FDA Briefing Document

Joint Meeting of the Antimicrobial Drugs Advisory Committee and the

Drug Safety and Risk Management Advisory Committee

November 5, 2015

The Benefits and Risks of Systemic Fluoroquinolone Antibacterial Drugs for the Treatment of Acute Bacterial Sinusitis (ABS), Acute Bacterial Exacerbation of Chronic Bronchitis in Patients Who Have Chronic Obstructive Pulmonary Disease (ABECB-COPD), and Uncomplicated Urinary Tract Infections (uUTI).

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Divisions or Offices. We have brought safety and efficacy information for the systemic fluoroquinolone antibacterial drugs in the context of three indications: acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis in patients with chronic obstructive pulmonary disease, and uncomplicated urinary tract infections. The purpose of the joint meeting is to gain the Committees' insights and opinions and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion at this joint meeting of the advisory committees. The FDA will not issue any final determinations on the issues at hand until input from the advisory committees processes have been considered and all reviews have been finalized. The final determinations may be affected by issues not discussed at the advisory committee meeting.

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I. INTRODUCTION

The control of infectious diseases is one of the top ten public health achievements of the twentieth century (CDC, 1999). The reduction in mortality associated with antibacterial drugs to treat serious and life-threatening infectious diseases such as bacterial pneumonia was a remarkable public health success (Dowling, 1972; Finland, 1943), and the introduction of the systemic fluoroquinolone antibacterial drugs contributed to this public health achievement. The benefits and risks of fluoroquinolone antibacterial drugs are favorable in the treatment of certain serious and life-threatening infectious diseases. However, while many infectious diseases are serious and life-threatening, a few infectious diseases have more recently been shown to be potentially self-limited in a large proportion of patients.

A pre-approval clinical trial safety database may not demonstrate adverse reactions that occur infrequently. During the life-cycle of any approved drug, adverse reactions that occur infrequently become evident as larger numbers of patients are exposed to the drug. During the life-cycle of the fluoroquinolone antibacterial drugs, adverse reactions such as tendinitis and tendon rupture, prolongation of the QT interval, and peripheral neuropathy only became evident post-approval.

We are asking the advisory committees to discuss the benefits and risks of the systemic fluoroquinolone antibacterial drugs for the treatment of acute bacterial sinusitis (ABS), acute bacterial exacerbation of chronic bronchitis in patients who have chronic obstructive pulmonary disease (ABECB-COPD), and uncomplicated urinary tract infections (uUTI).[1] The fluoroquinolone antibacterial drugs currently available with one or more of these three indications are ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin, and gemifloxacin. This document provides a summary of the treatment effects of antibacterial drugs for these three clinical conditions. In addition to a summary review of safety-related labeling changes for all fluoroquinolone drugs, we reviewed the safety findings of the fluoroquinolone antibacterial drugs in several contexts. An epidemiological review of publications characterized the incidence and relative risks of selected adverse reactions associated with fluoroquinolone antibacterial drugs. A search of the FDA Adverse Event Reporting System (FAERS) with a focus on adverse reactions associated with disability was reviewed. Finally, we evaluated the drug utilization of oral fluoroquinolone antibacterial drugs in the United States. This document will provide an assessment of efficacy, safety, and current drug use of fluoroquinolones for treatment of ABS, ABECB-COPD, and uUTI.

[1] The use of fluoroquinolone antibacterial drugs in this document refers to the systemic administration of fluoroquinolone antibacterial drugs.

II. TREATMENT EFFECTS OF ANTIBACTERIAL DRUGS FOR TREATMENT OF ABS, ABECB-COPD, AND uUTI

a. Regulatory Overview of Antibacterial Drug Development

Beginning in the 1980s, there was a change in the types of study designs that FDA was recommending for the efficacy evaluations of new antibacterial drugs. This change was driven by advances in our understanding of the pathophysiology of certain infections and implications for clinical trial design. In addition, new regulations were promulgated in 1985 that describe the characteristics of adequate and well-controlled studies (§21 CFR 314.126). During the 1990s and subsequently, FDA recommended clinical trials that were designed to enroll patients with infections involving a particular body site, rather than patients with any of a variety of different types of infections.[2] Clinical trials used to support the approval of antibacterial drugs from this point forward were generally designed as "equivalence" trials that were the predecessor for noninferiority (NI) trials. The equivalence trial is similar to the NI trial, except that equivalence trials were generally underpowered and had less confidence that a test drug was not inferior to a control drug. The NI trial focuses on the lower bound of the two-sided 95% confidence interval of the difference to establish a degree of confidence that a test drug is not inferior to a control drug.

