do think we could provide this information more easily as separate data files.

**It is acceptable for some of the information identified in Item #2 to be added to the Animal ID file submitted on 23rd November and for infusion data and blood culture data to be provided as separate data files. We also suggest that you put the telemetry data into a separate data file.**

For Item #5, is the reviewer referring to the discrepancy for one animal in the SAS analysis data set (calculated as day the decision was made to euthanize) versus how its data is presented in the survival graph (day the euthanasia was carried out)? If so, there was an explanation of the discrepancy on the animal provided in the body of the report on page 26. Did the reviewer see this explanation and is this acceptable? Or are there other discrepancies you noted? If it's the latter, is there additional information you could provide to help us to understand what the issue is?

**We noticed a discrepancy for animal X888 (a cohort 3 control). In the data set, time=4; while in Table 7 and Figure 2 in the study report, the day of death was 5. We also noted a discrepancy in the sex for animal U193 - please clarify if the animal is a male or female. In view of the above discrepancies, please double check and validate the dataset for consistency.**

Our team is working to turn this around as quickly as possible, but I also recognize the review team will be meeting around Day 45 (December 12<sup>th</sup>) to make an assessment on the filing. Is it necessary for these additional data to be in your hands before that time so you can make the determination? If so, what is the drop-dead date for delivery of this information?

**We would like to have the information by December 21st, 2011.**

I have a follow-up meeting scheduled with the team for Monday afternoon so any information we can have before then would be very much appreciated.

Kind regards,  
Melissa

**Melissa L. Gannon**  
**Director, Global Regulatory Leader for**  
**Women's Health/Urology/Anti-Infectives/Anti-Fungals**  
**Established Products**  
**Johnson & Johnson Pharmaceutical R&D**  
**920 Route 202 South**  
**Raritan, NJ 08869**  
**Phone: (908) 927-2382**

(b) (6)

**Fax: (908) 722-5113**

**e-mail: [mgannon2@its.jnj.com](mailto:mgannon2@its.jnj.com)**

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**From:** Dean, Jane [mailto:Jane.Dean@fda.hhs.gov]

**Sent:** Friday, December 02, 2011 11:50 AM

**To:** Gannon, Melissa [JRDUS]  
**Subject:** RE: sNDA020634/S-061 (Levaquin) - information request

Perfect – thanks!! Did you get the letters okay?

Jane

-----  
Jane A. Dean, RN, MSN  
Regulatory Health Project Manager  
Division of Anti-Infective Products  
Office of Antimicrobial Products  
FDA/CDER

Office: 301-796-1202  
Fax: 301-796-9881  
Rm. 6397, Bdg. 22

Email address: [jane.dean@fda.hhs.gov](mailto:jane.dean@fda.hhs.gov)



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**From:** Gannon, Melissa [JRDUS] [<mailto:MGannon2@its.jnj.com>]  
**Sent:** Friday, December 02, 2011 11:33 AM  
**To:** Dean, Jane  
**Subject:** RE: sNDA020634/S-061 (Levaquin) - information request

Hello Jane.

I will forward this to the team and request the time for delivery of these data.

Kind regards,  
Melissa

**Melissa L. Gannon**  
Director, Global Regulatory Leader for  
Women's Health/Urology/Anti-Infectives/Anti-Fungals  
Established Products

Johnson & Johnson Pharmaceutical R&D  
920 Route 202 South  
Raritan, NJ 08869

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✉e-mail: [mgannon2@its.jnj.com](mailto:mgannon2@its.jnj.com)

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**From:** Dean, Jane [mailto:Jane.Dean@fda.hhs.gov]  
**Sent:** Friday, December 02, 2011 10:50 AM  
**To:** Gannon, Melissa [JRDUS]  
**Subject:** sNDA020634/S-061 (Levaquin) - information request  
**Importance:** High

Hi, Melissa – the reviewers have the following information request:

In the dataset for the efficacy study FY07-70, fy07070.xpt, submitted on 11/27/2012, there is no information such as onset of fever, challenge (exposure) time, infusion time as shown in Appendix C - Individual Animal Data [in the study report](#). To facilitate the review of this sNDA, we have the following data requests:

1. Please add a column named datetime to include calendar date and time in hours (and minutes, if available) in the data set for each row.
2. Please add rows for each animal to include the following information, if available:
  - challenging dose in CFU/ml
  - onset of fever date and time, fever resolution date and time
  - dates and beginning and ending times for infusions
  - date and time for blood culture
  - date and time of death or euthanasia

All day and time values should be included in the datetime variable.

