DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

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Arnold L. Widen, M.D., M.S., F.A.C.P.
Babs Waldman, M.D.
Illinois Attorney General's Office
100 W. Randolph Street
Chicago, IL 60601

Jay Parkinson, M.D., M.P.H.
Sidney M. Wolfe, M.D.
Public Citizen
Health Research Group
1600 20th Street, N.W.
Washington, D.C. 20009

Re: Docket Nos. FDA-2005-P-0064 and
FDA-2006-P-0390

Dear Drs. Widen, Waldman, Parkinson, and Wolfe:

This letter responds to the citizen petition dated May 18, 2005 (Docket No. FDA-2005-P-0064) (Illinois Petition), submitted by the Office of the Illinois Attorney General, and to the related citizen petition dated August 29, 2006, submitted by Public Citizen's Health Research Group (FDA-2006-P-0390) (HRG Petition).[1] The Illinois Petition asks the Food and Drug Administration (FDA or the Agency) to require manufacturers of the fluoroquinolone class of antimicrobial drugs to take the following actions:

- Revise drug labeling to strengthen warnings for the potential for serious adverse events of tendinopathy and tendon rupture
- Create a "black box" warning to reflect the risk and severity of these side effects
- Issue a Dear Health Care Professional (DHCP) letter to inform health care providers about this hazard and announce the changes in labeling
- Supplement information provided to patients with bolded warnings about the risk of tendinopathy and tendon rupture

[1] These citizen petitions were originally assigned docket numbers 2005P-0205/CP1 and 2006P-0371/CP1, respectively. The numbers were changed to FDA-2005-P-0064 and FDA-2006-P-0390, respectively, as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008.

In addition, the Illinois Petition asks that we submit the class of fluoroquinolone drugs for review to the Agency's Drug Safety Oversight Board (DSOB). The HRG Petition calls for similar action: that FDA require the manufacturers of fluoroquinolones to (1) add a black box warning regarding the risks of tendinopathy and tendon rupture, (2) issue a DHCP letter, and (3) distribute an FDA-approved Medication Guide for patients.

We have reviewed the petitions, the supplement to the Illinois Petition dated August 29, 2006, and comments submitted to the docket for the Illinois Petition. For the reasons set forth below, the petitions are granted in part and denied in part.

I. BACKGROUND

A. Regulations and Guidance on Warnings in Drug Labeling

1. Boxed Warnings

FDA regulations state that the WARNINGS AND PRECAUTIONS section of drug product labeling (including the product's package insert) must describe clinically significant adverse reactions,[2] other potential safety hazards, limitations in use imposed by them, and steps that should be taken if these situations occur (21 CFR 201.57(c)(6)(i)). Labeling must be revised to include a warning as soon as there is reasonable evidence of a causal association of a clinically significant hazard with a drug. A summary of the most clinically significant warnings and precautions information must be included in the HIGHLIGHTS OF PRESCRIBING INFORMATION section for the drug product (§ 201.57(a)(10)).

Under § 201.57(c)(1), a boxed warning (also known as a "black box warning") may be required for certain contraindications or serious warnings, particularly those that may lead to death or serious injury. A boxed warning must contain, in uppercase letters, a heading that includes the word "WARNING" and conveys the general focus of information in the box. A boxed warning briefly explains the risk and refers to more detailed information in the CONTRAINDICATIONS or WARNINGS AND PRECAUTIONS section (§ 201.57(c)(1)). A summary of a boxed warning (with the

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[2] Section 201.57(c)(7) defines *adverse reaction* as an undesirable effect, reasonably associated with use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. FDA's draft guidance for industry entitled *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format* (Warnings Draft Guidance) (at 11) defines *serious adverse reaction* as any reaction occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability or incapacity, or a congenital anomaly or birth defect. (Guidances are available on FDA's Web site at http://www.fda.gov/cder/guidance/index.htm. The draft guidance, when finalized, will represent FDA's current thinking on this topic.) The Warnings Draft Guidance (at 2) states that the clinically significant adverse reactions observed in association with use of a drug that should be listed in the WARNINGS AND PRECAUTIONS section (see § 201.57(c)(6)) include those involving a serious adverse reaction, an adverse reaction that is otherwise clinically significant (e.g., requires discontinuation, could be prevented with appropriate patient selection, significantly affects patient compliance), and product interference with a laboratory test.

