**UNITED STATES DISTRICT COURT**
**FOR THE DISTRICT OF COLUMBIA**

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| PUBLIC CITIZEN, INC., | ) | |
| | ) | |
| Plaintiff, | ) | |
| | ) | |
| v. | ) | C. A. No. 08-00005(HHK) |
| | ) | |
| FOOD AND DRUG ADMINISTRATION, | ) | |
| | ) | |
| Defendant. | ) | |
| | ) | |

**PLAINTIFF'S MOTION FOR SUMMARY JUDGMENT**

Pursuant to Federal Rule of Civil Procedure 56, plaintiff Public Citizen moves for summary judgment because no genuine issue of material fact exists and plaintiff is entitled to judgment as a matter of law. In support of this motion, Public Citizen submits a memorandum of law, a statement of undisputed material facts with Exhibits A-G, and a proposed order.

Respectfully submitted,

*/s/ Michael T. Kirkpatrick*

Michael T. Kirkpatrick (DC Bar #486293)
Julia M. Graff (DE Bar #4708)
(DC Bar application pending)
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(202) 588-1000

Dated: June 9, 2008

Attorneys for Plaintiff

**UNITED STATES DISTRICT COURT**
**FOR THE DISTRICT OF COLUMBIA**

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| FOOD AND DRUG ADMINISTRATION, | ) | |
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| Defendant. | ) | |
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**PLAINTIFF'S MEMORANDUM IN SUPPORT**
**OF ITS MOTION FOR SUMMARY JUDGMENT**

Plaintiff Public Citizen brought this action under the Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. §§ 301-394, and the Administrative Procedure Act (APA), 5 U.S.C. §§ 702 and 706, to compel the United States Food and Drug Administration (FDA) to act on Public Citizen's petition seeking adequate warnings about the risk of tendon injury associated with fluoroquinolone antibiotics. On August 29, 2006, pursuant to 21 C.F.R. § 10.30, Public Citizen petitioned FDA to immediately add a black-box warning regarding the risks of tendinopathy and tendon rupture to the product labels of all fluoroquinolone antibiotics marketed in the United States, citing an alarming number of fluoroquinolone-induced tendon injuries reported to the agency. Public Citizen also urged FDA to mandate a "Dear Doctor" letter from fluoroquinolone manufacturers to warn physicians of these adverse effects and require the distribution of an FDA-approved Medication Guide for all patients, to be dispensed when the prescriptions are filled. Twenty-two months have passed since Public Citizen filed its petition, but FDA has neither granted nor denied the petition, nor has the agency taken action to warn physicians and patients about the risk of fluoroquinolone-induced tendinopathy and tendon rupture. These stronger warnings to doctors and patients could lead to

earlier intervention to stop tendon pain from progressing to frank tendon rupture by changing to other antibiotics. Therefore, to protect public safety and prevent needless injury, and for the reasons explained in detail below, the Court should grant plaintiff's motion for summary judgment and compel FDA to act on Public Citizen's petition.

**BACKGROUND**

Flouroquinolones are antibiotic drugs that are widely prescribed for gastrointestinal, respiratory, and genito-urinary tract infections. Flouroquinolone antibiotics presently on the market in the United States include ciprofloxacin (Cipro; Bayer); levofloxacin (Levaquin; Ortho-McNeil); moxifloxacin (Avelox; Bayer); norfloxacin (Noroxin; Merck); and ofloxacin (Floxin; Daiichi-Sankyo). Fact 1.[1] These antibiotics are drugs as defined by the FDCA. 21 U.S.C. § 321; Fact 2. The FDCA prohibits the introduction into interstate commerce of any drug that is misbranded. 28 U.S.C. § 331. A drug is misbranded unless its label bears adequate warnings. 28 U.S.C. § 352(f). By delegation from the Department of Health and Human Services, FDA is the agency responsible for administration of the FDCA, and FDA regulates the content and format of prescription drug labeling. FDA regulations permit concerned individuals to petition the FDA to take administrative action, and the FDA must respond to each petition within 180 days. 21 C.F.R. § 10.30(e)(1), (e)(2). The agency may approve or deny the petition or issue a tentative response "indicating why the agency has been unable to reach a decision on the petition . . . ." *Id.* Tentative responses "may also indicate the likely ultimate agency response and may specify when a final response may be furnished." *Id.*

[1]Pursuant to Local Rules 7(h) and 56.1, plaintiff's statement of undisputed material facts with attached exhibits accompanies this memorandum and will be cited as "Fact" and Ex." followed by the corresponding number or letter.

There is a well-established link between the use of flouroquinolone antibiotics and tendon injury. Tendinopathy and tendon rupture associated with flouroquinolone antibiotics have been observed since at least 1988, and reports of flouroquinolone-induced tendon injuries have appeared repeatedly in the medical literature. Fact 3; Exs. A, C, & E (citing medical literature).

In August 1996, Public Citizen successfully petitioned FDA to place a warning regarding the risk of tendon injury on the package inserts of all flouroquinolones. Fact 4; Ex. A. FDA issued a statement in the October 1996 issue of its Medical Bulletin to all manufacturers of flouroquinolones requesting a revision of the package inserts to include a new paragraph in the "Warnings" section acknowledging the risk of tendonitis and tendon rupture in patients using flouroquinolones. Fact 4; Ex. B. The warning is among a list of other potential side effects and is in plain, non-bold type. Although it was thought that at the time that such a warning would effectively educate physicians and patients about this serious adverse event, a simple non-bolded warning buried in a list of possible adverse reactions to flouroquinolones has proved inadequate. Flouroquinolone-induced tendon injuries continue to occur at an alarming rate.[2] Fact 5.

On May 18, 2005, the Office of the Illinois Attorney General submitted a citizen petition to FDA, requesting that the agency revise the labels on all flouroquinolone antibiotics to increase warnings about the risk of tendinopathy and tendon rupture; add a black-box warning; require manufacturers to issue a "Dear Health Care Professional" letter informing health care providers of

[2]For example, from November 1997 through December 31, 2005, FDA's adverse event database received reports of 262 cases of tendon ruptures, 258 cases of tendinitis, and 274 cases of other tendon disorders in patients using flouroquinolone antibiotics. Because only a small fraction of adverse events typically are reported to FDA, the actual number of injuries attributable to flouroquinolones is considerably higher. Analysis of the entire FDA adverse events database reveals that flouroquinolones are implicated significantly more often in tendon ruptures than any other class of drugs. Ex. E.

these adverse effects; supplement information provided to patients with bolded warnings; and submit the issue for review and analysis to FDA's Drug Safety Oversight Board. Fact 6, Ex. C. On November 16, 2005, FDA issued a tentative response that it had been unable to resolve the issues in the Illinois Attorney General's petition because the petition raises "complex issues requiring extensive review and analysis by Agency officials." Fact 6; Ex. D. FDA did not indicate the likely ultimate agency response and did not specify when a final response would be furnished. To date, FDA has not ruled on the Illinois Attorney General's petition. *Id.*

On August 29, 2006, Public Citizen petitioned FDA to add a black-box warning regarding the risks of tendinopathy and tendon rupture to the product labels of all fluoroquinolone antibiotics. Public Citizen also urged FDA to mandate a "Dear Doctor" letter from fluoroquinolone manufacturers to warn physicians of these adverse effects and require the distribution of an FDA-approved Medication Guide for all patients, to be dispensed when the prescriptions are filled. Fact 7; Ex. E. The Illinois Attorney General submitted a letter in support of Public Citizen's petition. Fact 7; Ex. F. On February 26, 2007, FDA issued a tentative response to Public Citizen's petition. FDA stated that it had been unable to resolve the issues in the petition because the petition raises "complex issues requiring extensive review and analysis." Fact 7; Ex. G. FDA did not indicate the likely ultimate agency response and did not specify when a final response would be furnished. To date, FDA has not ruled on Public Citizen's petition. *Id.*

## ARGUMENT

### I. SUMMARY JUDGMENT STANDARD

Under Rule 56 of the Federal Rules of Civil Procedure, a motion for summary judgment should be granted if it is shown "that there is no genuine issue as to any material fact and that the movant is entitled to judgment as a matter of law." Fed. R. Civ. P. 56(c). The moving party's "initial responsibility" consists of "informing the district court of the basis for its motion, and identifying those portions of the pleadings, depositions, answers to interrogatories, and admissions on file, together with the affidavits, if any, which it believes demonstrate the absence of a genuine issue of material fact." *Celotex Corp. v. Catrett*, 477 U.S. 317, 323 (1986) (internal quotation marks omitted). If the moving party meets its burden, the burden then shifts to the non-moving party to establish that a genuine issue as to any material fact actually exists. *See Matsushita Elec. Indus. Co. v. Zenith Radio Corp.*, 475 U.S. 574, 586 (1986). To meet this burden, the non-moving party must submit evidence that would permit a reasonable fact-finder to return a verdict in favor of the non-moving party. *Laningham v. United States Navy*, 813 F.2d 1236, 1241 (D.C. Cir.1987) (citing *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 248 (1986)). Such evidence must consist of more than unsupported allegations or denials; rather, the non-moving party must set forth specific facts showing that there is a genuine issue for trial. Fed. R. Civ. P. 56(e); *Celotex*, 477 U.S. at 321 n. 3. If the evidence is "merely colorable, or is not significantly probative, summary judgment may be granted." *Anderson*, 477 U.S. at 249-50.