3. Currently variable Time includes days or hours, depending on the values of other variables. Please redefine variables Phase and Time, so that they include days and hours, respectively.
4. Please update define.pdf accordingly.
5. It appears that there is some inconsistency between your data and the survival graph in the study report. Please double check and validate your data for consistency.

Please let me know what your anticipated TAT is – thanks!

Jane

-----  
Jane A. Dean, RN, MSN  
Regulatory Health Project Manager  
Division of Anti-Infective Products  
Office of Antimicrobial Products  
FDA/CDER

Office: 301-796-1202  
Fax: 301-796-9881  
Rm. 6397, Bdg. 22

Email address: [jane.dean@fda.hhs.gov](mailto:jane.dean@fda.hhs.gov)



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/s/

-----  
JANE A DEAN  
12/05/2011

**From:** Dean, Jane  
**Sent:** Friday, December 02, 2011 10:50 AM  
**To:** 'Gannon, Melissa [JRDUS]'  
**Subject:** sNDA020634/S-061 (Levaquin) - information request

**Importance:** High

Hi, Melissa – the reviewers have the following information request:

In the dataset for the efficacy study FY07-70, fy07070.xpt, submitted on 11/27/2012, there is no information such as onset of fever, challenge (exposure) time, infusion time as shown in Appendix C - Individual Animal Data [in the study report](#). To facilitate the review of this sNDA, we have the following data requests:

1. Please add a column named datetime to include calendar date and time in hours (and minutes, if available) in the data set for each row.
2. Please add rows for each animal to include the following information, if available:
  - challenging dose in CFU/ml
  - onset of fever date and time, fever resolution date and time
  - dates and beginning and ending times for infusions
  - date and time for blood culture
  - date and time of death or euthanasiaAll day and time values should be included in the datetime variable.
3. Currently variable Time includes days or hours, depending on the values of other variables. Please redefine variables Phase and Time, so that they include days and hours, respectively.
4. Please update define.pdf accordingly.
5. It appears that there is some inconsistency between your data and the survival graph in the study report. Please double check and validate your data for consistency.

Please let me know what your anticipated TAT is – thanks!

Jane

-----  
Jane A. Dean, RN, MSN  
Regulatory Health Project Manager  
Division of Anti-Infective Products  
Office of Antimicrobial Products  
FDA/CDER

Office: 301-796-1202  
Fax: 301-796-9881  
Rm. 6397, Bdg. 22

Email address: [jane.dean@fda.hhs.gov](mailto:jane.dean@fda.hhs.gov)



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/s/  
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JANE A DEAN  
12/02/2011



NDA 020634/S-061

**ACKNOWLEDGEMENT --  
PRIOR APPROVAL SUPPLEMENT**

Janssen Pharmaceuticals, Inc.  
c/o Johnson & Johnson Pharmaceutical Research and Development, LLC  
Attention: Melissa L. Gannon  
Director, Regulatory Affairs  
920 Route 202 South, PO Box 300  
Raritan, NJ 08869-0602

Dear Ms. Gannon:

We have received your October 27, 2011, Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

**NDA NUMBER:** 020634  
**SUPPLEMENT NUMBER:** S-061  
**PRODUCT NAME:** Levaquin (levofloxacin) Tablets  
**DATE OF SUBMISSION:** October 27, 2011  
**DATE OF RECEIPT:** October 28, 2011

This supplemental application provides for the use of Levaquin in the treatment of pneumonic plague following exposure to *Yersinia pestis* in adults and pediatric patients  $\geq$  6 months of age.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 27, 2011, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

## **FDAAA TITLE VIII RESPONSIBILITIES**

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

## **SUBMISSION REQUIREMENTS**

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Anti-Infective Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have questions, call Jane A. Dean, RN, MSN, Regulatory Health Project Manager, at (301) 796-1202.