heading WARNING and other words identifying the subject of the warning) must be included in the HIGHLIGHTS section in a box and in bold type (21 CFR 201.56(d)(1) and 201.57(a)(4)).

The Warnings Draft Guidance (at 9) states that a boxed warning ordinarily is used to highlight one of the following situations:

- 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 an adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug (e.g., patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another drug or managing patients in a specific manner, avoiding use in a specific clinical situation), or

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

The draft guidance states that there may be other situations in which a boxed warning may be appropriate to highlight information that is especially important to a prescriber (Warnings Draft Guidance at 9).

2. Medication Guides

A medication guide is FDA-approved patient labeling that conforms to the specifications in 21 CFR part 208 and other applicable regulations. The Agency will require a manufacturer of a prescription drug product to distribute a Medication Guide when we determine that the drug product poses a serious and significant public health concern and that patient labeling is needed to ensure the safe and effective use of the product (§ 208.1(a) and (b)). Under § 208.1(c), we will require a Medication Guide when we determine that one or more of the following circumstances exist:

- The drug product is one for which patient labeling could help prevent serious adverse effects.

- The drug product is one that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decision to use, or to continue to use, the product.

- The drug product is important to health and patient adherence to directions for use is crucial to the drug's effectiveness.

3. *Labeling Changes Based on "New Safety Information"*

Title IX, Subtitle A, section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amended the Federal Food, Drug, and Cosmetic Act (the Act) to authorize FDA to require holders of approved drug and biological product applications to make safety labeling changes for an approved drug based on new safety information[3] that becomes available after the approval of the drug (section 505(o)(4) of the Act (21 U.S.C. 355(o)(4))).

Section 901 of FDAAA also added section 505-1(a)(2) of the Act (21 U.S.C. 355-1(a)(2)), which authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) for an approved drug product if FDA becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh its risks.[4]

B. Fluoroquinolones and Adverse Events

Fluoroquinolones are a class of prescription antimicrobial drugs used to treat certain bacterial infections in patients. FDA approved the first fluoroquinolone, norfloxacin (Noroxin), in 1986. The fluoroquinolone class of drugs currently marketed in the United States includes norfloxacin; ciprofloxacin (Cipro), approved in 1987; ofloxacin (Floxin), approved in 1990;[5] levofloxacin (Levaquin), approved in 1996; moxifloxacin (Avelox), approved in 1999; and gemifloxacin (Factive), approved in 2003.[6] Although systemic

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[3] As defined in section 505-1(b)(3), *new safety information* is information derived from a clinical trial, an adverse event report, a postapproval study (including a study under section 505(o)(3)), or peer-reviewed biomedical literature; data derived from the postmarket risk identification and analysis system under section 505(k) of the Act; or other scientific data deemed appropriate by the Agency about, among other things, a serious or an unexpected serious risk associated with use of the drug that the Agency has become aware of (that may be based on a new analysis of existing information) since the drug was approved.

[4] Section 505-1(a)(1)(A) through (F) of the Act states that in making a determination on whether a REMS is needed, the Agency considers the following factors: the estimated size of the population likely to use the drug involved; the seriousness of the disease or condition that is to be treated with the drug; the expected benefit of the drug with respect to such disease or condition; the expected or actual duration of treatment with the drug; the seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug; and whether the drug is a new molecular entity.

[5] Only generic versions of ofloxacin are currently marketed in the United States.