## II. FDA HAS UNREASONABLY DELAYED ACTION ON PUBLIC CITIZEN'S PETITION.

The APA directs agencies to conclude matters presented to them "within a reasonable time," 5 U.S.C. § 555(b), and instructs reviewing courts to "compel agency action unlawfully withheld or unreasonably delayed . . . ." 5 U.S.C. § 706(1). The D.C. Circuit has identified three "factors that aid in determining whether an agency's foot-dragging constitutes unreasonable delay." *Cutler v. Hayes*, 818 F.2d 879, 897 (D.C. Cir. 1987).[3] First, the court should "ascertain the length of time that has elapsed since the agency came under a duty to act, and should evaluate any prospect of early completion." *Cutler*, 818 F.2d at 897; *see also Public Citizen Health Research Group (PCHRG) v. FDA*, 740 F.2d 21, 32 (D.C. Cir. 1984) ("There must be a 'rule of reason' to govern the time limit to administrative proceedings.") (citation omitted). Although "[t]here is 'no per se rule as to how long is too long' to wait for agency action, [] a reasonable time for agency action is typically counted in weeks or months, not years." *In re Am. Rivers & Idaho Rivers United*, 372 F.3d at 419 (citation omitted).

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[3]The three guidelines in *Cutler* reflect the six considerations enumerated in *Telecommunications Research & Action Center (TRAC) v. FCC,* 750 F.2d 70, 80 (D.C. Cir. 1984):

> (1) the time agencies take to make decisions must be governed by a rule of reason; (2) where Congress has provided a timetable or other indication of the speed with which it expects the agency to proceed in the enabling statute, that statutory scheme may supply content for this rule of reason; (3) delays that might be reasonable in the sphere of economic regulation are less tolerable when human health and welfare are at stake; (4) the court should consider the effect of expediting delayed action on agency activities of a higher or competing priority; (5) the court should also take into account the nature and extent of the interests prejudiced by delay; and (6) the court need not find any impropriety lurking behind agency lassitude in order to hold that agency action is unreasonably delayed.

*Id.* (citations and quotation marks omitted); *see also In re Am. Rivers & Idaho Rivers United*, 372 F.3d 413, 418 (D.C. Cir. 2004) (quoting the *TRAC* standard).

Second, "[t]he reasonableness of the delay must be judged 'in the context of the statute' which authorizes the agency's action." *Cutler*, 818 F.2d at 897 (quoting *Public Citizen Health Research Group (PCHRG) v. Auchter*, 702 F.2d 1150, 1158 n.30 (D.C. Cir. 1983)); *National Congress of Hispanic Am. Citizens v. Marshall*, 626 F.2d 882, 888 (D.C. Cir. 1979)). As part of this inquiry, a court must consider "the extent to which delay may be undermining the statutory scheme . . . by frustrating the statutory goal . . . ." *Id.* at 897-98. Thus, where the "agency is charged with the administration of a statutory scheme whose paramount concern is protection of the public health, the pace of agency decision-making must account for this statutory concern." *PCHRG v. FDA*, 740 F.2d at 34.

Third, "and perhaps most critically, the court must examine the consequences of the agency's delay." *Cutler*, 818 F.2d at 898. "The deference traditionally accorded an agency to develop its own schedule is sharply reduced when injury likely will result from avoidable delay." *Id.* Accordingly, "'[d]elays that might be altogether reasonable in the sphere of economic regulation are less tolerable when human lives are at stake[,]" *id.* (quoting *PCHRG v. Auchter*, 702 F.2d at 1157), and "[l]ack of alternative means of eliminating or reducing the hazard necessarily adds to unreasonableness of a delay." *Id.*

In this case, application of the *Cutler* factors demonstrates that FDA's failure to address Public Citizen's petition constitutes unreasonably delayed agency action.

**1. Length of the Delay.** It has been nearly two years since Public Citizen filed the petition at issue, and more than three years since the Illinois Attorney General filed a similar petition. Thus, there is no "prospect of early completion." *See id.*, 818 F.2d at 897. Further, FDA's regulations suggest that the agency should rule on citizen petitions within 180 days unless there is a compelling need for

additional time. FDA is required to respond to citizen petitions within 180 days by approving or denying the petition, or by providing a "tentative response, indicating why the agency has been unable to reach a decision on the petition . . . . The tentative response . . . may specify when a final response may be furnished." 21 C.F.R. § 10.30(e)(2). Here, FDA responded to the petitions filed by Public Citizen and the Illinois Attorney General with the same boilerplate language: "FDA has been unable to reach a decision on your petition because it raises complex issues requiring extensive review and analysis by Agency officials." Exs. D & G. FDA has offered no other justification for the delay and FDA has not specified "when a final response may be furnished." 21 C.F.R. § 10.30(e)(2). Thus, FDA's delay is unreasonable in light of the policy evinced by its own regulations.

**2. Statutory Context.** FDA's delay in acting on Public Citizen's petition is particularly unreasonable when considered in the context of the FDCA, as amended by the Food and Drug Administration Amendments Act of 2007 (FDAAA). The purpose of the FDCA is to protect public health, and it is clear that Congress intends for FDA to move quickly to effect labeling changes necessary to protect public safety. In September 2007, Congress passed the FDAAA to enhance FDA's ability to require labeling changes. Once FDA becomes aware of the need for labeling changes, the Act provides a framework to ensure that such changes are made expeditiously. Where such labeling change is needed, FDA "shall promptly notify the responsible person" who must then respond to the notification "within 30 days." 21 U.S.C. § 355(*o*)(4)(A) & (B). Subsequent discussions regarding labeling changes "shall not extend for more than 30 days after the response to the notification" and FDA may order labeling changes "[w]ithin 15 days of the conclusion of the discussions" and such orders must be acted upon within 15 days or appealed within 5 days. 21

U.S.C. § 355(*o*)(4)(D)(E) & (F). Moreover, if FDA "concludes that [] a labeling change is necessary to protect the public health," FDA "may accelerate the[se] timelines . . . ." 21 U.S.C. § 355(*o*)(4)(H). Thus, although the FDCA does not provide a specific deadline by which FDA must issue a final ruling on a citizen petition, the statutory scheme shows that FDA is expected to move quickly to provide warnings needed to mitigate drug risk. *See PCHRG v. FDA*, 740 F.2d at 34 ("When the public health may be at stake, the agency must move expeditiously to consider and resolve the issue before it.") (citing *PCHRG v. Auchter*, 702 F.2d at 1158); *accord Public Citizen Health Research Group (PCHRG) v. Brock*, 823 F.2d 626, 629 (D.C. Cir. 1987) ("When lives are at stake, as they assuredly are here, [the agency] must press forward with energy and perseverance[.]").

**3. Consequences.** The consequence of FDA's delay is needless injury. While FDA delays action on Public Citizen's petition, fluoroquinolone-induced tendon injuries continue to occur. Many of these injuries could be prevented by the enhanced warnings sought by Public Citizen, because such warnings would lead to earlier intervention to stop tendon pain from progressing to frank tendon rupture.

## CONCLUSION

For the foregoing reasons, the Court should grant plaintiff's motion for summary judgment, declare that FDA's failure to act on Public Citizen's petition constitutes agency action unlawfully withheld or unreasonably delayed, and order FDA to issue a decision on Public Citizen's petition.

Respectfully submitted,

*/s/ Michael T. Kirkpatrick*

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Dated: June 9, 2008

Attorney for Plaintiff

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**PLAINTIFF'S STATEMENT OF MATERIAL FACTS**
**AS TO WHICH THERE IS NO GENUINE ISSUE**

Pursuant to Local Rules 7(h) and 56.1, plaintiff Public Citizen submits this statement of material facts as to which there is no genuine issue in support of its motion for summary judgment.

1. Flouroquinolones are a class of prescription antimicrobial drugs used to treat various bacterial infections and microorganisms in patients. Flouroquinolone antibiotics presently on the market in the United States include ciprofloxacin (Cipro; Bayer); levofloxacin (Levaquin; Ortho-McNeil); moxifloxacin (Avelox; Bayer); norfloxacin (Noroxin; Merck); and ofloxacin (Floxin; Daiichi-Sankyo). Answer [Doc. 5] ¶ 5.

2. Flouroquinolones are drugs within the meaning of the FDCA, 21 U.S.C. § 321(g)(1), and new drugs within the meaning of 21 U.S.C. § 321(p). Answer [Doc. 5] ¶ 6.