Antibacterial drugs approved before the 1980s were in general used as the control antibacterial drugs in NI trials. Because placebo-controlled trials were not used as a basis for the approval of those drugs, a treatment effect of the control antibacterial drugs over placebo had not been clearly established for ABS, ABECB-COPD, or uUTI. Thus, these active-controlled studies may not provide a reliable means to evaluate efficacy of antibacterial drugs for these indications.

b. Anti-Infective Drugs Advisory Committee Discussions

On several occasions since 2000, FDA Advisory Committees have addressed issues regarding clinical development of antibacterial drugs that are seeking the indication for treatment of ABS or ABECB-COPD and are based on the demonstration of NI to an approved antibacterial drug. The treatment effect of antibacterial drugs for uUTI was not previously discussed at an FDA Advisory Committee.

In 2002, the Anti-Infective Drugs Advisory Committee (AIDAC) discussed clinical trials of antibacterial drugs for treatment of ABECB-COPD; the committee recommended placebo-controlled trials for subjects who are not severely ill in order to demonstrate efficacy. In 2003, AIDAC discussed the trial designs to demonstrate efficacy of an antibacterial drug for the

[2] These recommendations are described in documents that provide advice on designing clinical trials to evaluate antibacterial drugs for each of a variety of different infectious diseases. These documents include the Infectious Diseases Society of America (IDSA) and the FDA Guidelines for the Evaluation of Anti-Infective Drug Products (Beam, Gilbert, et al., 1992) and the FDA Points to Consider Document, *Clinical Development and Labeling of Anti-infective Drug Products*.

treatment of ABS. The committee recommended that trials be designed to show superiority of the test antibacterial drug, for example, through placebo-controlled clinical studies.

In September 2006, the AIDAC discussed an antibacterial drug for consideration of approval based on an active-controlled NI trial for the indication of ABS. The committee of 14 voting members was asked whether efficacy had been demonstrated based on a finding of NI from the NI trial design. Ten out of 14 committee members voted that efficacy for treatment of ABS had not been demonstrated. In December 2006, a joint meeting of the AIDAC and the Drug Safety and Risk Management Advisory Committee discussed safety data in the context of the FDA-approved indications for Ketek® (telithromycin), which were approved on the basis of active-controlled NI trials. The committee recommended removal of the ABS and ABECB-COPD indications from labeling because the risk of hepatotoxicity outweighed benefit, in part because it was not possible to reliably show the effect of the active drug for these two indications on the basis of the NI trial design. The Ketek® (telithromycin) product label was subsequently amended to remove the indications for ABS and ABECB-COPD.[3]

Following these advisory committee discussions, placebo-controlled trials were recommended to support the indications for ABS and ABECB-COPD. Final guidance documents from FDA on developing antibacterial drugs for treatment of ABS and mild ABECB-COPD recommend superiority trials with a placebo control. In the subsequent sections, we describe an assessment of the treatment effect of antibacterial drugs for these three clinical conditions. Any antibacterial drug, including fluoroquinolones, used in a placebo-controlled or non-antibacterial controlled trial was considered for this efficacy evaluation.

c. Acute Bacterial Sinusitis – Antibacterial Efficacy

We reviewed 20 placebo-controlled trials published in the medical literature (see bibliography in Appendix A). Fourteen studies did not show a statistically significant difference over placebo. Among the six studies that demonstrated a statistically significant difference in clinical outcomes, each study's primary efficacy outcome assessment was different and the timing of the outcome assessment was different. In addition to overlapping symptoms with common viral infections and the presence of several confounding treatments and host risk factors, when clinical trials have shown some clinical benefit, the benefit is observed only in patients who have prolonged and more severe symptoms and the statistically significant difference from placebo is not robust.