Sincerely,

*{See appended electronic signature page}*

Frances V. LeSane  
Chief, Project Management Staff  
Division of Anti-Infective Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

NDA 020635/S-067  
NDA 021721/S-028**ACKNOWLEDGEMENT --  
PRIOR APPROVAL SUPPLEMENT**

Janssen Pharmaceutical, Inc.  
c/o Johnson & Johnson Pharmaceutical Research and Development, LLC  
Attention: Melissa L. Gannon  
Director, Regulatory Affairs  
920 Route 202 South, PO Box 300  
Raritan, NJ 08869-0602

Dear Ms. Gannon:

We have received your November 4, 2011, Supplemental New Drug Applications (sNDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

<b>NDA #</b>	<b>Supplement number</b>	<b>Drug Name &amp; Dosage Form</b>	<b>Letter Date</b>	<b>Receipt Date</b>
020635	S-067	Levaquin (levofloxacin) Injection	November 4, 2011	November 7, 2011
021721	S-028	Levaquin (levofloxacin) Oral Solution	November 4, 2011	November 7, 2011

These supplemental applications provide for the use of Levaquin in the treatment of pneumonic plague following exposure to *Yersinia pestis* in adults and pediatric patients  $\geq$  6 months of age.

Unless we notify you within 60 days of the receipt date that the applications are not sufficiently complete to permit a substantive review, we will file these applications on January 6, 2012, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

## **FDAAA TITLE VIII RESPONSIBILITIES**

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

## **SUBMISSION REQUIREMENTS**

Cite the application numbers listed above at the top of the first page of all submissions to these applications. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
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If you have questions, call Jane A. Dean, RN, MSN, Regulatory Health Project Manager, at (301) 796-1202.

Sincerely,

*{See appended electronic signature page}*

Frances V. LeSane  
Chief, Project Management Staff  
Division of Anti-Infective Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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FRANCES V LESANE  
12/01/2011

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FRANCES V LESANE  
12/01/2011

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**From:** Dean, Jane  
**Sent:** Monday, June 06, 2011 2:31 PM  
**To:** 'Gannon, Melissa [PRDUS]'  
**Subject:** RE: NDA 20634/NDA 20635/NDA 21721 for Levaquin (levofloxacin) - December 1, 2010 Meeting Minutes and response to questions regarding Animal Rule and User Fees regarding levofloxacin for plague

Hi, Melissa – here are the responses you have been waiting for. Please note that any further discussion on these issues should be formally submitted through the Gateway rather than through email. Thanks.

**NDA 20-634, NDA 20635, NDA 21721**

The mock data set and data definitions submitted on 29 April 2011 followed the CDISC format where each data point is represented by a row in the SAS data set. Although the alternative telemetry data format does not follow the CDISC format, it is acceptable. As discussed before, please submit all data in SAS transport data format.

**Questions for FDA based on May 10, 2011 response**

**FDA Recommendation:** If contaminants are identified then these should be provided as well in the dataset; such information should include the species identified, the site/source (e.g., catheter) and bacterial counts (if available).

**J&JRD Response:** *Please clarify if these are to be included in the study reports or the SAS dataset for statistical analysis. It may be difficult to retrospectively put the data into a uniform format for a SAS dataset; it should be very straightforward to include them in the report(s) if the data are available.*

**FDA response:**

It is acceptable to provide the information in the study reports.

**FDA Recommendation:** We would like the different parameters such as for the aerosol and microbiology information in the datasets to be presented as columns for each animal rather than as rows.

**J&JRD Response:** *Please clarify whether this is the direction of all reviewers and not just the Microbiology reviewers. The guidance regarding CDISC format was followed for the mock dataset. We will submit a single format for each dataset, though we are willing to tailor dataset to column or row format. The data is almost never collected in a column per animal so it will require transformation in every case.*

**FDA Response:**

The content of the datasets is acceptable. With regard to the format of the datasets, enclosed please find sample datasets for hematology, telemetry, and bacteremia results. We suggest that:

- Chemistry results should be presented in a similar format to the hematology dataset, i.e. parameters should be presented as columns for each animal.
- Laboratory test results (hematology, chemistry, coagulation, blood gases) should be presented with normal ranges (upper and lower limit of normal).
- For aerosol and microbiology information, the different parameters should be presented as columns for each animal rather than as rows.