3. There is a link between the use of flouroquinolone antibiotics and tendon injury. Tendinopathy and tendon rupture associated with flouroquinolone antibiotics have been observed since at least 1988, and reports of flouroquinolone-induced tendon injuries have appeared repeatedly in the medical literature. Answer [Doc. 5] ¶ 8; *see* Exs. A, C, & E (citing medical literature).

4. On August 1, 1996, Public Citizen petitioned FDA to require a warning on all fluoroquinolone antibiotics regarding the risk of tendon injury. Ex. A. In the October 1996 issue of its Medical Bulletin, FDA asked prescribers and pharmacists to alert patients and other caregivers to the potential for tendinitis and tendon rupture while taking or after taking antimicrobial fluoroquinolones. FDA also announced that it was taking steps to have the manufactureres revise the package inserts to include warnings regarding the risk of tendon rupture. "Reports of Adverse Events with Fluoroquinolones," FDA Medical Bulletin (Oct. 1996) (attached as Ex. B); *see also* Answer [Doc. 5] ¶¶ 9 & 11.

5. Despite the revisions to the "WARNINGS" sections of the package inserts to address the risk of tendon injury associated with fluoroquinolones, such injuries have continued to be reported to FDA's adverse events database. Answer [Doc. 5] ¶¶ 10 & 11.

6. On May 18, 2005, the Office of the Illinois Attorney General submitted a citizen petition to FDA, requesting that the agency revise the labels on all flouroquinolone antibiotics to increase warnings about the risk of tendinopathy and tendon rupture; add a black-box warning; require manufacturers to issue a "Dear Health Care Professional" letter informing health care providers of these adverse effects; supplement information provided to patients with bolded warnings; and submit the issue for review and analysis to FDA's Drug Safety Oversight Board. Ex. C. On November 16, 2005, FDA issued a tentative response that it had been unable to resolve the issues in Illinois Attorney General's petition because the petition raises "complex issues requiring extensive review and analysis by Agency officials." Ex. D. FDA did not indicate the likely ultimate agency response, and did not specify when a final response would be furnished. *Id.* To date, FDA has not ruled on the Illinois Attorney General's petition. Answer [Doc. 5] ¶ 15.

7. On August 29, 2006, Public Citizen petitioned FDA to add a black-box warning regarding the risks of tendinopathy and tendon rupture to the product labels of all fluoroquinolone antibiotics. Public Citizen also urged FDA to mandate a "Dear Doctor" letter to warn physicians of these adverse effects and require the distribution of an FDA-approved Medication Guide for all patients, to be dispensed when the prescriptions are filled. Ex. E. On August 29, 2006, the Office of the Illinois Attorney General submitted a letter to FDA in support of Public Citizen's petition. Ex. F. On February 26, 2007, FDA issued a tentative response to Public Citizen's petition. Ex. G. FDA stated that it had been unable to resolve the issues in the petition because the petition raises "complex issues requiring extensive review and analysis." *Id.* FDA did not indicate the likely ultimate agency response, and did not specify when a final response would be furnished. To date, FDA has not ruled on Public Citizen's petition. Answer [Doc. 5] ¶¶ 14 & 17.

Respectfully submitted,

*/s/ Michael T. Kirkpatrick*

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Dated: June 9, 2008

Attorneys for Plaintiff

# EXHIBIT A

# Petition to Require a Warning on All Fluoroquinolone Antibiotics (HRG Publication #1399)

August 1, 1996

David A. Kessler, M.D., J.D.
Commissioner, Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Petition To Require A Warning On All Fluoroquinolone Antibiotics

Dear Dr. Kessler:

Based on more than 130 reports of tendon inflammation (many involving rupture), most frequently involving the Achilles tendon, in persons using the widely-prescribed class of antibiotics known as fluoroquinolones, Public Citizen, representing consumers nationwide, hereby petitions the F.D.A., pursuant to the Federal Food, Drug and Cosmetic Act 21, U.S.C. Section 355(e)(3), and C.F.R. 10.30, to add a warning about this serous problem to the label of all fluoroquinolone antibiotics marketed in the United States. These include: ciprofloxacin (Cipro, Bayer Corporation), enoxacin (Penetrex, Rhone-Poulenc Rorer), lomefloxacin (Maxaquin, G.D. Searle), norfloxacin (Noroxin, Merck & Company), and ofloxacin (Floxin, McNeil Pharmaceutical). (In 1995, there were 14.4 million prescriptions filled for these antibiotics in U.S. retail pharmacies according to data from IMS.) In addition, consumers must be warned through F.D.A. approved MedGuides (patient package inserts) how to recognize and react to this potentially serious adverse effect of fluoroquinolone antibiotics.

Only one fluoroquinolone antibiotic sold in the U.S., ofloxacin (Floxin) (which accounts for less than one-fifth of fluoroquinolone prescriptions), now carries any statement that tendinitis or rupture have been reported with its use, but even this statement is in a part of the label which misleadingly implies that tendon damage may have no relationship to using the drug.[1]

Doctors and the public must be warned to immediately discontinue use of fluoroquinolone antibiotics at the onset of tendon pain. The frequency of tendon damage from fluoroquinolones is unknown, but Achilles tendon rupture is a serious condition, often requiring surgical repair. Prompt cessation of use of these antibiotics if patients get tendinitis may avoid the progression to frank rupture of the Achilles or other tendons.

**Summary Of Evidence**

1. In France, 100 patients have been identified who had tendon disorders associated with the use of fluoroquinolone antibiotics, including 31 tendon ruptures.[2],[3]

2. British drug regulatory authorities have received 21 reports of tendon damage associated with fluoroquinolone antibiotics. In 15 of the 21 cases the Achilles tendon was involved. Severity ranged from tendinitis to partial or complete tendon rupture.[4]

3. Doctors in Belgium have reported that out of 230 renal transplant recipients 11 developed an Achilles tendon problem while taking fluoroquinolone antibiotics.[5]

4. In a letter published in January 1995, based on similar reports in F.D.A. files, including tendon ruptures occurring in the United States and published articles, F.D.A staff stated that the agency "will update the labeling [package insert] for all marketed fluoroquinolones to include a warning about the possibility of tendon rupture."[6]

Although F.D.A.'s legal mandate is to protect the public's health, the agency has behaved irresponsibly by failing to take action on a serious problem it has known about for at least 18 months. The situation concerning these drugs is especially dreadful. Despite the fact that the fluoroquinolones are essentially second-line drugs, there being few clinical situations in which they would be the first choice to treat an infection, they are heavily promoted and are often used as first-line drugs in situations where an equally or more effective, less expensive and possibly safer antibiotic would be preferable.

**Actions Requested**

1. Immediately require a warning in bold type in the official product labeling (package insert) for all fluoroquinolone antibiotics sold in the U.S. (see suggested wording below).

2. Immediately require that a MedGuide (patient package insert) be distributed with all new and refill fluoroquinolone prescriptions warning the public of possible tendon damage and informing the public to stop using the drug and contact their physicians if tendon pain develops (see suggested wording below).

3. Immediately inform all U.S. physicians through a "Dear Doctor Letter" by registered mail about the risk of tendon rupture with fluoroquinolone antibiotics.

4. Immediately inform all other U.S. health professionals through the *F.D.A. Medical Bulletin* about the new warning.

**Warning Label for Fluoroquinolone Antibiotics**

The following bold warning should be required in the doctor and pharmacist labelling for all fluoroquinolone antibiotics sold in the U.S.:

**Tendinitis and rupture have been reported both in the U.S. and abroad from the use of fluoroquinolone antibiotics most frequently involving the Achilles tendon. Reports have also been made involving the rotator cuff (the shoulder), the hand, the long tendon of the biceps and the long extensor of the thumb. This appears to be a rare but potentially serious class effect of fluoroquinolone antibiotics.**

**This reaction appears to be more common in those treated concurrently with corticosteroids; with increasing age; and in renal transplant recipients but cases have occurred in people without any of these risk factors. Onset of symptoms is sudden and has occurred as soon as 24 hours after beginning treatment. Most patients have recovered completely after one to two months.*The onset of tendon pain calls for immediate withdrawal of fluoroquinolone antibiotics.***

**Medication Guide--Informing the Public**

It is mandatory that the public have information about this adverse reaction. The public must know when and how to react to protect themselves at the first sign of an adverse drug reaction. Serious tendon damage may be averted only if the patient taking a fluoroquinolone antibiotic stops the drug at the first sign of tendon inflammation.

In its announcement proposing Medication Guides (patient package inserts) to provide prescription drug consumers with comprehensive and reliable drug information, the F.D.A. stated "F.D.A. believes that improved dissemination of information about prescription drug products is necessary to fulfill patients' need and right to be informed." and the F.D.A. would require approved Medication Guides for products "that pose a serious and significant public health concern" requiring immediate distribution of drug information to the public.[7]

The accumulating evidence presented in this petition clearly identifies the fluoroquinolone antibiotics as drugs that pose a significant public health concern.