Several publications have reviewed the literature regarding placebo-controlled trials for treatment of ABS. The Cochrane Collaboration conducted a review of antibacterial drugs for treatment of clinically diagnosed acute rhinosinusitis in adults and provided this statement in their conclusion: "Taking into account antibiotic resistance and the very low incidence of serious complications, we conclude that there is no place for antibiotics for the patient with clinically diagnosed, uncomplicated acute rhinosinusitis" (Lemiengre, van Driel, et al, 2012). Another

[3] See the February 12, 2007 approval letter and review documents at Drugs@FDA found at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/021144Orig1s012Approv.pdf

review by The Cochrane Collaboration of antibacterial drugs for treatment of acute maxillary sinusitis in adults provided the following statements in their conclusion: "There is moderate evidence that antibiotics provide a small benefit for clinical outcomes in immunocompetent primary care patients with uncomplicated acute sinusitis. However, about 80% of participants treated without antibiotics improved within two weeks" (Ahovuo-Saloranta A, UM Rautakorpi, 2014).

A practice guideline from the Infectious Diseases Society of America emphasized the inability to differentiate a viral cause from a bacterial cause of acute sinusitis, but noted that viral causes account for 90% or more in patients with symptoms of acute sinusitis. The guideline recommends antibacterial drug therapy for patients who present with more severe symptoms of acute sinusitis likely to be ABS and discourages the use of respiratory fluoroquinolone antibacterial drugs in favor of beta-lactam antibacterial drugs. The guideline also states a secondary goal to reduce excessive or inappropriate use of antibacterial drugs (Chow, Benninger, et al, 2012).

A meta-analysis of 9 randomized trials enrolling 2,547 patients assessed whether a particular group of signs and symptoms can be used to identify patients who benefit from antibacterial drugs. A subgroup of patients for whom antibacterial drug treatment is clearly justified based on a pattern of signs or symptoms could not be identified. From their analyses, the authors suggest that antibacterial drug treatment might offer no benefit at all or have harmful effects (Young, De Sutter, et al, 2008).

The ability to clearly identify a group of patients who have a bacterial etiology for their symptoms of acute sinusitis is difficult. Even when a bacterial pathogen was documented or the trial was enriched for patients who are more likely to have ABS, the antibacterial drug treatment effect appeared to be small with a large proportion of placebo-treated patients having favorable clinical responses. Current reviews by authoritative scientific bodies and meta-analyses published in the literature question the benefit of antibacterial drugs for treatment of ABS. The treatment effect of antibacterial drugs for ABS appears to be only very modest, at best.

d. Acute Exacerbations of Chronic Bronchitis – Antibacterial Efficacy

We reviewed 15 placebo-controlled studies of ABECB-COPD (see bibliography in Appendix A). Nine studies did not show a difference in clinical outcomes between patients who received placebo and patients who received an antibacterial drug. Six studies showed a statistically significant difference in favor of an antibacterial drug, although the studies enrolled patients with varying disease severity and used different outcome assessments. One study enrolled patients hospitalized with severe ABECB-COPD and found an absolute risk reduction in mortality of 17.5 (95% CI 4.3, 30.7) associated with antibacterial drug therapy (Nouria, Marghi, et al, 2001). Four out of eight studies enrolling only outpatients showed a statistically significant difference from placebo using an outcome assessment incorporating patient symptoms and their improvement. Thus, while outcome assessments based on subjective assessments by clinical investigators or pulmonary function testing did not demonstrate a treatment effect in the other

four studies, there appears to be a treatment effect in mild ABECB-COPD based on symptom improvement from the perspective of the patient.

A review by The Cochrane Collaboration on antibacterial drugs for the treatment of acute exacerbations of chronic obstructive pulmonary disease demonstrated effectiveness, as stated in their conclusions: "...this review supports antibiotics for patients with COPD exacerbations with increased cough and sputum purulence who are moderately or severely ill" (Ram, Rodriguez-Roisin, et al, 2006). A review of bacterial infections in patients with COPD also recommends antibacterial drug treatment for patients with moderate or severe symptoms of ABECB-COPD (Sethi, Murhpy, 2008). In addition, treatment guidelines from the American Thoracic Society and the European Respiratory Society on the management of COPD describe only the consideration of antibacterial drug therapy for outpatients with ABECB-COPD based on certain symptoms of greater severity (Celli, MacNee, et al, 2004). Clinical practice guidelines for treatment of ABECB-COPD published by the American College of Physicians stated, "Among patients with mild attacks, there were no significant differences between those who received antibiotics and those who received placebo" (Bach, Brown, et al, 2001). These publications have a common thread that patients with mild symptoms of ABECB-COPD are not recommended to receive antibacterial drug treatment.