[6] Although HRG includes enoxacin, lomefloxacin, and gatifloxacin among the fluoroquinolones presently marketed in the United States (HRG Petition at 1), these drugs are no longer marketed in this country. The new drug application (NDA) for Penetrex (enoxacin) was withdrawn on April 4, 2005; the NDAs for Maxaquin (lomefloxacin) and Tequin (gatifloxacin) have not been withdrawn.

fluoroquinolones[7] are effective for the treatment of certain bacterial infections and generally safe for the majority of patients, they are associated with adverse reactions, including infrequent serious adverse reactions that involve tendons, the gastrointestinal tract, skin and soft tissues, the cardiac conduction system, and the central and peripheral nervous system.

Tendon rupture is a serious adverse event that often requires surgical repair and can result in significant and prolonged disability. Case reports of tendon disorders associated with fluoroquinolone use began to appear in the literature in the 1980s, with the first report of tendon rupture appearing in 1991.[8]

Several articles in the medical literature have focused on tendon rupture. Achilles tendon rupture with fluoroquinolone usage was determined to occur at a rate three to four times higher in comparison to Achilles tendon rupture in patients that did not receive fluoroquinolones.[9] In patients over the age of 60 and on corticosteroids, the relative risk of Achilles tendon rupture was over 20 times greater than the general population in one report and over 40 times greater in another.[10] Estimates of tendon rupture risk in an early study were approximately 1 in 11,000 for norfloxacin and 3 in 11,000 for ofloxacin.[11] A more recent article estimated that one Achilles tendon rupture would occur for every approximately 6,000 patients treated with a fluoroquinolone, one in approximately 1,600 patients treated with a fluoroquinolone who were over age 60, and one in approximately 1,000 patients at any age also taking corticosteroids.[12] It is estimated that approximately 2 to 6 percent of Achilles tendon ruptures in people older than age 60 can be attributed to fluoroquinolones,[13] and the proportion of Achilles tendon ruptures in patients younger than age 60 related to the use of fluoroquinolones is less than 1 percent.[14]

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[7] The petitions relate to tendinopathies that are associated with fluoroquinolones for systemic use (e.g., tablets, capsules, injectable formulations); these adverse events are not generally associated with fluoroquinolones for ophthalmic or otic use (e.g., eye drops, ear drops).

[8] Franck, J.L., et al., "Rupture des tendons d'achille chez deux adultes traites par pefloxacine dont un cas bilateral" [letter], *Rev Rhum Mal Osteoartic* 58:904 (1991).

[9] Van der Linden, P.D., et al., "Increased Risk of Achilles Tendon Rupture With Quinolone Antibacterial Use, Especially in Elderly Patients Taking ORPl Corticosteroids," *Arch Intern Med* 163:1801-1807 (2003); Corrao, G., et al., "Evidence of tendinitis provoked by fluoroquinolone treatment: a case-control study," *Drug Safety* 29(10):889-896 (2006); Sode, J., et al., "Use of fluoroquinolone and risk of Achilles tendon rupture: a population-based cohort study," *Eur J Clin Pharmacol* 63(5):499-503 (2007).

[10] Van der Linden; Corrao.

[11] Wilton, L.V., G.L. Pearce, and R.D. Mann, "A comparison of ciprofloxacin, norfloxacin, ofloxacin, azithromycin and cefixime examined by observational cohort studies," *Br J Clin Pharmacol* 41:277-284 (1996).

[12] Corrao.

[13] Van der Linden.

[14] Sode.

C. Information on Tendon Disorders Included in Fluoroquinolone Labeling Through 2007

In response to postmarketing reports of tendinitis and tendon rupture, information on these disorders was added to the ADVERSE REACTIONS section of systemic fluoroquinolones package inserts in 1992. In 1995, we asked fluoroquinolone manufacturers to add statements on tendinopathies to the WARNINGS section of the package insert. Since the approval of Levaquin (levofloxacin) in 1996, all systemic fluoroquinolone package inserts have included a warning regarding tendinitis and tendon rupture in the product labeling as well as cautionary statements in the PRECAUTIONS/*Information for Patients* subsection.