## Additional Clinical Comments

For the Data Listings and Data Tabulations:

- a) There may be numerous data points for some measurements. For example, given that animals were monitored via telemetry, there may be thousands of data points for vital signs. We recommend submitting the following for each animal *in lieu* of the actual telemetry tracings:
- *Temperature* – from the time of the start of the study through the time of death of the animal, provide mean (standard deviation [SD] and range) hourly temperature per animal tabulated over time. This would therefore involve approximately 24 data points per day and 120 data points over 5 days. This will allow an assessment of trends and a clarification of the variation within the hourly temperature.
  - *Respiration* – provide mean (SD and range) hourly respiratory rates in a tabulated database, and clarify discrepancies between respiratory rates obtained by observation and by telemetry, if necessary.
  - *Heart Rate* – provide mean (SD and range) hourly heart rates in a tabulated database.
  - *Blood Pressure* – provide mean (SD and range) hourly systolic and diastolic blood pressure and pulse pressure.  
*Please clarify what the variable “pressure” refers to in the table entitled “Telemetry Data Definitions for Study 875” submitted on May 20, 2011*
- b) In addition, we request all data on the following measurements in summary tabulations at all the time points when the measurements were done.
- Body weight
  - Inoculum size delivered via aerosol
  - Clinical observations - signs and or symptoms of illness: Provide tabulation of animal activity over the study period, documenting behavior, and appetite, and response to stimuli at each time point when observations were collected from baseline to euthanasia or death.
  - Blood cultures: *Y. pestis* CFU/mL for each animal at baseline, during treatment and follow-up including date and time when the samples were collected.
  - X-rays: Please include the interpretive findings by radiologist
  - Gross pathology (including organ culture results)
  - Histopathology - For histopathology data, individual animal reports and a summary table describing the specific findings (e.g., severity, extent and nature of histologic changes, utilizing a standard scale) in each organ examined.
  - Complete medical record or document that was used to collect data for each animal used in the study. The complete medical record should provide the information on everything that occurred to the animal prior to entry into the study (e.g., when anesthetized, any medications administered, prior infections, vaccinations, screening for pathogens, etc.). Indicate in the dataset whether the animals that were used are “experimentally naïve” or if the animals were previously used in any other experimental study(ies).

Jane

-----  
Jane A. Dean, RN, MSN  
Regulatory Health Project Manager

Division of Anti-Infective Products  
Office of Antimicrobial Products  
FDA/CDER

Office: 301-796-1202  
Fax: 301-796-9881  
Rm. 6397, Bdg. 22

Email address: [jane.dean@fda.hhs.gov](mailto:jane.dean@fda.hhs.gov)

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**From:** Gannon, Melissa [PRDUS] [<mailto:MGannon2@its.jnj.com>]  
**Sent:** Wednesday, May 25, 2011 9:30 PM  
**To:** Dean, Jane  
**Cc:** McKinnon, Rebecca (Saville)  
**Subject:** RE: NDA 20634/NDA 20635/NDA 21721 for Levaquin (levofloxacin) - December 1, 2010 Meeting Minutes and response to questions regarding Animal Rule and User Fees regarding levofloxacin for plague

Hello Jane,

Yes, the submission pertaining to the questions below were submitted via the Gateway last week. I did fix up the presentation of the document where the J&J team was responding to FDA comments; I wanted to make it submission- and user-friendly. The content is still the same with regard to the responses. The other attachments pertaining to the mock data sets were the same as those included in the email.

Kind regards,  
Melissa

**Melissa L. Gannon**  
**Director, Global Regulatory Leader for**  
**Women's Health/Urology/Anti-Infectives/Anti-Fungals**  
**Established Products**  
**Johnson & Johnson Pharmaceutical R&D**  
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**e-mail: [mgannon2@its.jnj.com](mailto:mgannon2@its.jnj.com)**

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**From:** Dean, Jane [mailto:Jane.Dean@fda.hhs.gov]  
**Sent:** Wednesday, May 25, 2011 6:01 PM  
**To:** Gannon, Melissa [PRDUS]  
**Cc:** McKinnon, Rebecca (Saville)  
**Subject:** RE: NDA 20634/NDA 20635/NDA 21721 for Levaquin (levofloxacin) - December 1, 2010 Meeting Minutes and response to questions regarding Animal Rule and User Fees regarding levofloxacin for plague

Hi, Melissa – have you sent in a formal submission per my email of 5/17/11? I recently received a submission from you for IND 38368, IND 36627, NDA 20635, NDA 20634 and NDA 21721 with a letter date of 5/20/11. I have forwarded those submissions to the review team. Did those submissions relate to the questions below in the emails?

I will do my best to ensure the reviewers have what they need to adequately answer your questions but I cannot say what their turn around time will be.