Successful outcomes in the placebo arm have consistently been reported in half or more of the patients enrolling in clinical studies of ABECB-COPD. Adverse reactions were generally mild overall but occurred with greater frequency in the antibacterial drug-treated groups. However, one randomized, prospective, double-blind, placebo controlled trial enrolling outpatients with ABECB-COPD showed a rate of hospitalization due to worsening pulmonary status in the placebo group of 4% versus 2% in the antibacterial drug group (Echols, Tosiello, 2008).

The treatment effect of antibacterial drug therapy for patients who are hospitalized and have moderate or severe ABECB-COPD is clearly evident (e.g., reduction in mortality) and antibacterial therapy is warranted in such patients. However, patients enrolled in ABECB-COPD trials in new drug applications have, in general, included patients with outpatient, milder, or less well-characterized disease.

In outpatients with mild symptoms from ABECB-COPD, current practice guidelines and reviews by authoritative scientific bodies do not uniformly recommend antibacterial drug therapy for such patients. The treatment effect of antibacterial drug therapy from the perspective of the patient is only modest for outpatients with mild ABECB-COPD.

e. Uncomplicated Urinary Tract Infection – Antibacterial Efficacy

We reviewed published trials using a placebo or a non-antibacterial control. Details of our search criteria and the review of each trial are found in Appendix B. We identified five trials that met our criteria (Asbach, 1991; Christiaens, De Meyere, et al, 2002; Bleidorn, Gágyor, 2010; Ferry, Holm, et al, 2007; Dubi, Chappuis, et al, 1982). Four were placebo-controlled trials and one used ibuprofen as a control drug. In general, these trials enrolled mostly young adult women with symptoms such as dysuria and evaluated both resolution of symptoms and eradication of the

bacterial pathogen from urine (e.g., from a baseline urine culture of $\geq 10^5$ CFU/ml demonstrating a single bacterial uropathogen to $\leq 10^2$ CFU/ml or no growth on follow up urine culture).

Figures 1-5 show the results of fixed- and random-effects meta-analyses for these five trials. We considered ibuprofen to be a placebo in these analyses. Figures 1 and 2 show the separate outcome assessments as described in the three respective trials, and Figure 3 shows the responder outcome that was described in those two trials.

Figure 1: Microbiological Eradication Outcome Assessment (study name = first author)

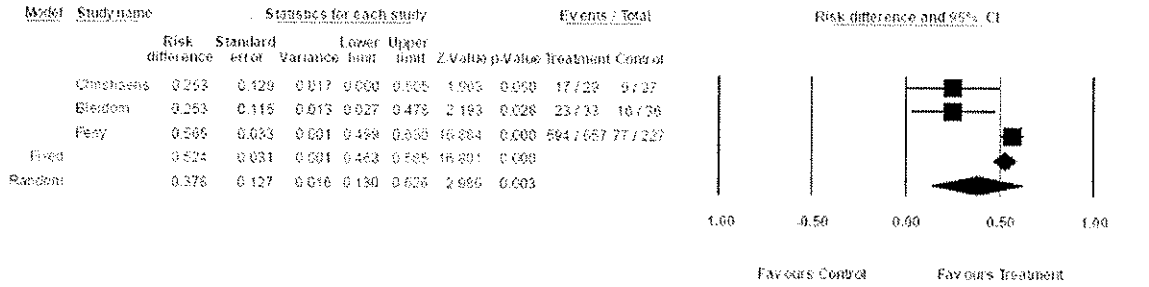


Figure 2: Clinical Resolution Outcome Assessment (study name = first author)

