DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
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MAY 12 2016

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Re: Docket No. FDA-2014-P-0856

Dear Dr. Bennett:

This letter responds to the citizen petition (Petition) submitted to the Food and Drug Administration (FDA or the Agency) by the Southern Network on Adverse Reactions (SONAR) and received on July 23, 2014. The Petition requests that FDA require changes in the professional labeling of Levaquin (levofloxacin) to reflect new safety information.[1]

Specifically, SONAR relies primarily on an April 17, 2013, FDA Pharmacovigilance Review entitled "Disabling Peripheral Neuropathy Associated with Systemic Fluoroquinolone Exposure" and requests that:

(1) language immediately be added to Levaquin's labeling regarding "Possible Mitochondrial Toxicity" in section 5 under the *Warnings and Precautions* heading (Petition at 1-2);

(2) a boxed warning immediately be added to Levaquin's labeling regarding "Possible Mitochondrial Toxicity" (Petition at 2); and

(3) Dear Health Care Provider (DHCP) letters[2] be distributed regarding these labeling changes and that the letter request that physicians inform patients about the potential impact of "Possible Mitochondrial Toxicity" if the patients were previously prescribed this drug (Petition at 2).

We have carefully reviewed the information in the Petition, as well as the comments submitted to the Petition docket. For the reasons stated below, we deny your request. However, as specified below, we have taken action to require certain changes to the labeling of Levaquin and other systemic fluoroquinolone antibacterial drugs to reflect new safety information.

[1] Although your Petition only cited the New Drug Application (NDA) number pertaining to the tablet form of Levaquin (levofloxacin), NDA 020634 (Petition at 1), we also considered your requests in light of NDAs 020635 and 021721 pertaining to the solution formulations of Levaquin (levofloxacin).

[2] The Petition refers to these letters as "Dear Doctor" letters; however, for the purposes of this petition response, we use the FDA-recognized term "Dear Health Care Provider letters" (DHCP letters).

I. BACKGROUND

A. Statutory and Regulatory Framework

FDA's regulation of drug safety is governed by the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 301 et seq.) and the Agency's implementing regulations (codified in Title 21 of the Code of Federal Regulations). The FD&C Act makes it unlawful to market a new drug product without first obtaining an approved New Drug Application (NDA) or abbreviated new drug application (ANDA).[3] Before approving an NDA, FDA must determine that the drug is both safe and effective for use under the conditions prescribed, recommended, or suggested in the product's labeling.[4]

NDAs contain, among other things, scientific data demonstrating the safety and effectiveness of the drug for the indication for which approval is sought. NDA applicants must, among other things, describe the benefits and risks of the drug, including a discussion of why the benefits exceed the risks under the conditions of use stated in the drug product's labeling.[5] Prescription drug labeling (also known as the package insert or prescribing information) is approved by FDA; it is a compilation of information about the product, based on the Agency's review of the NDA submitted by the applicant. It contains a summary of the essential scientific information needed for the safe and effective use of the drug.[6] The labeling is used to communicate essential, science-based prescribing information to health care professionals.

FDA regulations in § 201.57 state that the *Warnings and Precautions* section of labeling "must describe clinically significant adverse reactions . . . , other potential safety hazards . . . , limitations in use imposed by them . . . , and steps that should be taken if they occur . . . ."[7] FDA regulations also state that a contraindication or serious warning may be elevated to a boxed warning when it "may lead to death or serious injury."[8]

After an approved drug enters the marketplace, FDA may have cause to reassess the drug's safety and take regulatory action if warranted and appropriate. One possible action would be to require the inclusion of new safety information, including changes to boxed warnings, contraindications, warnings, precautions, or adverse reactions, in product labeling. Section 505(o)(4) of the FD&C Act authorizes FDA to require and, if necessary, order labeling changes

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[3] See section 505(a) of the FD&C Act (21 U.S.C. 355(a)); see also section 301(d) of the FD&C Act (21 U.S.C. 331(d)) (prohibiting the marketing of any article in violation of section 505).

[4] Section 505(b)(1) of the FD&C Act; section 505(d) of the FD&C Act.

[5] 21 CFR 314.50(d)(5)(viii).

[6] § 201.57(a)(1) (21 CFR 201.57(a)(1)).

[7] § 201.57(c)(6).