The following language is suggested for all patient Medication Guides for all fluoroquinolone antibiotics:

**The fluoroquinolone family of antibiotics includes: ciprofloxacin (Cipro), enoxacin (Penetrex), lomefloxacin (Maxaquin), norfloxacin (Noroxin), and ofloxacin (Floxin). These drugs have been reported to cause tendon inflammation and sometimes rupture (breakage). Most often this adverse drug effect has involved the Achilles tendon (the tendon running from the heel to the calf muscle). However, other areas of the body and tendons have also been effected. These include the area of the shoulder known as the rotator cuff, hand, long tendon of the biceps (muscle on the front of the upper arm) and the long tendon at the back of the thumb. This reaction appears to be more common in those people also being treated with oral steroid drugs such as prednisone (Deltasone), prednisolone (Delta-Cortef), dexamethasone (Decadron) and methylprednisolone (Medrol); in older persons; and in renal transplant recipients. But cases have occurred in people who do not fall into any of these three risk categories.**

**This is a rare but potentially serious adverse effect of all the fluoroquinolone family of antibiotics.**

**At the first sign of pain or inflammation that might be an indication of tendon damage stop taking the drug to reduce the likelihood that tendon rupture will occur and contact your doctor immediately to discuss the use of an alternative antibiotic. You should refrain from exercise until the diagnosis of tendinitis can be confidently excluded.**

**Statement of Grounds**

Fifteen case reports in the medical literature now describe in detail persons who have suffered tendon inflammation or rupture while taking a fluoroquinolone antibiotic; three of these are in renal transplant recipients. In France, 100 cases have been identified and from the U.K. 21 cases. In Belgium, 11 cases have been reported in renal transplant recipients.

Tables 1 and 2 below outline cases of tendon damage linked to fluoroquinolone antibiotics reported in the medical literature. In Table 2 are the cases of tendon damage in renal transplant recipients who used fluoroquinolones. The case reported is cited, the fluoroquinolone antibiotic implicated is listed along with the reason it was prescribed. After listing the age and gender of the patients, the details of the adverse reaction and the time of onset of symptoms after the drug was started are given.

**Table 1 - Case Reports of Fluoroquinolone Tendinitis or Rupture Reported in the Medical Literature**

| *Report* | *Fluoroquinolone/Dose/Reason for Treatment* | *Age/Sex* | *Onset of Symptons/Clinical Course* |
|---|---|---|---|
| Huston (1994)[8] | Enoxacin 400 mg twice daily for urinary infection | 85/M | Symptoms day 7<br>Bilateral Achilles tendinitis and right tendon rupture on day 14 |
| Borderie et al. (1993)[9] | Type of fluoroquinolone not stated.<br>Used for septic arthritis of the hip | 57/M | Spontaneous rupture of rotator cuff without trauma 28 days after starting treatment |
| | Type of fluoroquinolone not stated.<br>Used for septic arthritis of the knee | 61/M | Spontaneous rupture of rotator cuff without trauma 25 days after starting treatment |
| Ribard et al. (1992)[10] | Pefloxacin[a] 800 mg daily for bladder infection | 49/M | Symptoms after 24 hours Achilles tendinitis and tendon rupture on day 8 |
| | Pefloxacin 800 mg daily to prevent surgical infection | 75/M | Symptoms after 24 hours<br>Unilateral Achilles tendinitis only |
| | Ofloxacin 400 mg daily for bladder infection | 86/F | Symptoms after 72 hours<br>Unilateral Achilles tendinitis only |
| | Pefloxacin 800 mg daily for infection of the vertebrae | 68/M | Symptoms at 5 months<br>Bilateral Achilles tendinitis and tendon rupture day 60 |
| | Pefloxacin 800 mg daily for bladder infection | 40/F | Symptoms after 48 hours Achilles tendinitis and tendon rupture day 90 |
| | Ofloxacin 400 mg daily for bronchitis | 67/M | Symptoms after 8 days<br>Bilateral Achilles tendinitis only |
| | Pefloxacin 400 mg daily for sore throat | 70/M | Symptoms after 5 days Unilateral Achilles tendinitis only |
| McEwan and Davey (1988)[11] | Ciprofloxacin 750 mg twice daily for chest infection | 67/M | Symptoms after 3 days<br>Bilateral Achilles tendinitis only |

[a] Pefloxacin is not available in the United States

**Table 2 - Case Reports of Fluoroquinolone Associated Tendinitis or Rupture Reported in Renal Transplant Recipients in the Medical Literature**

| *Report* | *Fluoroquinolone/Dose/Reason for Treatment* | *Age/Sex* | *Onset of Symptoms/ Clinical Course* |
|---|---|---|---|
| Gillet et al. (1995)[12] | Norfloxacin 400 mg twice daily for urinary tract infection | 40/F | Symptoms after 8 days<br>Inflammation of the long tendon of the thumb |
| Lee and Collins (1992)[13] | Ciprofloxacin 500 mg twice daily for abdominal cavity infection | 33/M | Symptoms after 4 days<br>Bilateral Achilles tendon rupture |

| | | | |
|---|---|---|---|
| Bailey et al (1983)[14] | Norfloxacin for persistent urinary tract infection. Dose not stated. | 56/M | Symptoms after 13 days<br>Bilateral Achilles tendinitis |
| | Norfloxacin for persistent epididymo-orchitis and urinary tract infection. Dose not stated. | 34/M | Symptoms after 31 days<br>Acute pain, tenderness and swelling of tendon of the middle finger, of both hands.<br>Acute pain right ankle and hip |

**French Report of Fluoroquinolone Associated Tendinitis or Rupture**

Between 1985 and July 1992 100 cases of tendon disorders, including 31 ruptures had been identified in France. The ratio of men to women experiencing a tendon disorder was three-to-one in these cases. Their average age was 63 years and many had received steroid therapy. The Achilles tendon was affected most often and half the patients experienced bilateral tendinitis. Other tendons were also involved, such as the long head of the biceps and the long extensor of the thumb. The average time between the start of treatment and the onset of symptoms was 13 days, however in a few patients the tendinitis appeared within one or two days.[2,3]

Since 1992, French physicians have been informed of the risk of fluoroquinolone induced tendinitis as well as guidelines to prevent rupture.[2,3]

**British Report of Fluoroquinolone Associated Tendinitis or Rupture**

The U.K. Committee On Safety of Medicines (C.S.M.), the British equivalent of the F.D.A., has received 21 reports of tendon damage associated with fluoroquinolone antibiotics; 11 occurring with ciprofloxacin and 10 with ofloxacin. The reactions reported varied in severity from tendon inflammation to partial or complete rupture. In 15 of the 21 patients the Achilles tendon was involved. The C.S.M. stated that use of steroids may increase the risk of tendon damage and the adverse reaction appears to be common with increasing age.[4]

Additional cases of tendon damage in patients taking fluoroquinolone antibiotics have been received by the C.S.M. since their original report but the agency has not disclosed the number of such cases. The professional product information (package inserts) for ciprofloxacin, norfloxacin and ofloxacin sold in the U.K. contain clear warnings of the risk of tendon damage.[15]

**Belgian Report of Fluoroquinolone Associated Tendinitis or Rupture in Renal Transplant Recipients**

In Belgium, the records of 230 patients who received renal transplants between January 1, 1991 and December 31, 1992 were reviewed by researchers. Ninety patients were treated at least once with a fluoroquinolone antibiotic and 140 had never received a fluoroquinolone during the study period. In those treated with a fluoroquinolone there were 11 who developed an Achilles tendon problem; 7 with unilateral tendon inflammation, 1 case of unilateral inflammation and subsequent rupture, 2 cases of inflammation of both Achilles tendons, and 1 case of inflammation of both tendons with a single tendon rupture. Overall the incidence of Achilles tendon inflammation and rupture was 7 percent. In the subgroup of patients who were treated with fluoroquinolones, the incidence was 12 percent compared to none in those who had never received a fluoroquinolone antibiotic.[5]

**FDA Reports of Fluoroquinolone Associated Tendinitis or Rupture**

Through the third quarter of 1995 the F.D.A. had received 52 reports of tendon damage, including 38 ruptures, associated with fluoroquinolone antibiotic use (Table 3 below). The F.D.A.'s data base contains 1,100,000 adverse reaction reports and only 87 reports link any drug to tendon rupture but fluoroquinolone antibiotics accounted for more than 43 percent of these drug-associated tendon rupture cases. In contrast, of these 1,100,000 adverse reaction reports in the FDA data base, 14,067 or only 1.3% were for these five fluoroquinolones. This significant (33-fold) over-representation of fluoroquinolone use among cases of Achilles tendon rupture argues strongly in favor of a causal role of these drugs. Many of the reports in FDA's data base are from foreign countries but some are from the U.S.