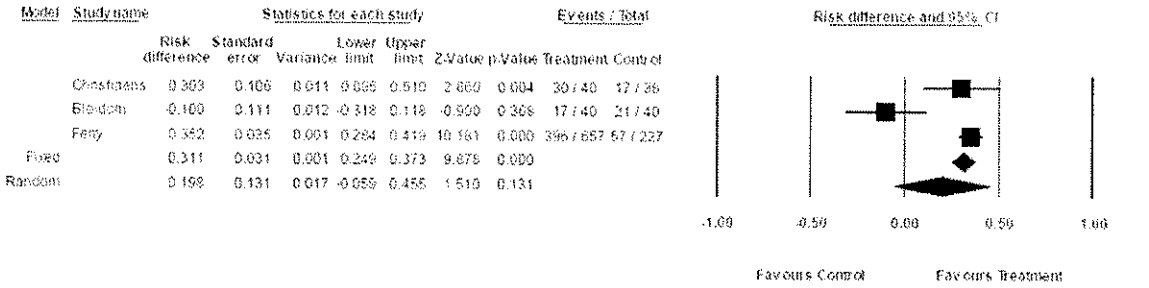
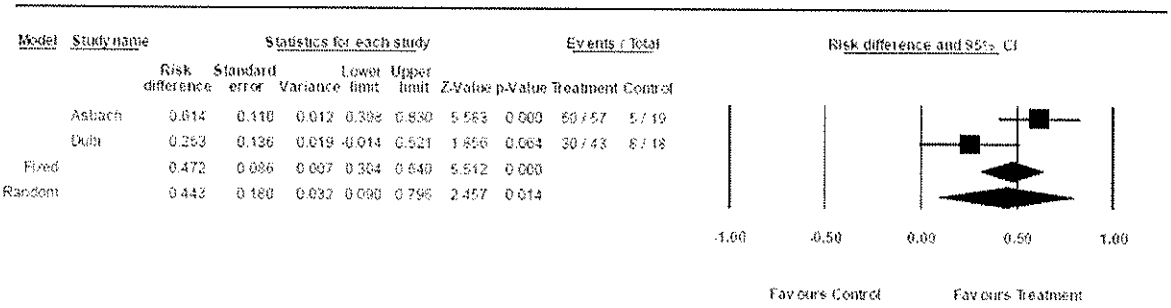


Figure 3: Clinical + Micro Responder Outcome Assessment (study name = first author)



The lower limit of the two-sided 95% confidence interval for a treatment effect based on microbiological eradication was 13% based on a random-effects meta-analysis of the three trials. The lower limit of the two-sided 95% confidence interval crossed zero for clinical resolution outcome assessment because the analysis included ibuprofen as a placebo (Bleidorn, Gágyor, 2010). The other two trials describing the responder outcome assessment did not describe the endpoints separately and we did not have access to patient level data, but the analysis showed a lower limit of the two-sided 95% confidence interval for a treatment effect of 9% based on the random-effects meta-analysis.

The analyses in Figures 4 and 5 were performed by imputing the results of the responder outcome in all trials for each outcome assessment: microbiological eradication and clinical resolution. This assumption may represent a conservative approach because patients who were failures based on one component of the responder endpoint (e.g., failure on clinical resolution and success on microbiological eradication) would still be considered failures on each outcome assessment (e.g., imputed as a failure on microbiological eradication instead of success). However, this assumption may result in the introduction of bias towards a treatment effect if one outcome assessment alone is driving the results of the responder outcome. As shown in Figures 4 and 5, the lower limit of the two-sided 95% confidence interval of a treatment effect is 24% and 10% for the outcome assessments of microbiological eradication and clinical resolution, respectively, based on random-effects meta-analyses.

Figure 4: Microbiological Eradication Outcome Assessment (study name = first author)