[8] § 201.57(c)(l).

if FDA becomes aware of new safety information that FDA believes should be included in the labeling of the drug.[9]

B. Levaquin

Levaquin is approved under NDAs 020634, 020635, and 021721, and the sponsor is Janssen Pharmaceuticals. Levaquin contains levofloxacin, a synthetic broad spectrum fluoroquinolone antibacterial agent for oral and intravenous administration. Chemically, levofloxacin, a chiral fluorinated carboxyquinolone, is the pure (-)-(S)-enantiomer of the racemic drug substance ofloxacin. Levaquin is indicated in adults (≥ 18 years of age) with infections caused by designated susceptible bacteria listed in section 1 of the labeling for the following conditions: nosocomial pneumonia; community-acquired pneumonia; acute bacterial sinusitis; acute bacterial exacerbation of chronic bronchitis; complicated skin and skin structure infections; uncomplicated skin and skin structure infections (mild to moderate), including abscesses, cellulitis, furuncles, impetigo, pyoderma, and wound infections; chronic bacterial prostatitis; complicated urinary tract infections; acute pyelonephritis; uncomplicated urinary tract infections (mild to moderate); and inhalational anthrax (post-exposure). Levaquin is also indicated for treatment of plague, including pneumonic and septicemic plague, due to *Yersenia pestis* and prophylaxis for plague in adults and pediatric patients, 6 months of age and older.[10]

C. FDA's April 17, 2013, Pharmacovigilance Review

FDA's Division of Pharmacovigilance (DPV) in the Office of Surveillance and Epidemiology (OSE) prepared a Pharmacovigilance Review dated April 17, 2013, entitled "Disabling Peripheral Neuropathy Associated with Systemic Fluoroquinolone Exposure" ("2013 DPV Pharmacovigilance Review"). This pharmacovigilance review addressed the association of systemic fluoroquinolone (oral and parenteral formulations) exposure and disabling peripheral neuropathy.

OSE conducted the 2013 DPV Pharmacovigilance Review after receiving consumer communications describing prolonged, disabling neuropathy thought to be associated with systemic fluoroquinolone administration. OSE had already completed two previous reviews of fluoroquinolone-associated peripheral neuropathy, one in 2001 and the other in 2003. The review, dated April 17, 2013, focused on serious cases of prolonged, disabling neuropathy with the search criteria being restricted to U.S. cases with an outcome of disability from 2003 to 2012.

The 2013 DPV Pharmacovigilance Review concluded that fluoroquinolone labels at that time were inconsistent in their description of the risk of peripheral neuropathy. The labels did not reflect the rapid onset and possible permanence of peripheral neuropathy, and they did not include the need to consider discontinuation of drug with the first symptoms. The review did not

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[9] Section 901 of Title IX of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amended the FD&C Act by adding new section 505(o).

[10] See current labeling for Levaquin (NDA 020634, 020635, and 021721), available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020634s066,020635s072,021721s033lbl.pdf.

identify a relationship between peripheral neuropathy and the duration of therapy, dose of the drug, or the age of the patient, and no specific risk factors were identified.

Mitochondrial toxicity, which is more appropriately understood as a pharmacological mechanism of action rather than a specific adverse reaction,[11] was discussed in the review. The review did not conclude, however, that fluoroquinolones cause mitochondrial injury. Mitochondria are organelles that produce energy in human cells in the form of adenosine triphosphate, which is commonly known as ATP. Damage to the mitochondria results in the cell making less energy, leading to cellular injury or death. Mitochondrial dysfunction or toxicity can result in adverse reactions that affect many organ systems in the body.

The 2013 DPV Pharmacovigilance Review recommended the following measures: (1) Updating the information in the *Warnings and Precautions* section of fluoroquinolone labels, replacing language suggesting that discontinuation of the drug may prevent an irreversible condition with language reflecting the rapid onset and possible permanence of peripheral neuropathy, and adding language to discontinue the fluoroquinolone immediately with the first symptoms of peripheral neuropathy, unless the benefit of continued treatment with a fluoroquinolone outweighs the risk; (2) making labeling consistent for all fluoroquinolones; (3) updating the patient education section of the label to reflect this information; and (4) considering a Drug Safety Communication (DSC) or other forums to communicate to health care professionals and patients that peripheral neuropathy may occur rapidly and potentially be permanent, and that if clinically appropriate, the drug should be discontinued immediately. FDA subsequently acted on these recommendations, including approving updates to the *Warnings and Precautions* and patient education sections of fluoroquinolone labels consistent with the 2013 recommendations, revising the Medication Guide for patients, and publishing a DSC on August 15, 2013, in which the Agency explained that it had required that drug labels and Medication Guides for all systemic fluoroquinolone antibacterial drugs be updated to better describe the serious side effect of peripheral neuropathy.[12]