In 2001, because of information showing that the risk of tendinopathy and tendon rupture was greater in elderly patients and those on corticosteroids, the manufacturer of levofloxacin added this information to the WARNINGS section of the package insert. By 2004, the manufacturers of the other fluoroquinolones added this information to the WARNINGS section of their product package inserts. The WARNINGS section of the current package inserts for each of the fluoroquinolones includes a specific subsection heading on *Tendon Effects* and information on tendinitis and tendon ruptures, such as provided in the following example from the ciprofloxacin labeling:

> *Tendon Effects:* Ruptures of the shoulder, hand, Achilles tendon or other tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving quinolones, including ciprofloxacin. Post-marketing surveillance reports indicate that this risk may be increased in patients receiving concomitant corticosteroids, especially the elderly. Ciprofloxacin should be discontinued if the patient experiences pain, inflammation, or rupture of a tendon. Patients should rest and refrain from exercise until the diagnosis of tendinitis or tendon rupture has been excluded. Tendon rupture can occur during or after therapy with quinolones, including ciprofloxacin.

In 2006, after reviewing the Illinois and HRG Petitions, the medical literature, and reports in FDA's Adverse Event Reporting System (AERS)[15] involving tendon disorders and fluoroquinolones, we asked the manufacturers of fluoroquinolones to make further changes to the package inserts of their products to address the heightened risk of tendinopathies and tendon rupture and to emphasize that the risk is particularly increased among elderly patients receiving fluoroquinolones, especially those who are also on steroids. These labeling changes, which were implemented in 2007, included the addition of information to the PRECAUTIONS/*Information for Patients* subsection and the PRECAUTIONS/*Geriatric Use* subsection.[16] In addition, the Patient Package Inserts (PPIs) for the fluoroquinolones include information on tendinitis and tendon rupture.

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[15] The AERS reporting system may be found on the FDA Web site at http://www.fda.gov/cder/aers/default.htm.

[16] Although the labeling for Noroxin was not revised at that time, we subsequently requested that the product's labeling be changed in accordance with the labeling of the other fluoroquinolones (although Noroxin is no longer marketed, generic norfloxacin products remain on the market).

This information first appeared in the PPI for levofloxacin in 2000, and additional statements were added to the PPIs for the fluoroquinolones in 2007.

II. DISCUSSION

A. FDAAA Drug Safety Labeling Changes: Boxed Warning, Related Package Insert Changes, and Medication Guide

1. Petition Requests

The Illinois Petition requests that we strengthen the warnings regarding the potential for tendinopathy and tendon rupture with the use of fluoroquinolones. The petition states that the Office of the Attorney General has received numerous complaints from Illinois citizens who have suffered from tendinopathies induced by the use of levofloxacin. The petition states that a review of available medical literature and interviews of physicians and academic medical center staff have led the State of Illinois to conclude that fluoroquinolone-induced tendinopathies are not rare complications of fluoroquinolone use and are not adequately appreciated by physicians. The petition further states that because tendinopathies have been reported as an adverse effect from more than one fluoroquinolone antimicrobial, this complication should be regarded as a therapeutic class characteristic (Illinois Petition at 3).

The Illinois Petition (at 3) states that although fluoroquinolone product labeling mentions tendinopathy, including tendon rupture, this information is buried in lists of potential side effects that are less frequent and less severe. Therefore, the petition (at 2) asks that we require the use of a boxed warning concerning tendinopathy and tendon rupture on fluoroquinolone product labeling to read as follows:

> Serious tendonopathies including tendon rupture have occurred in patients taking fluoroquinolone antibiotics. The Achilles tendon is most frequently involved but the tendons of the rotator cuff, biceps and hand have been affected. Multiple tendons may be involved and significant disabilities can result. Onset of tendonopathies is highly variable after use of fluoroquinolone antibiotics, varying from onset within 30 days of use, during which frequency is greatest, to several months after cessation of the drug. The risk of tendonitis and tendon rupture is increased in elderly patients, patients on corticosteroids and renal transplant recipients. Patients should be advised to immediately stop the fluoroquinolone at the onset of tendon pain and contact their physician.