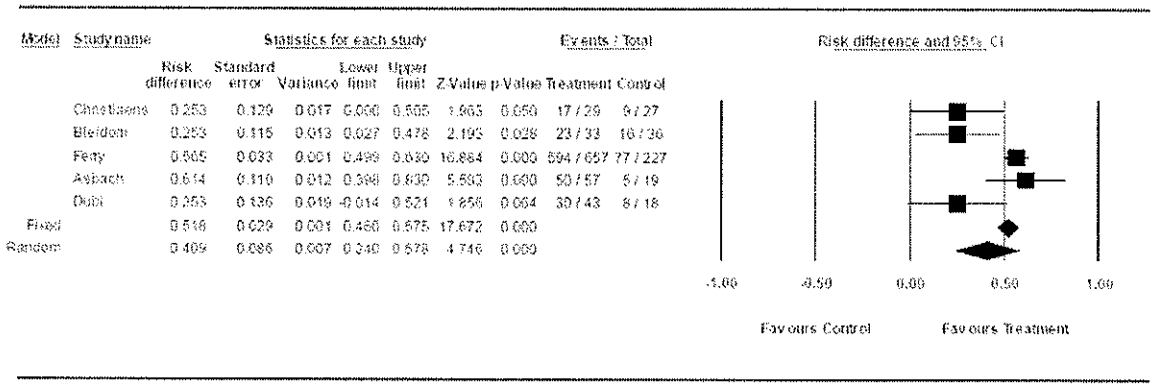
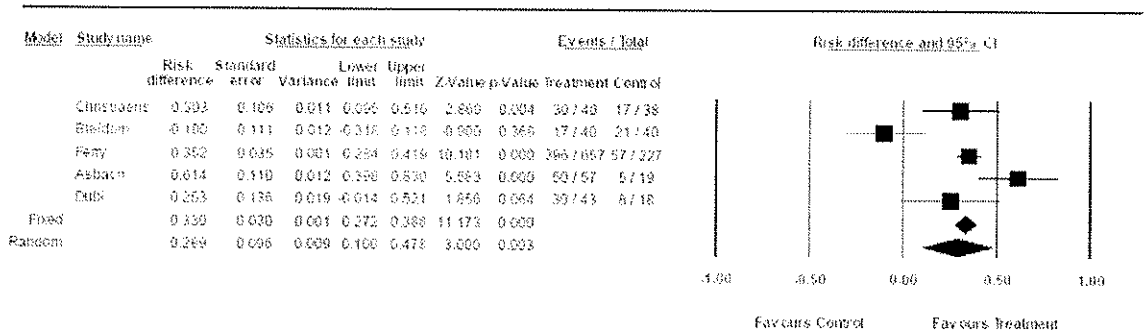


Figure 5: Clinical Resolution Outcome Assessment (study name = first author)



All of these placebo control and non-antibacterial control trials were conducted in Europe; however, the pre-study hypotheses—that the symptomatic improvement and natural course of untreated uUTI is not significantly worse than with the use of antibacterial treatments—suggest ongoing equipoise regarding the role of antibacterial treatment with bacteriological eradication on disease progression/recurrence and the symptomatic aspects of treatment. This includes an ongoing trial with the goal of enrolling approximately 300 patients to evaluate ibuprofen versus mecillinam in the treatment of uncomplicated cystitis in healthy, adult, non-pregnant women (Vik, Bollestad, et al, 2014). Many of these trials are smaller pilot trials, with largely descriptive statistical analysis of various outcomes, but there appeared to be evidence of antibacterial treatment effect over placebo on symptom resolution, with an even larger treatment effect on microbiologic eradication. We did not have access to patient-level data to evaluate a responder outcome assessment of symptom resolution plus microbiological eradication for all trials.

In our literature search we were not able to find a study that clearly defines the course of untreated uUTI and potential infectious complications in a large population. While the fact that placebo-controlled trials found that most patients with uUTI had uneventful short-term courses without antibacterial drug therapy, the incidence of progression to complicated urinary tract infection or pyelonephritis has not been clearly elucidated. In contrast, the incidence of pyelonephritis in untreated pregnant women with asymptomatic bacteriuria has been elucidated; the relative risk of pyelonephritis without screening and antibacterial drug treatment was 3.37 (95% CI 1.68, 6.78) in one study (Gratacós E, Torres P, et al, 1994). Among the five controlled studies there was one patient randomized to receive placebo who was treated for pyelonephritis.

The primary objective of the Cochrane Collaboration review of uUTI was to compare the effectiveness of different antibacterial drug therapies for treatment of acute uUTI; treatment effect against placebo was not under evaluation (Zalmanovici Trestioreanu, Green, et al, 2010). Guidelines prepared by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases (IDSA/ESMID) do not discuss an option of non-antibacterial therapy (Gupta, Hooton, et al, 2011).

These updated IDSA/ESMID guidelines state that three-day regimens of fluoroquinolones have a propensity for the emergence of antimicrobial resistance among uropathogens and should therefore be considered secondary options for treatment.