Jane

-----  
Jane A. Dean, RN, MSN  
Regulatory Health Project Manager  
Division of Anti-Infective and Ophthalmology Products  
Office of Antimicrobial Products  
FDA/CDER

Office: 301-796-1202  
Fax: 301-796-9881  
Rm. 6397, Bdg. 22

Email address: [jane.dean@fda.hhs.gov](mailto:jane.dean@fda.hhs.gov)

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**From:** Gannon, Melissa [PRDUS] [mailto:MGannon2@its.jnj.com]  
**Sent:** Wednesday, May 25, 2011 5:51 PM  
**To:** Dean, Jane  
**Cc:** McKinnon, Rebecca (Saville)  
**Subject:** RE: NDA 20634/NDA 20635/NDA 21721 for Levaquin (levofloxacin) - December 1, 2010 Meeting Minutes and response to questions regarding Animal Rule and User Fees regarding levofloxacin for plague

Hello Jane,

I just want to follow-up on the request for information in the email below to see if we will have a response from the reviewers this week?

Kind regards,  
Melissa

**Melissa L. Gannon**  
**Director, Global Regulatory Leader for**  
**Women's Health/Urology/Anti-Infectives/Anti-Fungals**  
**Established Products**  
**Johnson & Johnson Pharmaceutical R&D**  
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**Raritan, NJ 08869**  
**Phone: (908) 927-2382**

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**Fax: (908) 722-5113**

**e-mail: [mgannon2@its.jnj.com](mailto:mgannon2@its.jnj.com)**

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**From:** Gannon, Melissa [PRDUS]  
**Sent:** Tuesday, May 17, 2011 5:16 PM  
**To:** Dean, Jane  
**Cc:** Rebecca.Saville@fda.hhs.gov  
**Subject:** RE: NDA 20634/NDA 20635/NDA 21721 for Levaquin (levofloxacin) - December 1, 2010 Meeting Minutes and response to questions regarding Animal Rule and User Fees regarding levofloxacin for plague

Hello Jane,

Thank you for your response. I will prepare the submission as requested.

Kind regards,  
Melissa

**Melissa L. Gannon**  
**Director, Global Regulatory Leader for**  
**Women's Health/Urology/Anti-Infectives/Anti-Fungals**  
**Established Products**  
**Johnson & Johnson Pharmaceutical R&D**  
**920 Route 202 South**  
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**From:** Dean, Jane [mailto:Jane.Dean@fda.hhs.gov]

**Sent:** Tuesday, May 17, 2011 4:59 PM

**To:** Gannon, Melissa [PRDUS]; McKinnon, Rebecca (Saville)

**Subject:** RE: NDA 20634/NDA 20635/NDA 21721 for Levaquin (levofloxacin) - December 1, 2010 Meeting Minutes and response to questions regarding Animal Rule and User Fees regarding levofloxacin for plague

Hi, Melissa – I know transitioning from the familiar practices of one RPM to the unknown practices of a new RPM can cause anxiety. However, I do strive to develop an open relationship with my sponsors at the onset.

That being said, if you wish to continue to cc Rebecca on your emails, I have no objection to that. It actually would be kind of helpful for me as I try to come up to speed on your submission.

As far as your comments contained in your email below, in light of the complexity and the many questions you have, please submit this, including your original questions, or at least, a summary of the email conversation below, through the Gateway so it can be tracked properly. In this way, there will be a clearly documented record of the agreements made and the responses the Agency is providing for your questions.

Jane

-----  
Jane A. Dean, RN, MSN  
Regulatory Health Project Manager  
Division of Anti-Infective and Ophthalmology Products  
Office of Antimicrobial Products  
FDA/CDER

Office: 301-796-1202

Fax: 301-796-9881

Rm. 6397, Bdg. 22

Email address: [jane.dean@fda.hhs.gov](mailto:jane.dean@fda.hhs.gov)

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**From:** Gannon, Melissa [PRDUS] [mailto:MGannon2@its.jnj.com]  
**Sent:** Tuesday, May 17, 2011 4:31 PM  
**To:** McKinnon, Rebecca (Saville)  
**Cc:** Dean, Jane  
**Subject:** RE: NDA 20634/NDA 20635/NDA 21721 for Levaquin (levofloxacin) - December 1, 2010 Meeting Minutes and response to questions regarding Animal Rule and User Fees regarding levofloxacin for plague

Hello Rebecca,

I know this project is transitioning to a new project manager (Jane Dean) but I am not sure if it has been officially transferred. As such, I thought I would still correspond with you and copy Jane on the email. Please let me know if this is acceptable or if I should begin corresponding with Jane directly.