**Table 3 - Reports of Tendinitis or Rupture with Fluoroquinolone Antibiotics Through the Third Quarter of 1995 - F.D.A. Adverse Drug Reaction Data Base**

| *Fluoroquinolone/ Date Marketed in the U.S.* | *Total Number of Adverse Reaction Reports* | *Number of Reports Tendinitis or Rupture* | *Number of Reports Ruptures Only* |
|---|---|---|---|
| Lomefloxacin (Maxaquin) 1992 | 1,404 | 1 | 0 |

| | | | |
|---|---|---|---|
| Enoxacin (Penetrex) 1991 | 59 | 1 | 1 |
| Ofloxacin (Floxin) 1990 | 4,410 | 15 | 7 |
| Ciprofloxacin (Cipro) 1987 | 6,513 | 12 | 9 |
| Norfloxacin (Noroxin) 1986 | 1,681 | 23 | 21 |
| TOTAL | 14,067 | 52 | 38 |

**Actual Incidence of Fluoroquinolone Associated Tendinitis or Rupture (as opposed to spontaneously/passively reported cases)**

Tendinitis or tendon rupture associated with prescription drug use appears to be a rare adverse event. However, a low number of adverse reaction reports may result for one of two reasons. First, the adverse reaction is truly rare. Second, the adverse reaction is grossly under-reported because the association between a drug and an adverse effect seems so unlikely that the adverse event is not attributed to the drug by prescribers. Assuming that a small number of reports indicates a rare adverse drug reaction can therefore be a dangerous assumption.

A report from the 17th French Pharmacovigilance Meeting illustrates the hazard of making the assumption that an adverse reaction is rare based on the number of adverse reactions spontaneously reported to drug regulatory authorities. The Nancy (France) pharmacovigilance centre studied the frequency of adverse drug reaction reports per 100,000 patients of rheumatological adverse effects of fluoroquinolone antibiotics such as joint pain and tendon damage using three different methods.

Method one was traditional spontaneous reporting. This is the same system used in the U.S. If an adverse reaction is suspected by a health professional the reaction is hopefully reported to the F.D.A. Method two was "encouraged" reporting in which prescribers were asked by Nancy pharmacovigilance centre if they had observed rheumatological side effects with fluoroquinolones. Method three was termed "reinforced" reporting. Prescribers of fluoroquinolones were identified using prescription records and were asked the same questions about fluoroquinolones by social security authorities.

The reporting of adverse rheumatological effects from fluoroquinolones varied enormously between the three methods. The traditional spontaneous reporting system produced 1 report per 100,000 patients; "encouraged" reporting 18 per 100,000; and the "reinforced" method 342 reports of adverse rheumatological effects --including joint pain and tendon damage--per 100,000 patients.[16] Thus, the rate of reports of these adverse reactions to fluoroquinolones was 342 times higher in the group of doctors identified as having prescribed the drugs and specifically asked if they had observed these adverse reactions.

**FDA Inaction**

In a January 19, 1995 letter to the *New England Journal of Medicine* F.D.A. staff wrote that the agency knew of 25 cases of tendon rupture, 22 of them occurring outside the U.S. In this letter it was stated on the basis of postmarketing reports and published articles, the F.D.A."will update the labeling [package insert] for all marketed fluoroquinolones to include a warning about the possibility of tendon rupture." The updated product labeling would also include a recommendation to discontinue treatment with these drugs at the first sign of tendon pain or inflammation and to refrain from exercise until the diagnosis of tendinitis can be confidently excluded.[6]

**Conclusion**

It is 18 months since F.D.A. staff published their letter and the agency now has at least 38 reports of tendon rupture. This includes 12 reported hospitalizations from fluoroquinolone antibiotics. Yet, nothing has been done to warn doctors, pharmacists or the public about this potentially serious adverse effect. This is irresponsible.

British and French package inserts for the very same drugs warn doctors and pharmacists about the risk of tendon damage. In the rest of Europe, consumers are warned of possible tendon damage from fluoroquinolone antibiotics. European Community regulations now require that prescription drug consumers receive drug information written specifically for them that accurately reflects the same information given to doctors and pharmacists with each new and refill prescription. Sadly, this simple solution--routine patient package inserts for all prescription drugs--to preventing drug induced injury has been denied to U.S. consumers by organized pharmacy and medicine and the drug industry since the early 1980s. Very recently, attempts have been made in Congress to pass legislation which would stop the FDA from implementing programs to increase the number of patient package inserts and thereby

allow U.S. consumers to receive objective useful information about prescription drugs.

**Certification**

We certify that, to our best knowledge and belief, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

Sincerely,

Larry D. Sasich, Pharm.D., FASHP
Research Analyst
Public Citizen's Health Research Group

Sidney M. Wolfe, M.D.
Director
Public Citizen's Health Research Group

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# EXHIBIT B

U.S. Food and Drug Administration

FDA Medical Bulletin * October 1996 * Volume 26 Number 3

# REPORTS OF ADVERSE EVENTS WITH FLUOROQUINOLONES

FDA is asking prescribers and pharmacists to alert patients and other caregivers to the potential for tendinitis and tendon rupture while taking or after taking antimicrobial fluoroquinolones. The Agency has taken steps to have the package insert revised for the following antimicrobial agents: ciprofloxacin, enoxacin, lomefloxacin, norfloxacin, and ofloxacin. Letters have been issued to the manufacturers requesting that they revise their package inserts to include the following information: The **WARNINGS** section will have a new paragraph that should read: "Ruptures of the shoulder, hand, and Achilles tendons that required surgical repair or resulted in prolonged disability have been reported with [the specific drug name]. [The specific drug name] 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 confidently excluded. Tendon rupture can occur at any time during or after therapy with [the specific drug name]."

As an added precaution, the following statement will be added to the **Information for Patients** subsection of the **PRECAUTIONS** section: "Patients should be advised to discontinue treatment and inform their physician if they experience pain, inflammation, or rupture of a tendon, and to rest and refrain from exercise."

The revisions have been made to the ciprofloxacin, enoxacin, and norfloxacin package inserts. The lomefloxacin and ofloxacin revisions should be completed shortly.

**REPORT SERIOUS ADVERSE EVENTS AND PRODUCT PROBLEMS TO MEDWATCH 1-800-FDA-1088**

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# EXHIBIT C

OFFICE OF THE ATTORNEY GENERAL
STATE OF ILLINOIS

Lisa Madigan
ATTORNEY GENERAL

May 18, 2005

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

**CITIZEN PETITION**

The undersigned submit this petition under the Federal Food, Drug, and Cosmetic Act to request the Commissioner of Food and Drugs to require manufacturers of the fluoroquinolone class of drugs to: 1) revise drug labeling to strengthen warnings of the potential for the serious adverse event of tendonopathy and tendon rupture; 2) create a "black box" warning to reflect the risk and the severity of this adverse side effect; 3) require manufacturers of fluoroquinolone antibiotics to issue a Dear Health Care Professional letter to inform health care providers about this significant hazard to health and announce the changes in drug package labeling; 4) supplement information provided to patients with bolded warnings about the risk of tendonopathy and tendon rupture; and 5) submit the class of fluoroquinolone drugs for review to the FDA's newly established Drug Safety Oversight Board.

**A. Action Requested**

On behalf of the Office of the Illinois Attorney General, we are writing to you to request action by your agency in regard to a medication side-effect, which although already recognized, is not well-known by practicing physicians and other health care

professionals. We are referring to the condition of fluoroquinolone-induced tendonopathy, including actual tendon ruptures, which can be multiple, can cause severe and protracted disability, and can require surgical correction. Specifically we request:

1. Revise drug labeling to strengthen warnings of the potential for the serious adverse event of tendonopathy and tendon rupture;

2. Create a "black box" warning to reflect the need to discontinue the use of Fluoroquinolone drugs at the onset of tendon pain. We suggest the use of the following language:

> **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.**

3. Require manufacturers to issue a Dear Health Care Professional letter to inform them about this significant hazard to health and announce the changes in drug package labeling;

4. Supplement information provided to patients with bolded warnings about the risk of tendonopathy and tendon rupture. We suggest the use of the following language:

> **The current family of fluoroquinolone antibiotics includes: ciprofloxacin (Cipro and generics), ofloxacin (Floxin and generics), levofloxacin (Levaquin), gatifloxacin (Tequin), moxifloxacin (Avelox). These medications have been known to cause serious tendonitis (inflammation) and even tendon rupture (breakage). Most often this adverse drug effect has involved the Achilles tendon ( the tendon running along the back side of the ankle) but has also involved the tendons of the shoulder, upper arm and hand. This reaction is more**

**common in older patients; people on corticosteroids such as prednisone, dexamethasone, prednisilone or methylprednisolone; and patients who have received kidney transplants. However, this complication has also occurred in people who do not fit into any of these categories.**

**At the first sign of pain or inflammation of a tendon, stop taking the medication and contact your doctor immediately. Refrain from exercise or excessive use of the joint until the diagnosis of tendonitis can be excluded.**

5. Finally, we recommend that fluoroquinolone antibiotics be reviewed by the FDA's newly established Drug Safety Oversight Board.