The HRG Petition echoes the State of Illinois' concern that the existing warnings about the risk of tendinopathies are not sufficiently prominent in fluoroquinolone labeling and states that fluoroquinolone tendon ruptures continue to occur at an alarming rate (HRG Petition at 2 and 5). Therefore, HRG calls for a boxed warning similar to that proposed

by the State of Illinois.[17] The HRG Petition (at 1) also requests that we require distribution of a Medication Guide to patients addressing these adverse effects.

2. *FDA Actions*

a. Boxed Warning and Related Labeling Changes

In 2008, we conducted an updated review and new analysis of the AERS reports involving tendon disorders and fluoroquinolones as well as the recent medical literature on this matter. Despite the warning statements that had been previously added to the product labeling (described in section I.C of this response) concerning tendinitis and tendon rupture, we continued to receive additional reports for these adverse events associated with fluoroquinolone products. In addition, the recent medical literature (described in section I.B of this response) further confirmed the increased risk of tendon rupture from fluoroquinolone use, particularly for patients over age 60, on corticosteroids, or who received transplants.

Based on this evidence, we concluded that the current labeling of fluoroquinolone drug products does not adequately warn health care providers and patients about these possible, rare serious events. In particular, we determined that taking steps to ensure that health care providers and their patients are better informed about the risk of tendon rupture, specific factors that increase this risk, and actions to take if tendon-related symptoms occur might help to decrease the number of these adverse events. For example, increased awareness of the risks associated with fluoroquinolones should encourage consideration of alternative treatment options that may have a more favorable benefit-risk ratio in patients at elevated risk of tendon rupture (e.g., patients over age 60, those on concomitant corticosteroid therapy, transplant recipients) or in patients with generally self-limited conditions. In addition, increased awareness and advising patients to call their health care provider if they develop tendon-related symptoms (before a tendon rupture), may provide an opportunity for patients to take steps to avoid a tendon rupture, such as resting the affected area and discontinuing fluoroquinolone therapy. Based on this analysis, we determined that the significance of this risk of tendon disorders and the benefits of increased patient awareness of the risk justify the need for a

[17] HRG's proposed boxed warning (HRG Petition at 6) states the following:

> Fluoroquinolone antibiotics should be used with extreme caution because there is an increased risk of tendonitis and the possibility of complete tendon rupture with all fluoroquinolone antibiotics. This adverse reaction most frequently involves the Achilles tendon, the tendon that runs from the back of the heel to the calf. Rupture of the Achilles tendon may require surgical repair. Tendons in the rotator cuff (the shoulder), the hand, the biceps, and the thumb have also been involved. This reaction appears to be more common in those taking steroid drugs, in older patients, and in kidney transplant recipients, but many cases have occurred in people without any of these risk factors. The onset of symptoms is sudden and has occurred as soon as 24 hours after starting treatment with a fluoroquinolone. If you experience pain in any tendon while taking these medications you should stop the medication and immediately contact your physician so you can be switched to another antibiotic.

boxed warning under § 201.57(c)(1), as well as the recommendations in the Warnings Draft Guidance regarding assessment of the benefit-risk ratio and prevention of the adverse event.

We considered our updated review and analysis of the AERS reports and literature on fluoroquinolone-associated tendon disorders to be "new safety information" as defined in FDAAA. This new safety information provided the basis for our conclusion that a boxed warning on tendinitis and tendon rupture should be included in the labeling for all systemic fluoroquinolone products in accordance with section 505(o)(4) of the Act.