In reference to FDA's communication of May 10, 2011, the J&J team has reviewed the comments and has some additional information/questions for the reviewers.

- Does the Microbiology team intend to provide additional feedback regarding the acceptability of the proposed format and content of the overall sham datasets as outlined in our communication of April 29th, 2011?
- The mock dataset and data definitions submitted on 4/29/2011 followed the CDISC format where each data point is represented by a row in the SAS dataset. In discussions with the laboratories performing the studies, it was noted that the raw data is obtained in a file for each animal, with rows for time points and columns for the parameters (temperature, heart rate, etc.). As this is the format closer to the raw data, we wanted to present this alternative approach to telemetry datasets for consideration in review of the mock dataset. (See Alternative Telemetry Documents – Attached)
- Regarding items listed under #2 of the May 10th, 2011 communication, we have the following responses:

**2. In reference to the sham datasets submitted on April 29, 2011, we recommend the following:**

**The microbiological culture results for the target organs (i.e., necropsy tissues) including the source, time point at which the sample was collected and bacterial colony counts.**

J&J Response:

These data will be added to the gross necropsy dataset. Please note that as survivors were not necropsied, tissue microbiological data is only available for natural history and control animals. Additional parameters have been added to the data definitions file.

**If contaminants are identified then these should be provided as well in the dataset; such information should include the species identified, the site/source (e.g., catheter) and bacterial counts (if available).**

J&J Response:

Please clarify if these are to be included in the study reports or the SAS dataset for statistical analysis. It may be difficult to retrospectively put the data into a uniform format for a SAS dataset; it should be very straightforward to include them in the report(s) if the data are available.

**We would like the different parameters such as for the aerosol and microbiology information in the datasets to be presented as columns for each animal rather than as rows.**

J&J Response:

Please clarify whether this is the direction of all reviewers and not just the Microbiology reviewers. The guidance regarding CDISC format was followed for the mock dataset. We will submit a single format for each dataset, though we are willing to tailor datasets to column or row format. The data is almost never collected in a column per animal, so it will require transformation in every case.

**For the aerosol challenge sham dataset, you have provided the list of parameters and the formulas for some of the calculated parameters under the columns headings “Codes” and “Comments”, respectively. However, there appears to be some typographical errors in the formulas used in the “Comments” column. For example, for the LD50 equivalents in the “Codes column” the formula should be  $\text{Calculated} = \text{INHDOSE} / \text{AERO} * \text{TATV}$  in the “Comments” column but is shown as  $\text{Calculated} = \text{AERO} * \text{TATV}$ . Please check for accuracy of the formulas.**

J&J Response:

Thank you for the observation. There was an extra line in the comments, such that calculations below it (LD50 and SF) don't match up with the proper code; a tracked change version has been attached which corrects this. The mock dataset submitted 4/29 contained the correct calculations.

The team respectfully requests responses to the additional questions by next week if possible so that they will have time to implement changes.

Would you also please let me know if this email communication is sufficient or if I should submit this information formally through the Gateway?

Kind regards,  
Melissa

Melissa L. Gannon  
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**From:** McKinnon, Rebecca (Saville)  
[mailto:Rebecca.Saville@fda.hhs.gov]  
**Sent:** Tuesday, May 10, 2011 12:51 PM  
**To:** Gannon, Melissa [PRDUS]  
**Cc:** Willard, Diana M; Dean, Jane  
**Subject:** RE: NDA 20634/NDA 20635/NDA 21721 for Levaquin (levofloxacin) - December 1, 2010 Meeting Minutes and response to questions regarding Animal Rule and User Fees regarding levofloxacin for plague

Hi Melissa,

Attached, please find a response from our Microbiology team regarding your April 29, 2011 submission.

Have a good afternoon!

Regards,  
Rebecca

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**From:** McKinnon, Rebecca (Saville)  
**Sent:** Wednesday, May 04, 2011 9:15 PM  
**To:** 'Gannon, Melissa [PRDUS]'  
**Cc:** Willard, Diana M; Dean, Jane; Izadi, Fariba  
**Subject:** RE: NDA 20634/NDA 20635/NDA 21721 for Levaquin (levofloxacin) - December 1, 2010 Meeting Minutes and response

to questions regarding Animal Rule and User Fees regarding levofloxacin for plague

Hi Melissa,

I forwarded the manuscript to the OCP team and requested a response for you by the end of next week. (b) (6)

I also requested a response from the micro team. A few comments have been drafted, but Dr. Bala needs to sign off on them. (b) (6)

We should have a response for you by the end of the week or early next week.