### B. Statement of Grounds

Our request for your action has been evoked by the fact that our office has received complaints from Illinois citizens who have suffered significantly from tendonopathies induced by their use of a fluoroquinolone antibiotic, namely Levaquin (Levofloxacin). These complaints motivated our office to conduct an extensive review of the medical literature, and to interview physicians on the staff of academic medical centers, about fluoroquinolone-induced tendonopathies. Our study has led us to conclude that fluoroquinolone-induced tendonopathies are not a rare complication of fluoroquinolone use, and also to realize that this serious side-effect is not adequately appreciated by practicing physicians. Since tendonopathies have been reported as an adverse effect from more than one fluoroquinolone antibiotic, we believe this complication is a therapeutic class characteristic. The current fluoroquinolone antibiotics available in the United States include: ciprofloxacin, ofloxacin, levofloxacin, gatifloxacin, and moxifloxacin. We recognize that the drug information documents distributed by the pharmaceutical manufacturers of fluoroquinolone antibiotics do mention that tendonopathy, including tendon rupture, can be caused by fluoroquinolone antibiotics. However, currently this information is buried in lists of potential side effects which are both less frequent and less severe. The prevalence of this serious side-effect, and the inadequate knowledge about it on the part of physicians and other health professionals, prompts us to write to you to ask that a "black-box" warning about fluoroquinolone-induced tendonopathy be required by your agency in all of the pharmaceutical manufacturers' drug information literature. In

addition, we feel it is necessary that your agency require pharmaceutical manufacturers to send a "Dear Health Care Professional" letter to practicing health care providers drawing their attention to this fluoroquinolone complication, such as your agency has appropriately done in regard to other pharmaceuticals in the past. We urge you to rewrite patient information with bolden information warning of this potentially devastating adverse side effect. Finally, fluroquinolone antibiotics should be re-evaluated by the newly established Drug Safety Oversight Board. Besides the risk of tendon rupture, there are other serious issues regarding this class of antibiotics such as cardiac arrhythmias.

We would like to share with you a brief summary of our review of the medical literature:

> Fluoroquinolones are modeled on naxadilic acid, a synthetic antibiotic approved by the U.S. Food and Drug Administration (FDA) in 1963 for the treatment of urinary tract infections.[1] In the 1980s, structural modifications improved their anti-bacterial activity, but also increased their potential toxicity to consumers.[1] In 1992, Abbott Laboratories recalled its drug Omniflox (temafloxacin) after several reports of liver failure and deaths.[2] In 1999, Raxar (grepafloxacin) was taken off the market by Glaxo Wellcome as a result of cardiac arrhythmias and seven deaths.[2] Later that year, the FDA restricted the use of Trovan (trovafloxacin, Pfizer) after more than a dozen reports of acute liver failure, five of which resulted in death.[2]
>
> Many adverse drug reactions of fluoroquinolones have been reported. The most common adverse effects are nausea and vomiting, diarrhea, headache, dizziness, rash, and increased sensitivity to the sun.[1] Fluoroquinolone-induced tendonopathy was noted as early as 1983.[3] The first case of a ciprofloxacin-induced tendon rupture was reported in 1987.[4] A pefloxacin-related tendon rupture reported in 1991 led to the published recognition of this complication in the VIDAL (French version of the PDR) in 1992.[5] Prescribers and pharmacists were asked to alert patients and other caregivers to the potential for tendonitis and tendon rupture while taking or after taking antimicrobial fluoroquinolones in a Report of Adverse Events issued by the U.S. FDA in October 1996.[6] The FDA also took steps to revise the package inserts to include a warning of possible tendonitis/tendon rupture.[7] According to the *Southern Medical Journal*, this action was taken "after more than 200 reports of fluoroquinolone-related tendonopathy over a 10-year period."[7] The risk for tendonopathies is increased in patients receiving concomitant corticosteroids, especially in the elderly, according to a warning based on postmarketing surveillance reports, which was added to the PDR in December 2001.[8] In March of 2002, the Italian Health Ministry issued a Dear Doctor Letter in order to

inform physicians of the risk of tendon rupture.[9] According to the Fluoroquinolone Toxicity Research Foundation, Dear Doctor letters were also issued by France and Belgium in 2002.[10]

Fluoroquinolone-induced tendonopathy presents suddenly and is characterized by sharp pain upon walking or with palpation.[7] When tendon ruptures occur it is usually after two weeks of fluoroquinolone therapy;[8] however, they can occur as early as a few hours after the first dose or up to six months after the last dose.[8] Although there is a predilection for the Achilles tendon, shoulder and hand involvement have also been reported.[11]

Severity of the injury directly correlates with the length of treatment.[11] Therefore, timely recognition of fluoroquinolone-induced tendonopathies and immediate discontinuation of fluoroquinolone therapy is a critical first step.[12] Taking either a surgical or conservative approach, tendon rupture still requires casting and prolonged rest.[11] Conservative Achilles tendonitis treatment should include rest, non-steroidal anti-inflammatory drugs, orthotics, cortisone injections, icing, ultrasound, and conventional physical therapy.[11]

Although the exact mechanism underlying fluoroquinolone-induced tendonopathy is poorly understood, a study in *The American Journal of Sports Medicine* suggests that the fluoroquinolone antibiotics alter tendon fibroblast metabolism.[13] In Achilles tendon and shoulder specimens maintained in culture with ciprofloxacin, a study reports a 66% to 68% decrease in cell proliferation and a 36% to 48% decrease in collagen synthesis. Another study reported "necrosis with neovascularization, interstitial edema, and degenerative lesions with fissures but without inflammatory cell infiltrate or angiitis."[7] These clinicians note that most tendon ruptures are at a site of vascular deficiency which suggests that tendon ruptures could be the result of an ischemic process. High dose administration of fluoroquinolones has also been found to cause lesions or cartilaginous erosions in juvenile dogs.[14] The lesions in dog cartilage have caused concern that similar effects might be seen in children.

Postmarketing surveillance has shown a number of factors which increase the risk for tendonitis/tendon rupture.[8] The most commonly reported risk factors are corticosteroid therapy and renal insufficiency.[8,16,17] Other conditions that may predispose a patient to a fluoroquinolone-induced tendon rupture include advanced age, prior tendonopathy, magnesium deficiency, hyperparathyroidism, diuretic use, peripheral vascular disease, rheumatoid arthritis, diabetes mellitus, and strenuous sports activities.[7,8,12]

There have been relatively few studies that have attempted to quantify the incidence of tendonopathy related to the use of fluoroquinolones. A retrospective cohort study published in 1999 in the *British Journal of Clinical Pharmacology* found that during the period from 1995-1996 and based on 1,841 users of fluoroquinolones, the adjusted relative risk of tendonitis from fluoroquinolones was 3.7 for Achilles tendonitis and 1.3 for other types of tendinitis.[17]

A case-control study conducted in the UK between July 1992 and June 1998 and published in the *British Medical Journal* reports the adjusted relative risk of Achilles tendon disorders with current use of fluoroquinolones was 1.9, while the relative risk among patients aged 60 and over was 3.2. Current use was defined as the time patients were on the quinolone plus thirty days. The study also notes that in patients aged 60 and over, concurrent use of corticosteroids and fluoroquinolones increased the risk to 6.2.[16]

A population-based, case-control study, conducted in the UK during the period of 1988-1998 and published in the *Archives of Internal Medicine*, reports the adjusted odds ratio (OR) for Achilles tendon rupture as 4.3 for current exposure to quinolones, 2.4 for recent exposure (30 to 90 days) and 1.4 for past exposure (more than 90 days). The OR of Achilles tendon ruptures was 6.4 in patients 60 to 79 years and 20.4 for patients 80 years and older. [18]

We do appreciate the efforts of the Food and Drug Administration (FDA) to collect and disseminate information about post-approval adverse drug reactions, and we applaud the steps that the FDA has taken in the past to include information about fluoroquinolone-induced tendonopathies in the pharmaceutical manufacturers' information. However, it is our firm belief that the prevalence and severity of this particular drug complication, and the relative lack of knowledge about it among health professionals, warrants a more aggressive educational approach. Consequently, we strongly urge your office to require a "black-box" warning regarding fluoroquinolone-induced tendonopathy in the drug information documents, require manufacturers to send an educational letter to all practicing health professionals about this serious adverse-effect, and to reflect these risks in patient information more accurately and to review fluoroquinolone antibiotics more thoroughly.

We thank you for your consideration of our request, and we hope to receive a letter indicating your response.