D. FDA's November 5, 2015, Advisory Committee Meeting and Safety Labeling Changes

After the Petition was submitted, on November 5, 2015, FDA held a joint meeting of the Antimicrobial Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee to discuss the risks and benefits of the systemic fluoroquinolone antibacterial drugs for the treatment of acute bacterial sinusitis (ABS), acute bacterial exacerbation of chronic bronchitis in patients who have chronic obstructive pulmonary disease (ABECB-COPD), and uncomplicated urinary tract infections (uUTI) in the context of available safety information and the treatment effect of antibacterial drugs in these clinical conditions. The Advisory Committee

[11] See, e.g., sections 3.3.2 and 8.6 of the 2013 DPV Pharmacovigilance Review that are both titled "Possible Mechanism of Action: Mitochondrial Toxicity."

[12] FDA Drug Safety Communication: FDA requires label changes to warn of risk for possibly permanent nerve damage from antibacterial fluoroquinolone drugs taken by mouth or by injection, August 15, 2013, available at http://www.fda.gov/Drugs/DrugSafety/ucm365050.htm.

members voted that the benefits and risks of fluoroquinolones do not support the current labeled indications for ABS (Yes, 0; No, 21; Abstain, 0), ABECB-COPD (Yes, 2; No, 18; Abstain, 0), and uUTI (Yes, 1; No, 20; Abstain, 0).

FDA considered the Committee's recommendations and reviewed the available information. Based on "new safety information" as defined in section 505-1(b)(3) of the FD&C Act (21 U.S.C. 355-1(b)(3)), FDA has concluded that changes should be made to the labeling for systemic fluoroquinolone antibacterial drugs. Today, we issued letters notifying fluoroquinolone NDA and ANDA holders that their products' labeling must be modified to reflect a new limitation of use statement to make it clear that the use of fluoroquinolones for acute bacterial sinusitis, acute exacerbation of chronic bronchitis, and uncomplicated urinary tract infections is to be reserved for patients who do not have other treatment options. The letters also inform NDA and ANDA holders that fluoroquinolone labeling must be modified to reflect the serious risk of disabling and potentially irreversible adverse reactions that have been observed to occur together, including tendinitis, tendon rupture, peripheral neuropathy, and central nervous system effects. We issued these letters based on our authority with respect to safety labeling changes under section 505(o)(4) of the FD&C Act.[13]

II. DISCUSSION

In your Petition, you request that FDA require changes in the professional labeling of Levaquin (levofloxacin) to reflect new safety information.[14] Specifically, you request that (1) language be added to Levaquin's labeling regarding "Possible Mitochondrial Toxicity" in section 5 under the *Warnings and Precautions* heading (Petition at 1-2), (2) a boxed warning be added to Levaquin's labeling regarding "Possible Mitochondrial Toxicity" (Petition at 2), (3) the above-mentioned labeling changes be made immediately (Petition at 2), and (4) DHCP letters be distributed regarding these labeling changes and that the letters ask that physicians inform patients about the potential impact of "Possible Mitochondrial Toxicity" if the patients were previously prescribed this drug (Petition at 2). For the reasons described below, your requests are denied.

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[13] In accordance with section 505(o)(4) of the FD&C Act, the fluoroquinolone NDA and ANDA holders are required to submit within 30 days following notification either a supplement containing the proposed labeling changes, or notify the Agency that they do not believe labeling changes are warranted and submit a statement detailing the reasons the changes are not warranted. If the fluoroquinolone NDA and ANDA holders do not submit proposed safety labeling changes, or if we disagree with the language proposed or the statement setting forth the reasons why no labeling change is necessary, the FD&C Act provides strict timelines under section 505(o)(4) for discussions regarding the labeling changes. At the conclusion of these discussions, section 505(o)(4)(E) allows FDA to issue an order directing labeling changes as deemed appropriate to address the new safety information. We are awaiting the responses of the fluoroquinolone NDA and ANDA holders, under these FDAAA procedures, to our notification that revisions to product labeling are necessary. The specific language we have recommended is subject to change depending on what language the NDA and ANDA holders propose. Thus, we have not required specific labeling changes at this stage of the process under section 505(o)(4) of the FD&C Act. However, we have taken all the necessary steps required under section 505(o)(4) of the FD&C Act to pursue the necessary changes.