We recently underwent reorganization, so the Levaquin applications have been transferred to DAIP. Fabriba Izadi will be the PM (b) (4) I think. Jane Dean will most likely be the PM for the plague sNDA. I have updated Jane on the datasets and the manuscript and have cc:d both of them on this email. All our microbiology reviewers have transferred to DAIP. We will try to make this transition as smooth as possible for you as you prepare the sNDAs.

It's been a pleasure working on Levaquin the past 7 years. I'll miss it. Please feel free to contact me if you have any questions about any outstanding items.

Thanks!

Regards,  
Rebecca

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**From:** Gannon, Melissa [PRDUS] [mailto:MGannon2@its.jnj.com]  
**Sent:** Wednesday, May 04, 2011 3:23 PM  
**To:** McKinnon, Rebecca (Saville); Willard, Diana M  
**Subject:** RE: NDA 20634/NDA 20635/NDA 21721 for Levaquin (levofloxacin) - December 1, 2010 Meeting Minutes and response to questions regarding Animal Rule and User Fees regarding levofloxacin for plague

Hello Rebecca,

I just have a couple items for you pertaining to our upcoming submission and action items discussed in our December 1, 2010 preNDA meeting.

DSPTP indicated that J&JPRD should submit the manuscript the pediatric dose selection (this was a joint collaboration between J&JPRD and FDA during the review of the pediatric anthrax sNDAs in 2008) and DSPTP will let J&JPRD know

if a final internal J&JPRD report will be needed in the submission. The manuscript is attached. Could you please let me know if this is acceptable for the submission?

In addition, do you know when we will have clarification on the microbiology datasets question (below)?

Kind regards,  
Melissa

**Melissa L. Gannon**  
**Director, Global Regulatory Leader for**  
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**From:** Gannon, Melissa [PRDUS]

**Sent:** Monday, April 25, 2011 11:07 AM

**To:** Rebecca.Saville@fda.hhs.gov; Willard, Diana M

**Subject:** RE: NDA 20634/NDA 20635/NDA 21721 for Levaquin (levofloxacin) - December 1, 2010 Meeting Minutes and response to questions regarding Animal Rule and User Fees regarding levofloxacin for plague

Hello Rebecca,

As agreed in our December 1, 2010 preNDA meeting with the Division, the team is preparing to send mock data sets and data definition files for the animal studies by the beginning of next week. The microbiology team is trying to prepare the same but is in need of some clarification on the specific microbiology datasets (and from what studies) that are being requested:

If the FDA is only interested in microbiology datasets from the efficacy study conducted in African Green Monkeys (FY07-070) then this would consist of

bacterial counts from blood samples and target organs from individual monkeys in this study. If the FDA is interested in other microbiology datasets, then these could include (i) susceptibility data from MIC endpoint studies performed by USAMRIID and HPA in which collections of *Y. pestis* isolates were tested against Levofloxacin, and/or (ii) microbiology endpoint data as included in Natural History Studies [Battelle (617-G607610), Lovelace (FY06-126), and USAMRIID] which would include bacterial counts from blood samples and/ or target organs from individual monkeys in these studies. Note that no quantitative microbiology endpoint data were collected in the two NIAID-sponsored efficacy studies of Levofloxacin conducted in mice so the FDA request for microbiology datasets would not apply to these two studies.

Could you please provide us with additional information so that we can prepare these data as well?

Kind regards,  
Melissa

**Melissa L. Gannon**  
**Director, Global Regulatory Leader for**  
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**From:** Willard, Diana M [mailto:Diana.Willard@fda.hhs.gov]

**Sent:** Monday, February 07, 2011 12:35 PM

**To:** Gannon, Melissa [PRDUS]

**Cc:** McKinnon, Rebecca (Saville)

**Subject:** NDA 20634/NDA 20635/NDA 21721 for Levaquin (levofloxacin) - December 1, 2010 Meeting Minutes and response to questions regarding Animal Rule and User Fees regarding levofloxacin for plague

Hi! Melissa - attached are letters Dr. Albrecht signed this AM regarding the above applications and issues in the "Subject" line.

Please let me know if you have any questions.

Regards,  
Diana

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JANE A DEAN  
06/06/2011