## C. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which is unfavorable to the petition.

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# EXHIBIT D

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

November 16, 2005

Arnold L. Widen, MD, MS, FACP
Babs Waldman, MD
Office of the Attorney General
State of Illinois
100 W. Randolph Street
Chicago, IL 60601

Re: Docket No. 2005P-0205

Dear Drs. Widen and Waldman:

I am writing to inform you that the Food and Drug Administration (FDA) has not yet resolved the issues raised in your citizen petition submitted on May 24, 2005. Your petition requests that the Agency take the following actions with respect to the entire class of fluoroquinolone drug products and the potential adverse event of tendonopathy and tendon rupture to: 1) revise the labeling to increase the warnings, 2) provide "Black Box" warnings, 3) require manufacturers to issue a "Dear Health Care Professional" letter that informs these professionals of the potential health hazards associated with the use of this class of drugs and details your proposed labeling changes, 4) supplement information provided to patients with bolded warnings, and 5) submit the issue for review and analysis to FDA's Drug Safety Oversight Board.

FDA has been unable to reach a decision on your petition because it raises complex issues requiring extensive review and analysis by Agency officials. This interim response is provided in accordance with FDA regulations on citizen petitions (21 CFR 10.30(e)(2)). We will respond to your petition as soon as we have reached a decision on your request.

Sincerely,

Jane A. Axelrad

Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

# EXHIBIT E

06-6974

Public Citizen 35 YEARS
Protecting Health, Safety & Democracy
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Joan Claybrook, President

August 29, 2006

Andrew Von Eschenbach, M.D., Acting Commissioner
U.S. Food and Drug Administration
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Von Eschenbach:

Public Citizen, representing more than 100,000 consumers nationwide, hereby petitions the Food and Drug Administration (FDA), pursuant to the Federal Food, Drug and Cosmetic Act 21 U.S.C. Section 355(e)(3), and 21 C.F.R. 10.30, to immediately add a black box warning regarding the risks of tendinopathy and tendon rupture to the product labels of all fluoroquinolone antibiotics presently on the market in the United States [Ciprofloxacin (Cipro; Bayer), Enoxacin (Penetrex; Aventis), Gatifloxacin (Tequin; Bristol-Myers Squibb), Levofloxacin (Levaquin; Ortho-McNeil), Lomefloxacin (Maxaquin; Unimed), Moxifloxacin (Avelox; Bayer), Norfloxacin (Noroxin; Merck), Ofloxacin (Floxin; Daiichi-Sankyo)]. We also urge the FDA to mandate a "Dear Doctor" letter to warn physicians of these adverse effects and require the distribution of an FDA-approved Medication Guide for all patients, to be dispensed when the prescriptions are filled. From November 1997 through December 31, 2005, the FDA had received reports of 262 cases of tendon rupture in patients using one of the above-listed fluoroquinolone antibiotics.

Public Citizen supports the Office of the Illinois Attorney General in their previous petition to add a black box warning to fluoroquinolones regarding this serious adverse event. Dr. Arnold Widen, Medical Director of the Illinois Attorney General's Office and Dr. Babs Waldman, Medical Director of the Health Care Bureau of the Attorney General's Office filed the petition on May 28, 2005, but have not received a substantive response from the agency.

Public Citizen has a ten year history of concern about fluoroquinolone-induced tendinitis and tendon rupture.



2006P-0371

CP 1

We successfully petitioned the FDA on August 6, 1996 to place a warning regarding the risk of tendinitis and tendon rupture on the package inserts of all fluoroquinolones. Although, at the time, we thought this would effectively educate physicians and patients about this adverse event, a simple non-bolded warning buried in the list of possible adverse reactions to fluoroquinolones has been grossly inadequate. Fluoroquinolone-induced tendon ruptures continue to occur at an alarming rate (175 reports of rupture since the beginning of 2003) and there is thus an urgent need for a black box warning regarding the risk of tendinitis and tendon rupture.

Public Citizen's concern is based, in part, on our analysis of the FDA adverse event database in patients receiving fluoroquinolones. That analysis shows 1) 262 cases of tendon ruptures; 2) 258 cases of tendinitis; and 3) 274 cases of other tendon disorders (see Table 1).

**Methodology**

We searched the FDA Adverse Event database (November 1997 to December 31, 2005) for all adverse reaction reports in which the primary suspect drug was one of the fluoroquinolones presently on the market in the United States. We used the terms "tendon rupture," "tendon disorder," "tendon disorder NOS," tendon injury," "tendonitis," "tendonitis exacerbated (the preferred dictionary spelling is tendinitis but the FDA database uses tendonitis)," "rotator cuff syndrome," and "rotator cuff." We limited the search to initial (not follow-up) reports. It should be noted that reports of tendon rupture and other tendon pathology prior to November 1997 are not included in our analysis since they are in another FDA database. We also limited this search to initial reports to avoid counting duplicate reports.

The entire FDA Adverse Event database for all drugs was also searched for "tendon rupture" to determine the drugs most commonly associated with this event. .

**Results**

The FDA estimates that only about ten percent of all adverse events are actually reported to the adverse event database and therefore the number of tendon ruptures is likely approximately ten times these numbers.

Table 1. Types of Tendon Pathology

| Type of Tendon Pathology | Totals |
|---|---|
| **Tendon Rupture** | 262 |
| **Tendinitis** | 258 |
| **Tendon Disorder (other)** | 274 |
| **Total** | 794 |

Although 61 percent of fluoroquinolone-associated tendon ruptures were associated with levofloxacin, (see Table 2 below), this drug has been the most heavily prescribed fluoroquinolone over the past four years, accounting for approximately 45 percent of all fluoroquinolone prescriptions during that time.

Table 2. Tendon Ruptures for each fluoroquinolone

| Drug | N | Percentage |
|---|---|---|
| Levofloxacin | 159 | 61% |
| Ciprofloxacin | 60 | 23% |
| Moxifloxacin | 23 | 8.8% |
| Gatifloxacin | 11 | 4.2% |
| Ofloxacin | 7 | 2.7% |
| Norfloxacin | 1 | 0.3% |
| Lomefloxacin | 1 | 0.3% |
| **Total** | **262** | **100%** |

An analysis of the entire FDA Adverse Event database revealed that fluoroquinolones were implicated significantly more often in tendon ruptures than any other class of drugs (38 percent of all tendon ruptures were thought due to fluoroquinolones). The mean age of patients with tendinopathy was 58.9 years for the cases in the database. Three hundred and twenty four males and 318 females experienced tendinopathy (gender was reported in only 642 cases).

While performing the analysis, we discovered a curious association between statins and tendon ruptures. Statin-induced tendinopathy has been reported as case reports in the literature.[1] However, fluoroquinolones were approximately 5 times more likely to be associated with tendon rupture than statins after adjusting for the much larger number of prescriptions written

for statins than fluoroquinolones over this given time period. Nevertheless, the association between statins and tendinopathy warrants further evaluation.

Table 3. Tendon Ruptures by Drug Class

| Drug | N | Percentage |
|---|---|---|
| Fluoroquinolones | 262 | 38.1% |
| Statins | 168 | 24.5% |
| Corticosteroids | 27 | 4.0% |
| Other (drugs <15 cases) | 230 | 33.5% |
| **Total** | **687** | **100%** |

**BACKGROUND**

Achilles tendon rupture causes sudden severe pain; difficulty walking; and swelling and bruise formation in the affected area prompting immediate medical attention. The treatment is either surgery or casting for 6 to 8 weeks followed by months of physical rehabilitation. Tendonitis causes pain and swelling in the affected tendon and is treated by removing the offending agent, anti-inflammatory medication, rest, and physical rehabilitation.

A recent review of the literature regarding fluoroquinolone-associated tendinopathy found 98 cases, 88 (89.8 percent) of which involved the Achilles tendon.[ii] There were 40 cases of tendon rupture in these 98 patients. The mean age in this review was 59 years, which was the same as the mean age of 59 years in the FDA Adverse Event database. The ratio of men to women in this review was 1.9:1 and the ratio was 1.02:1 in the FDA database.

Achilles tendon rupture has classically been a sports-related injury with an average age of 35 years in the general population. Two-thirds of achilles tendon ruptures occur in men.[iii] The demographics of tendon rupture are vastly different in people who recently took fluoroquinolones compared to the demographics of tendon rupture in the general population. This finding suggests a strong causative link between fluoroquinolone use and tendon rupture. The mean age in the FDA adverse event database as well as in the literature-reported quinolone-associated cases is nearly twenty-five years older than the mean age of Achilles tendon rupture in the general population. The predilection toward males in those Achilles tendon ruptures occurring in the general population was not seen in the FDA adverse event database as evidenced by the nearly equal distribution of cases between genders. It is hypothesized that men, usually younger men, in the general

population participate in more high-impact activities that increase their risk of Achilles tendon rupture. The older age and female predominance of quinolone-associated tendon injury presumably reflect patterns of drug use.