[14] As indicated above in the first footnote, although your Petition only cited the NDA number pertaining to the tablet form of Levaquin (levofloxacin), NDA 026034 (Petition at 1), we also considered your requests in light of NDAs 020635 and 021721 pertaining to the solution formulations of Levaquin (levofloxacin).

A. Scientific or Regulatory Support for the Requested Changes in the Professional Labeling of Levaquin and the Request for DHCP Letters

1. The 2013 DPV Pharmacovigilance Review

The Petition's Statement of Grounds section indicates that the Petition's requests are based on information in the 2013 DPV Pharmacovigilance Review. The purpose of the DPV review was to further describe cases of disabling peripheral neuropathy associated with the use of systemic fluoroquinolones. The review was conducted after receiving consumer communications describing prolonged, disabling neuropathy thought to be associated with systemic fluoroquinolone administration. In addition, a literature search was done to try to find a possible mechanism by which peripheral neuropathy might occur in patients taking systemic fluoroquinolones. Although no definitive mechanism of action for peripheral neuropathy was identified, several articles suggested that mitochondrial toxicity may play a part in this adverse reaction.

The Petition points to the literature cited in the review as supporting the Petition's requests.[15] The Petition further claims that 17 references in the 2013 DPV Pharmacovigilance Review were "identified by the FDA as being relevant to 'Possible Mitochondrial Toxicity' associated with fluoroquinolones, including Levaquin."[16] We concur with the Petition's assessment that the 2013 DPV Pharmacovigilance Review describes the literature on mitochondrial toxicity and includes a list of references. However, we note that the pertinent sections of the 2013 DPV Pharmacovigilance Review[17] address mitochondrial toxicity in the context of the focus of the Review, which was the clinical adverse reaction of peripheral neuropathy. Mitochondrial toxicity was included as a possible explanation for the association between systemic fluoroquinolone drugs and the development of peripheral neuropathy. The literature discussed in the Review, which is based primarily on animal data and in vitro data, provides insufficient support for the proposition that levofloxacin causes mitochondrial toxicity, and that this toxicity results in levofloxacin-induced peripheral neuropathy.

In further support of the Petition's requests, the Petition points to section 3.3.2 of the 2013 DPV Pharmacovigilance Review (titled "Possible Mechanism of Action: Mitochondrial Toxicity"),[18]

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[15] Petition at 3.

[16] Petition at 5-6.

[17] Sections 2.3.2 and 7 of the 2013 DPV Pharmacovigilance Review

[18] Petition at 3. For example, the Petition cites language from section 3.3.2 of the DPV Pharmacovigilance Review stating that "Fluoroquinolones have been found to affect mammalian topoisomerase II, especially in mitochondria. In vitro studies in drug-treated mammalian cells found that nalidixic acid and ciprofloxacin caused a loss of mitochondrial DNA (mtDNA), resulting in a decrease of mitochondrial respiration and an arrest in cell growth" (citing pages 11-12 of the 2013 DPV Pharmacovigilance Review). The Petition also cites language from this section stating that "Mitochondrial conditions that are due to an insufficiency of ATP, especially in organs that rely on mitochondria for their energy source, include developmental disorders of the brain, optic neuropathy, neuropathic pain, hearing loss, muscle weakness, cardiomyopathy, and lactic acidosis. Neurodegenerative diseases, like

as well as section 8.6 (titled "Possible Mechanism of Action: Mitochondrial Toxicity").[19] Specifically, the Petition indicates that "[i]n addition to providing information about 'Mitochondrial Toxicity,' this [last] section discusses [two] fluoroquinolone drugs, [trovafloxacin and gatifloxacin,] already removed from the market due to toxicity."[20] The Petition observes that "Levaquin has 'class effect' with other fluoroquinolones, as indicated in numerous sections of the Levaquin label, in multiple label versions, over the past decade" and that it is assumed "that Levaquin has class effect with Trovafloxacin and Gatifloxacin, both of which were removed from the market due to Mitochondrial Toxicity as described" in section 8.6 (at page 25) of the 2013 DPV Pharmacovigilance Review. We disagree with the Petition's claim that the 2013 DPV Pharmacovigilance Review indicates trovafloxacin or gatifloxacin were removed from the market due to "Mitochondrial Toxicity."[21] The drugs were removed from the market due to the life-threatening clinical adverse reactions of liver failure with trovafloxacin, and severe glucose disturbances with gatifloxacin, and not because of mitochondrial toxicity.[22]