Therefore, on July 8, 2008, we announced that we had notified the manufacturers of fluoroquinolone antimicrobial drugs, pursuant to our new FDAAA authority, that a boxed warning is necessary.[18] We requested that the boxed warning state that fluoroquinolones are associated with an increased risk of tendinitis and tendon rupture and note that the risk is increased in patients over age 60, patients on concomitant corticosteroid therapy, and kidney, heart, and lung transplant recipients.[19] In addition to requesting the boxed warning, we asked the fluoroquinolone manufacturers to make related changes to other aspects of the package insert of these products, including to the WARNINGS/*Tendon Effects* subsection, the PRECAUTIONS/ *Information for Patients* subsection, and the PRECAUTIONS/*Geriatric Use* subsection.

b. Medication Guide

In addition to the labeling changes described above, based on our recent analysis of the available data, we asked the manufacturers of fluoroquinolones pursuant to our new FDAAA authority to provide a Medication Guide to patients. Pursuant to section 505-1(e)(2) of the Act and part 208, we have determined that the fluoroquinolone drugs pose a serious and significant public health concern requiring distribution of a Medication Guide. We consider this Medication Guide to be part of the labeling for which safety labeling changes are necessary under section 505(o)(4) of the Act, as well as an element of a REMS under section 505-1(e)(2) of the Act.

Based on our review of the available evidence, we determined that a patient's awareness of the symptoms of adverse tendon effects may provide an opportunity for patients to take steps to avoid a tendon rupture, such as resting the affected area and discontinuing fluoroquinolone therapy. For example, a recent publication suggests that early

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[18] See the FDA press release, FDA Requests Boxed Warnings on Fluoroquinolone Antimicrobial Drugs, available on the Internet at http://www.fda.gov/bbs/topics/NEWS/2008/NEW01858.html.

[19] Although not identical to the boxed warnings recommended by either the State of Illinois or HRG, our proposed boxed warning includes most of the key elements in these suggested boxed warnings. In addition, our proposed boxed warning references the WARNINGS section of product labeling, which provides additional information and addresses all matters stated in the petitioners' recommended boxed warnings, including the following: the involvement of Achilles and other tendons; the risk of tendon rupture; patients at greater risk of tendon injury; when tendon events are likely to occur; symptoms of tendon injury; the importance of contacting a healthcare provider; and the need to discontinue use of the fluoroquinolone.

intervention in the setting of tendon injury may lead to complete recovery without permanent disability. In addition, we determined that patients' awareness of these risks may impact their decisions on whether to use a fluoroquinolone or continue use of a fluoroquinolone. Issuance of a Medication Guide increases the likelihood that patients will receive the appropriate educational material and be aware of the risks associated with fluoroquinolones, particularly to prevent the serious injury of tendon rupture.

Based on this analysis, we determined that the significance of this risk of tendon disorders and the benefits of increased patient awareness of the risk justify the necessity of a Medication Guide for all systemic fluoroquinolone products in accordance with § 208.1(c)(1) and (c)(2). We determined on the basis of the new safety information regarding tendinitis and tendon rupture that a REMS is necessary for these drug products in accordance with section 505-1(a)(2) of the Act to help ensure that the benefits of these products outweigh their risks, and that a Medication Guide should be an element of the REMS under section 505-1(e)(2)) of the Act. Based on this analysis, we also considered the Medication Guide to be part of the labeling for which safety labeling changes are necessary under section 505(o)(4) of the Act.

3. Next Steps for Safety Labeling Changes and REMS Under FDAAA

Our letters notifying manufacturers of the need to update the labeling for the fluoroquinolones by adding a boxed warning, developing a Medication Guide, and making related labeling changes regarding tendinitis and tendon rupture were issued on July 7, 2008, based on our new authority with respect to safety labeling changes under section 505(o)(4) of the Act.

