CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020634Orig1s061, 020635Orig1s067, 021721Orig1s028

CHEMISTRY REVIEW(S)

CHEMICAL MANUFACTURING CONTROLS
FILING CHECKLIST FOR Supplement

Filing Checklist

NDA Number:	Supplement Number and Type:	Established/Proper Name:
1. 20-634	1. S-061	1. Levaquin® (levofloxacin) Tablets
2. 20-635	2. S-067	2. Levaquin® (levofloxacin) Injection
3. 21-721	3. S-028	3. Levaquin® (levofloxacin) Oral Solution

Applicant:	Letter Date:	Stamp Date:
Johnson & Johnson	1. October 27, 2011	1. October 28, 2011
	2. November 4, 2011	2. November 7, 2011
	3. November 4, 2011	3. 3. November 7, 2011

** These are efficacy supplements (provide for use of Levaquin® for the treatment of pneumonic plague). No CMC changes have been proposed; therefore, no CMC information has been provided. EA has been addressed.*

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?			N/A*
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?			N/A*
3.	Are all the pages in the CMC section legible?			N/A*
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?			N/A*

B. FACILITIES*				
	Parameter	**Yes**	**No**	**Comment**

Dec 2008 version of Filing Template
from:http://inside.fda.gov/ProgramsInitiatives/Drugs/21stCenturyReview/UCM034686.html

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5.	Is a single, comprehensive list of all involved facilities available in one location in the application?		✓	N/A*
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**		✓	N/A*
7.	Are drug substances manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)		✓	N/A*

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8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)		✓	N/A*
9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)		✓	N/A*
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?		✓	N/A*

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

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C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	✓		Categorical exclusion

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?		✓	N/A*
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?		✓	N/A*
14.	Does the section contain information regarding the characterization of the DS?		✓	N/A*
15.	Does the section contain controls for the DS?		✓	N/A*
16.	Has stability data and analysis been provided for the drug substance?		✓	N/A*
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		✓	N/A*
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		✓	N/A*

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E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?		✓	N/A*
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?		✓	N/A*
21.	Is there a batch production record and a proposed master batch record?		✓	N/A*
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?		✓	N/A*
23.	Have any biowaivers been requested?		✓	N/A*
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?		✓	N/A*
25.	Does the section contain controls of the final drug product?		✓	N/A*
26.	Has stability data and analysis been provided to support the requested expiration date?		✓	N/A*
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		✓	N/A*
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		✓	N/A*

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F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?		✓	N/A*

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?		✓	N/A*

H. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?		✓	N/A*

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
32.	Has the draft package insert been provided?	✓		
33.	Have the immediate container and carton labels been provided?		✓	N/A (no changes proposed)

J. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
34.	**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**	✓		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.		✓	N/A*
36.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?		✓	

**** These are efficacy supplements No CMC changes have been proposed; therefore, no CMC information has been provided. EA has been addressed.***

CHEMICAL MANUFACTURING CONTROLS
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{See appended electronic signature page}

Dorota Matecka, Ph.D.
CMC Lead — Date
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment

{See appended electronic signature page}

Thomas Oliver, Ph.D.
Branch Chief — Date
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment

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/s/

DOROTA M MATECKA
12/20/2011

THOMAS F OLIVER
12/20/2011

Memorandum

Date: April 19, 2012

To: Efficacy supplements:
20-634/S-061 [Levaquin® (levofloxacin) Tablets]
20-635/S-067 [Levaquin® (levofloxacin) Injection]
21-721/S-028 [Levaquin® (levofloxacin) Oral Solution]

From: Dorota Matecka, Ph.D., CMC Lead, DNDQA II, ONDQA

Through: Thomas Oliver, Ph.D. Branch Chief, Branch VI, DNDQA II, ONDQA

Re: CMC filing review

The purpose of this memo is to revise the statement on page 6 of the filing checklist (Item I. Labeling) dated December 20, 2011 (in DARRTS), which currently indicates that container labels have not been provided in these supplements. The labels for the three Levaquin drug products were submitted in these submissions; however, no changes to the container labels have been proposed or made via these efficacy supplements.

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/s/

DOROTA M MATECKA
04/19/2012

THOMAS F OLIVER
04/20/2012

CMC REVIEW	1. ORGANIZATION	2. NDA NUMBER
	ONDQA, DNDQA II, Branch V and DAIP	20-634; 20-635; 21-721

3. NAME AND ADDRESS OF APPLICANT	4. COMMUNICATION, DATE
Johnson & Johnson PRD 920 Route 202 South Raritan, NJ 08869-0602	20-634/S-061, dated 27-Oct-2011 20-635/S-067, dated 04-Nov-2011 21-721/S-028, dated 04-Nov-2011 Efficacy - PAS

5. PROPRIETARY NAME	6. NAME OF THE DRUG	7. AMENDMENTS, REPORT, DATE
Levaquin® (levofloxacin) Tablets Levaquin® (levofloxacin) Injection Levaquin® (levofloxacin) Oral Solution	Levofloxacin	N/A

8. COMMUNICATION PROVIDES FOR:

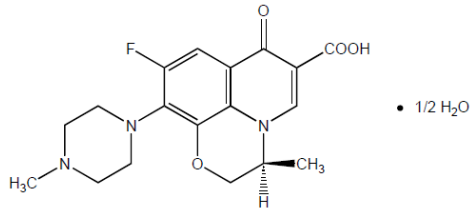
Efficacy supplements – provide for the use of LEVAQUIN® in the treatment of pneumonic plague following the exposure to *Yersinia pestis* in adults and pediatric patients >50 kg and ≥6 months of age.

9. PHARMACOLOGICAL CATEGORY	10. HOW DISPENSED	11. RELATED IND, NDA, DMF
Anti-infective	Rx	N/A
12. DOSAGE FORM	**13. POTENCY**	
Tablets (20-634) Injection (20-635) Oral Solution (21-721)	250 mg, 500 mg, 750 mg 25 mg/mL, 5 mg/mL 25 mg/mL	

14. CHEMICAL NAME AND STRUCTURE

Chemical name: (-)-(S)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid hemihydrate

$C_{18}H_{20}FN_3O_4 \times ½ H_2O$ MW = 370.38



15. COMMENTS

These efficacy supplements do not contain a Quality Module as the CMC information remains unchanged from that of the approved NDAs. The applicant stated that the estimated concentration of the substance at the point of entry into the aquatic environment (the total (b) (4) year production estimate for all formulations) will be below 1 part per billion (b) (4) Therefore, the applicant claims a categorical exclusion from the requirement to prepare an environmental assessment in accordance with 21 CFR 25.31(b) and stated that to the knowledge of J&J PRD, no extraordinary circumstances exist. The applicant's request for categorical exclusion from environmental assessment is acceptable.

16. CONCLUSION AND RECOMMENDATION

APPROVAL

17. NAME	18. REVIEWERS SIGNATURE	19. DATE COMPLETED
Dorota Matecka	In DARRTS	28-Feb-2012

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/s/

DOROTA M MATECKA
03/08/2012

THOMAS F OLIVER
03/08/2012