The Petition is asking that mitochondrial toxicity be added to the label as a class effect. We disagree with adding mitochondrial toxicity to the label as a class effect for several reasons. First, we do not consider possible mitochondrial toxicity in itself a specific clinical adverse reaction. The addition of possible mitochondrial toxicity to all fluoroquinolone labels will not help a clinician or patient identify or treat a particular adverse reaction. Second, it is not scientifically sound to extrapolate the mitochondrial toxicity mechanism of action to all drugs in the class based solely on the data cited by the Petition from studies in cultured hepatocytes that identified the mitochondria as the source of trovafloxacin's hepatotoxicity. Furthermore, not all fluoroquinolones have the same degree of effect of a particular adverse reaction, although in some cases they may. When the Agency looks at class effect or class labeling, it is looking at clinical adverse reactions that appear across a class of drugs. If a serious adverse reaction is found in most, if not all, drugs in a class, class labeling may be appropriate, but in this case, mitochondrial toxicity is not in itself a serious adverse reaction and we do not have a basis to extrapolate the mitochondrial toxicity mechanism of action to all drugs in the class.

Parkinson's, Alzheimer's and amyotrophic lateral sclerosis (ALS) have been associated with the loss of neurons due to oxidative stress" (citing page 12 of the 2013 DPV Pharmacovigilance Review).

[19] Petition at 4.

[20] Petition at 4. The Petition points out that: "Trovafloxacin was withdrawn from the market in 2001 due to cases of liver failure. Studies in cultured hepatocytes identified the mitochondria as the source of trovafloxacin's hepatotoxicity" (citing page 25 of the 2013 DPV Pharmacovigilance Review) and that "Gatifloxacin was withdrawn from the market in 2006 because of severe glucose disturbances . . . . An in vitro study found that high glucose resulted in excessive ROS and mitochondrial dysfunction, which result in a high frequency of Schwann cell apoptosis. . . . A study done in type 2 diabetic mice saw that with an increase in extracellular glucose, there was excessive mitochondrial fission; this was thought to result in dorsal root ganglia (DRG) neuron oxidative stress and neuronal injury, or activation of the caspase cascade, leading to programmed cell death. Another study saw damage mitochondria with 1-2 hours of exposure to elevated glucose" (also citing page 25 of the 2013 DPV Pharmacovigilance Review).

[21] Petition at 4-5.

[22] See note 20, above. See also proposed rule, "Additions and Modifications to the List of Drug Products That Have Been Withdrawn or Removed From the Market for Reasons of Safety or Effectiveness," 79 FR 37687 at 37690-37691 (July 2, 2014).

The Petition also highlights language from section 8.6 of the 2013 Pharmacovigilance Review discussing loss of mitochondrial DNA that has been associated with the fluoroquinolone ciprofloxacin,[23] as well as language discussing oxidative stress and the association between neurodegenerative diseases, like Parkinson's, Alzheimer's, and amyotrophic lateral sclerosis (ALS), and the loss of neurons due to oxidative stress.[24] We note that section 8.6 of the 2013 DPV Pharmacovigilance Review discussed multiple articles describing possible mechanisms related to mitochondrial toxicity based on animal and in vitro data. Only one article identified in the literature review for the 2013 DPV Pharmacovigilance Review described a human study. This human study examined oxidative stress in patients being treated for complicated urinary tract infections with one of three different fluoroquinolones (ciprofloxacin, levofloxacin, and gatifloxacin). The study did not evaluate a clinical adverse reaction.

The data available to the Agency indicate that the possibility that levofloxacin might cause mitochondrial toxicity is currently speculative and based almost entirely on animal and in vitro data. There is insufficient evidence in the 2013 DPV Pharmacovigilance Review to conclude that levofloxacin causes mitochondrial injury, and the 2013 DPV Pharmacovigilance Review itself did not conclude that levofloxacin causes mitochondrial injury.

2. *Lack of Evidence Demonstrating That Levofloxacin Causes Mitochondrial Injury*

Although the 2013 DPV Pharmacovigilance Review did not conclude that levofloxacin causes mitochondrial injury, FDA has conducted additional analyses of the information available to it to assess whether there could be a structural link between levofloxacin and mitochondrial toxicity. As described in further detail below, FDA has concluded that there is no structure-activity relationship (SAR) or published evidence showing that levofloxacin itself can cause mitochondrial injury.

a. SAR analysis

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[23] "In vitro studies in drug-treated mammalian cells found that nalidixic acid and ciprofloxacin caused a loss of mitochondrial DNA (mtDNA), resulting in a decrease of mitochondrial respiration and an arrest in cell growth. Further analysis found protein-linked double-stranded DNA breaks in the mtDNA from ciprofloxacin-treated cell, suggesting that ciprofloxacin was targeting topoisomerase II activity in the mitochondria" (2013 DPV Pharmacovigilance Review, page 24).