In addition, as explained above, based on the new safety information regarding tendinopathies, the notification letters informed the manufacturers of fluoroquinolones that a REMS is necessary for their drug products in accordance with section 505-1(a)(2) of the Act to help ensure that the benefits of these products outweigh their risks. The REMS that each fluoroquinolone manufacturer should submit must include the Medication Guide and a timetable for submission of assessments of the REMS.[20]

In accordance with section 505(o)(4) of the Act, the fluoroquinolone manufacturers are required to submit within 30 days of the date of our notification letter (issued on July 7, 2008) prior approval supplements containing the proposed labeling changes (including the boxed warning, other package insert revisions, and the Medication Guide), or notify the Agency that they do not believe labeling changes are warranted and submit a

[20] Assessments must be provided no later than 18 months, 3 years, and 7 years after the REMS is approved. Information needed for the assessment of the REMS should include, but may not be limited to, the following: a survey of patients' and prescribers' understanding of the serious risks of the drug; a report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with § 208.24; and a report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance.

statement detailing the reasons why changes are not warranted. The fluoroquinolone manufacturers must submit a prior approval supplement containing a proposed REMS within 120 days of the notification letter.

If the fluoroquinolone manufacturers do not submit proposed labeling changes, or if we disagree with the language that the companies propose, the Act provides strict timelines under section 505(o)(4) for resolving the labeling changes. Section 505(o)(4) also allows us to issue an order directing labeling changes as deemed appropriate to address the new safety information. We are awaiting the response of the fluoroquinolone manufacturers under these FDAAA procedures to our notification that a boxed warning, related changes to the package insert, and a Medication Guide are necessary. The specific language we have recommended is subject to change depending on what language the drug manufacturers propose and their reasoning. Thus, we cannot require specific labeling changes at this stage of the process under section 505(o)(4). However, at this time we have taken all the necessary steps that are required under the carefully prescribed procedures of FDAAA for pursuing these changes. In this manner, we are granting in part the requests for a boxed warning and a Medication Guide.

B. Notification of Physicians and Patients

1. Petition Requests

In addition to the labeling changes, the Illinois Petition requests that we require manufacturers to issue a DHCP letter to physicians and other health care professionals to inform them of the risk of tendinopathies posed by fluoroquinolones. The petition also requests that we provide patients with bolded warnings about the risk of tendinopathy and tendon rupture, and suggests language that (1) describes these adverse events, (2) discusses some circumstances under which they are likely to occur, and (3) advises patients to seek medical care if a tendon problem occurs (Illinois Petition at 2 and 3-4). The HRG Petition (at 1) supports the State of Illinois' request for a DHCP letter.

2. FDA Actions

We have made extensive efforts to inform physicians, patients, and other interested persons about the addition of the boxed warning on fluoroquinolone-associated tendinitis and tendon ruptures, the Medication Guide, and related labeling changes. Specifically, we issued a press release, hosted a teleconference (including a question and answer session) with media, and posted additional information on the FDA Web site. Material on the Web site includes an Information for Healthcare Professionals Sheet that describes the risk of tendon disorders associated with fluoroquinolones (including the increased risk for certain types of patients), offers recommendations for health care professionals to consider regarding fluoroquinolones, and contains information that health care professionals can provide when counseling patients about fluoroquinolone use and tendon injuries. We also distributed the Information for Healthcare Professionals Sheet to an estimated 102,000 stakeholders, including both health care professionals and their patients, through the Medwatch Partners program and the Medwatch listserve. Many

individual Medwatch listserve recipients represent entire institutions, such as academic health care centers and large integrated group practices, which in turn disseminate the notification to individuals within their institutions. Other recipients include Medscape, a service that posts information to health care providers on its website and disseminates it electronically. The information also was widely covered by the news media available on the Internet, in print, and on television.

In addition, the Information for Healthcare Professionals Sheet addresses the information that the Illinois Petition asked to be provided in bolded warnings for patients. In particular, the section entitled "Information for Healthcare Professionals to Provide When Counseling Patients" includes patient information described in the petition request. We also note that a Medication Guide is designed to provide specific information to patients about the risks of a product. For these reasons, we have granted in part this request that supplemental information be provided to patients.