Although the exact mechanism of injury in fluoroquinolone-associated tendinopathy is unknown, it is widely speculated that fluoroquinolones are directly toxic to tendon fibers possibly associated with further decreased blood supply that particularly targets tendons that generally have a limited blood supply to begin with.[iv] Achilles tendon ruptures normally occur 2 to 6 cm above the calcaneus (heel bone), which correlates with the area of the tendon with the poorest blood supply[2]. There have also been reported cases of tendinopathies occuring after a single dose suggesting a direct toxic effect.[v] Patients with poor renal function also have a higher risk of fluoroquinolone-associated tendinopathy. This is likely due to increased toxicity of the drugs due to decreased renal clearance[3].

**THE CURRENT LABEL**

The FDA issued a statement in the October 1996 issue of its Medical Bulletin to all manufacturers of fluoroquinolones requesting a revision of the package inserts to include a new paragraph in the "Warnings" section acknowledging the risk of tendonitis and tendon rupture in fluoroquinolones. The warning is among a list of other potential side effects and is in plain, non-bold type. While the wording of the warning is accurate, it is inappropriately buried in a long list of potential adverse reactions. Physicians need to be educated about this risk as evidenced by the markedly increased number of reported tendon ruptures since 1998 as seen in Table 3. This could either be due to an increase in physician reporting of this adverse reaction or increased number of prescriptions written. No matter the cause, fluoroquinolone-induced tendon ruptures persist (and may be increasing) despite the re-labeling of the package insert in 1996 with a buried warning. Fluoroquinolone-induced tendon rupture is quite characteristic of this class of drug and we feel this serious reaction warrants a more pronounced black box warning that will better alert physicians and patients of this complication.

Table 3. Number of reported tendon ruptures in the FDA Adverse Event database per year: 1998-2005

| Year | Reported tendon ruptures |
|---|---|
| 1998 | 5 |
| 1999 | 0 |
| 2000 | 19 |
| 2001 | 26 |
| 2002 | 37 |
| 2003 | 65 |
| 2004 | 47 |
| 2005 | 63 |
| **Total** | **262** |

The content for our model "Black Box" warning would be:

**Fluoroquinolone antibiotics should be used with extreme caution because there is an increased risk of tendinitis 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.**

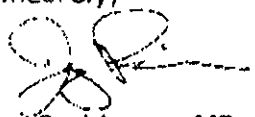
**If you experience pain in any tendon while taking these medications you should stop the medication and immediately contact your physician so you can be switched to another antibiotic.**

**ENVIRONMENTAL IMPACT STATEMENT**
Nothing requested in this petition will have an impact on the environment.

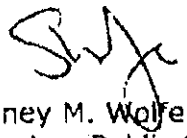
**CERTIFICATION**
We certify that, to the best of our knowledge and belief, this petition includes all information and views on which this petition relies, and that it

includes representative data and information known to the petitioners which are unfavorable to the petition.

Sincerely,



Jay Parkinson, MD, MPH
Research Analyst



Sidney M. Wolfe, MD
Director, Public Citizen's Health Research Group

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[i] Chazerain, P. Four Cases of Tendinopathy in Patients on Statin Therapy. Joint Bone Spine 2001 ; 68 : 430-3.
[ii] Khaliq. Y. Fluoroquinolone-Associated Tendinopathy: A Critical Review of the Literature. Clinical Infectious Diseases 2003; 36:1404–10.
[iii] Ufberg. J. Orthopedic Pitfalls in the ED: Achilles Tendon Rupture. American Journal of Emergency Medicine 2004; 22: 596-600.

[iv] Le Huec. J. Epicondylitis after treatment with fluoroquinolone antibiotics. J Bone Joint Surg Br 1995; 77:293–5.
[v] Van der Linden, P. Fluoroquinolones and risk of Achilles tendon disorders: case-control study. BMJ 2002; 324: 1306-07.

# EXHIBIT F

OFFICE OF THE ATTORNEY GENERAL
STATE OF ILLINOIS

Lisa Madigan
ATTORNEY GENERAL

August 29, 2006

Andrew von Eschenbach, M.D., Acting Commissioner
U.S. Food and Drug Administration
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: **Illinois Attorney General's Office Citizen Petition, Docket No. 2005P-0205 Fluoroquinolone-Induced Tendonopathies**

Dear Dr. von Eschenbach:

The Illinois Attorney General's Office is writing to supplement its Citizen Petition (Docket No. 2005-P-0205), pursuant to 21 C.F.R.§ 10.30(g), to include the enclosed Citizen Petition of the Public Citizen's Health Research Group submitted to the Food and Drug Administration on August 29, 2006. Both our Citizen Petition, and the Citizen Petition filed today by Public Citizen, address the problem of fluoroquinolone-induced tendonopathy. Public Citizen's petition contains additional data and analysis supporting our shared concerns, and therefore is provided as a supplement to our petition.

Our Office submitted its Citizen Petition to the Food and Drug Administration (FDA), on May 28, 2005. This petition urges the FDA to require manufacturers of the fluoroquinolone class of drugs to: (1) revise drug labeling to strengthen warnings of the potential for the serious adverse event of tendonopathy and tendon rupture; (2) create a "Black Box" warning to reflect the risk and severity of this adverse side effect; (3) require manufacturers of fluoroquinolone antibiotics to issue a "Dear Health Care Professional" letter to inform health care providers about this significant hazard to health and announce the changes in drug package labeling; (4) supplement information provided to patients with bolded warnings about the risk of tendonopathy and tendon rupture; and (5) submit the class of fluoroquinolone drugs for review to the FDA's Drug Safety Oversight Board. The FDA sent our Office a tentative response on November 16, 2005, indicating that our petition was still being analyzed, and noting that the "petition raises complex issues requiring extensive review and

analysis by [FDA] officials." Our Office has not received further notification or response. It has been 15 months since the FDA received our initial petition.

At this time, we respectfully request that the FDA provide to our Office information regarding: (1) the status of the FDA's review and when we might expect a ruling; (2) whether any preliminary decisions or conclusions have been made regarding our petition; and (3) whether any additional materials could be provided by our Office to the FDA to assist it in coming to a satisfactory and timely resolution on this issue. As you are aware, the severity and prevalence of fluoroquinolone-induced tendonopathies are not well-known by health care providers, and therefore we strongly urge the FDA to fully and promptly consider the documents and references provided in the original petition of the Illinois Attorney General's Office as well as the supplemental information included within Public Citizen's Citizen Petition.

It seems to us that your commitment to the good health of the public requires your action in response to these two petitions. Thank you in advance for your prompt attention.

Sincerely,

Arnold Widen, MD

Arnold Widen, M.D., M.S., F.A.C.P.
Medical Director
Illinois Attorney General's Office
100 W. Randolph Street
Chicago, IL 60601
(312) 814-8555

Babs Waldman, M.D.
Medical Director, Health Care Bureau
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# EXHIBIT G

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
Rockville MD 20857

2007

Jay Parkinson, MD, MPH
Sidney M. Wolfe, MD
Public Citizen's Health Research Group
1600 20th Street, NW
Washington, DC 20009

Re: Docket No. 2006P-0371

Dear Drs. Parkinson and Wolfe:

I am writing to inform you that the Food and Drug Administration (FDA) has not yet resolved the issues raised in your citizen petition submitted on August 29, 2006. Your petition requests that the Agency add a black box warning regarding the risks of tendinopathy and tendon rupture to the product labels of all fluoroquinolone antibiotics presently on the market in the United States. You also request that FDA mandate a "Dear Doctor" letter to warn physicians of the adverse effects associated with these drug products and require the distribution of a Medication Guide.

FDA has been unable to reach a decision on your petition because it raises complex issues requiring extensive review and analysis by Agency officials. This interim response is provided in accordance with FDA regulations on citizen petitions (21 CFR 10.30(e)(2)). We will respond to your petition as soon as we have reached a decision on your request.

Sincerely,

Jane A. Axelrad

Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

**UNITED STATES DISTRICT COURT**
**FOR THE DISTRICT OF COLUMBIA**

| | | |
|---|---|---|
| PUBLIC CITIZEN, INC., | ) | |
| | ) | |
| Plaintiff, | ) | |
| | ) | |
| v. | ) | C. A. No. 08-00005(HHK) |
| | ) | |
| FOOD AND DRUG ADMINISTRATION, | ) | |
| | ) | |
| Defendant. | ) | |
| _____ | ) | |

**[PROPOSED] ORDER**

This matter having come before the Court on Plaintiff's Motion for Summary Judgment, it is hereby **ORDERED** that plaintiffs' motion for summary judgment is **GRANTED.** It is further **ORDERED** that defendant shall issue a response to plaintiff's citizen petition.

**SO ORDERED** on this ____ day of _____, 2008.

_____
HENRY H. KENNEDY
United States District Judge