[24] For example, the Petition highlights the following language from pages 24-25 of the 2013 DPV Pharmacovigilance Review:

> Mitochondrial conditions that are due to an insufficiency of ATP, especially in organs that rely on mitochondria for their energy source, include developmental disorders of the brain, optic neuropathy, neuropathic pain, hearing loss, muscle weakness, cardiomyopathy, and lactic acidosis. Neurodegenerative diseases, like Parkinson's, Alzheimer's and amyotrophic lateral sclerosis (ALS) have been associated with the loss of neurons due to oxidative stress generated by ROS . . . . The phototoxic effects of fluoroquinolones were found to be due to the mitochondrial formation of a singlet oxygen (02) and superoxide anion (02).

FDA has evaluated levofloxacin for its potential to cause mitochondrial disruption using the program *Lhasa Derek Nexus* (*DX v. 4.0.5*). This program is an expert rule-based SAR knowledge base. The knowledge base for Derek v4.0.5 contains 24 prototype (preliminary) alerts for "mitochondrial dysfunction" and two standard alerts for "uncoupling of oxidative phosphorylation." No structural alerts were triggered by levofloxacin for the endpoints of "mitochondrial dysfunction" and "uncoupler of oxidative phosphorylation."

b. Published data

In concert with the SAR findings, there is little scientific literature suggesting that levofloxacin causes mitochondrial injury. The effects of levofloxacin were studied on cultured primary rabbit chondrocytes.[25] The study found some effects on incorporation of $^{35}SO_4$ and of thymidine at concentrations at or above 10 micrograms (µg)/milliliter (mL). Accumulation of rhodamine 123 was reduced at concentrations of 10 µg/mL and higher, although no data on the mechanism of altered level were reported. Depending on circumstances and cell type, rhodamine 123 can report on mitochondrial membrane potential, redox status, cell viability, or multi-drug resistance protein 1 transporter activity. Direct damage to mitochondria with other fluoroquinolones has been observed, but only with in vitro systems at concentrations 2 to 8 times higher than the clinical maximum concentration.[26]

Furthermore, there is limited evidence that some, but not all, fluoroquinolones can cause production of reactive oxygen species (ROS) in mammalian cells that may result in downstream (secondary) injury to multiple cellular systems, including mitochondria. Phototoxicity with ofloxacin has been shown to result from production of ROS that leads to multiple effects, including lysosomal degradation, apoptosis, and mitochondrial injury.[27] Depletion of glutathione, attributed to oxidative stress has been observed in human hepatocytes treated in vitro with levofloxacin with a TC_{50} of 130 µg/mL.[28] In a study with human tendon cells, ciprofloxacin at 50 µg/mL or higher induced oxidative stress and alteration of mitochondrial membrane

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[25] Kato M, Takada S, Ogawara S, Takayama S. Effect of levofloxacin on glycosaminoglycan and DNA synthesis of cultured rabbit chondrocytes at concentrations inducing cartilage lesions in vivo. *Antimicrob Agents Chemotherap* 39, 1979-1983 (1995).

[26] Lawrence JW, Claire DC, Weissing V, Rowe TC. Delayed cytotoxicity and cleavage of mitochondrial DNA in ciprofloxacin-treated mammalian cells. *Mol. Pharmacol* 50, 1178-1186 (1996); Tartaglione TA, Raffalovich AC, Poynor WJ, Espinel-Ingroff-A, Kerkering TM. Pharmacokinetics and tolerance of ciprofloxacin after sequential increasing oral doses. *Antimicrob Agents Chemotherap* 29, 62-66 (1986).

[27] Dwivede A, Mujtaba SF, Yadav N, Kuswaha HN, Amar SK, Singh SK, Pant MC, Ray RS. Cellular and molecular mechanism of ofloxacin induced apoptotic cell death under ambient UV-A and sunlight exposure. *Free Radic Res* 48, 333-346 (2014).