We believe that these extensive efforts were effective in communicating the information on fluoroquinolone-associated tendon disorders broadly, and we do not believe it is necessary at this time to ask each manufacturer of a fluoroquinolone to issue a DHCP letter addressing the risk of tendon ruptures associated with fluoroquinolone use. Therefore, we are denying the request that we require manufacturers of fluoroquinolones to issue a DHCP letter. However, we believe that some manufacturers may decide to issue DHCP letters, and for companies that choose to do so, we will provide input on the content of the DHCP letter and will consider posting the letter on the Medwatch page on our Web site. We believe that, taken together, these efforts will effectively communicate the nature, frequency, and severity of these adverse events to physicians and patients. If future developments indicate that further action may be warranted, we would consider appropriate steps at that time.

C. Referral to the Drug Safety Oversight Board

The Illinois Petition (at 3 and 4) asks that FDA's Drug Safety Oversight Board review fluoroquinolone antimicrobials.[21] The DSOB considered the issue of fluoroquinolone safety in October 2006, including a review of adverse event reports and other information about tendinopathies, and provided input regarding fluoroquinolone safety to the Division

[21] The Illinois Petition (at 4) states that, in addition to the risk of tendon rupture, there are other serious issues with fluoroquinolones for the DSOB to consider, such as cardiac arrhythmias. We agree that there is evidence that some fluoroquinolones may cause QT interval prolongation for some patients. Although no cases of Torsades de Pointes (TdP) (ventricular tachycardia that is characterized by fluctuation of the QRS complexes around the electrocardiographic baseline and is typically caused by a long QT interval) had been seen in any of the preapproval clinical development programs for the currently marketed fluoroquinolones, some cases of TdP have been observed with some fluoroquinolones in postapproval data. Many of these cases have occurred in patients with multiple risk factors for this arrhythmia. The package inserts for the fluoroquinolones reflect the varying levels of risk of arrhythmia posed by the different fluoroquinolones. We believe that these labeling statements provide adequate notice to patients and physicians of the risk of cardiac arrhythmias associated with the use of fluoroquinolones. We continue to monitor the fluoroquinolones for these and other adverse events and if necessary will request labeling changes in the future.

of Special Pathogen and Transplant Products in the Center for Drug Evaluation and Research. Therefore, we have granted your request that the DSOB review the safety of fluoroquinolones.

III. CONCLUSION

For the reasons discussed above, the petitions submitted by the State of Illinois and HRG are granted with respect to the request for referral of fluoroquinolone safety issues to the DSOB; granted in part with respect to the request for a boxed warning, related labeling changes, and a Medication Guide; granted in part with respect to the request that we supplement information to patients; and denied with respect to the request for issuance of a DHCP letter.

We have issued letters to the manufacturers of systemic fluoroquinolones explaining the need to add a boxed warning on tendinitis and tendon ruptures, make related changes to other parts of the package insert, and issue a Medication Guide to fully advise patients of the risk of tendon problems associated with fluoroquinolones. Because we have issued a press release and an Information for Healthcare Professionals Sheet, as well as provided information through the Medwatch Partners program to further increase awareness of this adverse event, we conclude that it is not necessary to require each manufacturer of fluoroquinolones to issue a DHCP letter, although we will provide comments to manufacturers on the content of their DHCP letters if they decide to send such letters in addition to the measures we have already taken or requested. Finally, as the State of Illinois requested, the DSOB reviewed the safety of fluoroquinolones, in particular the reports of adverse events involving tendon disorders.

Through the FDAAA new drug safety labeling procedures, we will work with the manufacturers of fluoroquinolones to quickly implement the boxed warning and other labeling changes we have requested, as well as the REMS plans, to ensure that the benefits of these drug products outweigh their risks. We will continue to closely monitor the safety of fluoroquinolones, particularly with respect to tendon disorders, and, if necessary, we will take further action to address this concern.

Sincerely,

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