[28] Liguori MJ, Anderson MB, Bukofzer S, McKim J, Pregenzer JF, Retief J, Spear B, Waring JF. Microarray analysis in human hepatocytes suggests a mechanism for hepatotoxicity induced by trovafloxacin. *Hepatology* 41, 177-186 (2005).

potential and treatment with an anti-oxidant protected against both changes.[29] Oxidative stress has been observed in patients treated with ciprofloxacin or levofloxacin but not gatifloxacin.[30] Although these data may be suggestive of the possibility of mitochondrial toxicity, these studies are almost exclusively in vitro and are not conclusive that these drugs cause a clinical adverse reaction.

c. Language regarding mitochondrial toxicity is not appropriate for inclusion in the *Warnings and Precautions* section or a boxed warning in a label

We believe the quality and type of information in support of possible mitochondrial toxicity is insufficient to warrant new labeling language regarding mitochondrial toxicity for Levaquin in either the *Warnings and Precautions* section of the label or in a boxed warning.

i. Warnings and precautions

As explained above, the *Warnings and Precautions* section of labeling must describe clinically significant adverse reactions, other potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur.[31] Specifically, § 201.57(c)(6) requires that the *Warnings and Precautions* section of labeling:

> . . . describe clinically significant adverse reactions (including any that are potentially fatal, are serious even if infrequent, or can be prevented or mitigated through appropriate use of the drug), other potential safety hazards (including those that are expected for the pharmacological class or those resulting from drug/drug interactions), limitations in use imposed by them (e.g., avoiding certain concomitant therapy), and steps that should be taken if they occur (e.g., dosage modification). . . . [T]he labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitively established.

In addition, in the October 2011 guidance for industry *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format*,[32] FDA clarified that:

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[29] Lowes DA, Wallace C, Murphy MP, Webster NR, Galley HF. The mitochondria targeted antioxidant MitoQ protects against fluoroquinolone-induced oxidative stress and mitochondrial membrane damage in human Achilles tendon cells. *Free Radic Res* 43, 323-328 (2009).

[30] Talla V, Veerareddy PR. Oxidative stress induced by fluoroquinolones on treatment for complicated urinary tract infections in Indian patients. *J Young Pharmacists* 3, 304-309 (2011).

[31] § 201.57(c)(6).

[32] Guidance at 3. Available at http://www.fda.gov/downloads/Drugs/Guidances/ucm075096.pdf.

> [t]he WARNINGS AND PRECAUTIONS section is intended to identify and describe a discrete set of adverse reactions and other potential safety hazards that are *serious* and *otherwise clinically significant* because they have implications for prescribing decisions or for patient management. To include an adverse event in the section, there should be reasonable evidence of a causal association between the drug and the adverse event, but a causal relationship need not have been definitively established.

Section 201.57(c)(6) does not apply here. As mentioned above, mitochondrial toxicity is more appropriately understood as a pharmacological mechanism of action rather than a discrete adverse reaction, and also, the data available to the Agency indicate that this possible mechanism is currently speculative and based almost entirely on animal and in vitro data. As such, there is insufficient data to indicate that mitochondrial toxicity constitutes a clinically significant adverse reaction, and we have no reason to believe, based on the above-mentioned studies, that there is adequate evidence of a causal association between mitochondrial toxicity and Levaquin.

ii. Boxed warning

As explained above, FDA may require that "[c]ertain contraindications or serious warnings, particularly those that may lead to death or serious injury . . . be presented in a box" on a drug product's labeling.[33] Specifically, § 201.57(c)(1) states:

> Certain contraindications or serious warnings, particularly those that may lead to death or serious injury, may be required by the FDA to be presented in a box. The boxed warning ordinarily must be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data. The box must contain, in uppercase letters, a heading inside the box that includes the word "WARNING" and conveys the general focus of the information in the box. The box must briefly explain the risk and refer to more detailed information in the "Contraindications" or "Warnings and Precautions" section, accompanied by the identifying number for the section or subsection containing the detailed information.

Furthermore, in the October 2011 guidance for industry,[34] FDA explained that a boxed warning is ordinarily used to highlight one of the following situations:[35]

- "There is an adverse reaction so serious in proportion to the potential benefit from the drug (e.g., a fatal, life-threatening or permanently disabling adverse reaction) that it is essential that it be considered in assessing the risks and benefits of using the drug;" or

- "There is a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug . . .;" or

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[33] § 201.57(c)(1).

[34] See the guidance for industry *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format*, October 2011, available at http://www.fda.gov/downloads/Drugs/Guidances/ucm075096.pdf.

[35] Id. at 11.

- "FDA approved the drug with restrictions to ensure safe use because FDA concluded that the drug can be safely used only if distribution or use is restricted . . . ."

Section 201.57(c)(1) is not applicable here. Based on the data available to the Agency at this time, mitochondrial toxicity does not constitute a serious adverse reaction, nor is the quality and type of information in support of possible mitochondrial toxicity adequate to conclude that it is the mechanism of action underlying the association between fluoroquinolones and serious adverse reactions.

For all of these reasons, we believe the quality and type of information in support of possible mitochondrial toxicity is insufficient to warrant new labeling language regarding mitochondrial toxicity for Levaquin.

3. The Quality and Type of Information in Support of Possible Mitochondrial Toxicity Is Insufficient for Issuing DHCP Letters

The Petition also requests that DHCP letters be distributed requesting that physicians inform patients about the potential impact of "Possible Mitochondrial Toxicity" if the patients were previously prescribed this drug (Petition at 2). We disagree because, as already explained above, there is a lack of evidence to substantiate a claim that mitochondrial toxicity is associated with Levaquin.

B. FDA Is Not Aware of Any Data Implicating the Use of Levaquin With the Development of Neurodegenerative Disorders Such as Parkinson's, Alzheimer's, or ALS

The Petition proposed that certain wording linking fluoroquinolones to neurodegenerative disorders be added to the *Warnings and Precautions* and boxed warning. Specifically, the Petition requested that the following wording, which includes references to neurodegenerative disorders, be added in section 5 under the *Warnings and Precautions* heading of the Levaquin label:[36]

> Possible Mitochondrial Toxicity
> Fluoroquinolones, including Levaquin, may cause Mitochondrial Toxicity due, in part, to an insufficiency of ATP. Mitochondrial conditions that are due to an insufficiency of ATP include developmental disorders of the brain, optic neuropathy, neuropathic pain, hearing loss, muscle weakness, cardiomyopathy, and lactic acidosis. Neurodegenerative diseases, like Parkinson's, Alzheimer's and amyotrophic lateral sclerosis (ALS) have been associated with the loss of neurons due to oxidative stress generated by reactive oxygen species (ROS) related to Mitochondrial Toxicity. Peripheral neuropathy, hepatotoxicity, glucose disturbances, and phototoxicity may result from Mitochondrial Toxicity.

[36] Petition at 1-2.

Furthermore, the Petition requested that a boxed warning containing the following language be added to Levaquin's labeling regarding "Possible Mitochondrial Toxicity":[37]

> WARNING: POSSIBLE MITOCHONDRIAL TOXICITY
> Fluoroquinolones may cause Mitochondrial Toxicity. Mitochondrial Toxicity has been implicated in conditions such as peripheral neuropathy, hepatoxicity, glucose disturbances, phototoxicity, developmental disorders of the brain, optic neuropathy, neuropathic pain, hearing loss, muscle weakness, cardiomyopathy, lactic acidosis, Parkinson's, Alzheimer's, and amyotrophic lateral sclerosis (ALS).

We deny your request to require these labeling changes. We believe that inclusion of neurodegenerative disorders, including Parkinson's disease, Alzheimer's disease, and ALS, under the category of possible mitochondrial toxicity and associating these disorders with fluoroquinolone use would be highly misleading. Although the 2013 DPV Pharmacovigilance Review indicates neurodegenerative diseases, like Parkinson's, Alzheimer's, and ALS, have been associated with the loss of neurons due to oxidative stress generated by ROS,[38] there is no scientific evidence that taking a fluoroquinolone can cause any of these three neurodegenerative disorders.

III. CONCLUSION

As explained above, we have carefully reviewed the information in the Petition, as well as the comments submitted to the Petition docket; however, there is inadequate scientific support to grant the requested changes in the labeling of Levaquin and the request for DHCP letters. Accordingly, your requests are denied.

However, we can assure you that FDA takes concerns raised about safety of approved drugs very seriously. As mentioned in the Background section of this response, in November 2015, FDA held an Advisory Committee meeting to discuss the benefits and risks of systemic fluoroquinolone antibacterial drugs and has decided to require certain labeling changes for these drugs.

FDA is committed to keeping health care professionals and the public informed of the latest safety information, and we will continue to evaluate the safety of all marketed fluoroquinolone antibiotics and consider labeling revisions when appropriate.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

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[37] Petition at 2.

[38] 2013 DPV Pharmacovigilance Review at 12 and 24-25.