There is a clear and consistent treatment effect of antibacterial drug therapy for treatment of uUTI on the outcome assessment of microbiologic eradication. In studies that used a placebo control, there is a similar treatment effect using an outcome assessment based on symptom resolution. In a study that used ibuprofen as a control, there was no treatment difference on symptom resolution in comparison to an antibacterial drug. The risk of infectious complications has not been clearly elucidated for otherwise healthy nonpregnant adults who convert from symptomatic to asymptomatic bacteriuria with the use of a nonsteroidal anti-inflammatory drug such as ibuprofen.

f. Summary of Treatment Effects for ABS, ABECB-COPD and uUTI

The treatment effects of antibacterial drug therapy for ABS and mild ABECB-COPD are very modest, at best. The FDA's guidance documents for these two indications are included as attachments in Appendix C and recommend placebo-controlled trial to demonstrate efficacy. The treatment effect of antibacterial therapy for moderate-to-severe ABECB-COPD is robust, and antibacterial therapy is warranted in such patients who are often hospitalized for their illness. In placebo-controlled trials, the treatment effect of antibacterial therapy for uUTI is evident for microbiological eradication of bacteria and resolution of symptoms. In an ibuprofen-controlled trial, there was a treatment effect of antibacterial drug therapy on microbiological eradication outcome assessment, but both treatment groups in this trial showed similar proportions with symptom resolution. See Appendix D for a summary of the labeled indications of ABS, ABECB-COPD, and uUTI for each of the currently available systemic fluoroquinolone antibacterial drugs.

III. FLUOROQUINOLONE SAFETY ISSUES

a. History of Safety-Related Labeling Changes

Since the 1986 approval of norfloxacin, the labeling and accompanying patient information or Medication Guides for the fluoroquinolones have been updated based on analyses of clinical trials, spontaneous safety reports, and information published in the literature. The changes have included revisions to the Warnings and Precautions and Adverse Reactions sections to include the description of the musculoskeletal, cardiac, dermatologic, neurologic, and neuro-psychiatric risks associated with the use of fluoroquinolones. The labeling for all fluoroquinolone antibacterial drugs is in the Physician Labeling Rule (PLR) format. We briefly describe the rationale for selected safety-related labeling changes to the Boxed Warning and Warnings and Precautions section, and specific examples are provided in Appendix E.

Tendinitis and Tendon Rupture Boxed Warning

While original product labeling for norfloxacin (1986) and ciprofloxacin (1987) included nonclinical information on joint pathology in the Warnings and Precautions sections, clinical evidence for tendon/joint toxicity associated with fluoroquinolone use became apparent post-marketing and the labels for all marketed fluoroquinolones were updated to include a warning of tendon rupture in 1996. At the time of approval, the warning of tendon rupture was included in the labels for levofloxacin, moxifloxacin, and gatifloxacin, reflecting the recognition of the class effect of fluoroquinolones on tendon toxicity, even though this adverse reaction was not observed in clinical trials for these products. In 2004, the warning was expanded to include information on the at-risk populations: those on steroid medications and the elderly. Subsequently, language regarding serious tendon effects requiring surgical intervention and guidance on management were added. A Boxed Warning for tendinitis and tendon rupture was added in 2008.[4] This labeling change also provided information regarding the risk of these effects in transplant recipients, in the presence of strenuous physical activity, and renal failure, as well as updated the list of the specific tendon sites prone to rupture. In addition, FDA issued a Medication Guide to patients about serious adverse reactions, including tendinitis, associated with fluoroquinolone use. The Medication Guides continue to be part of the approved labeling for all fluoroquinolones.

Central Nervous System (CNS) Effects Warning

Ciprofloxacin was first in the fluoroquinolone class to include effects on CNS (seizures, tremors, and alterations of mental state) in the Warnings and Precautions sections of the label at the time of approval. The accumulation of postmarketing clinical evidence along with elucidation of the mechanism for fluoroquinolone-mediated CNS toxicity (inhibition of GABA-A receptors in addition to activation of excitatory NMDA receptors) led to updated labeling for all fluoroquinolones. CNS/psychiatric adverse reactions associated with fluoroquinolones, including increased intracranial pressure and psychosis was in the ofloxacin label in 1990 and subsequently was included in Warning and Precautions Section in all fluoroquinolones. In 2011, pseudotumor cerebri was added to the CNS toxicity warning.

Peripheral Neuropathy Warning

After review of the accumulated postmarketing safety data for the approved fluoroquinolones, in 2004 the FDA requested the sponsors for all fluoroquinolone antibacterial drugs to include a warning regarding peripheral neuropathy. A 2013 FDA review identified permanently disabling cases of peripheral neuropathy associated with fluoroquinolone use. No relationship between the duration of therapy and symptom onset and reversibility was noted. Additional safety labeling

[4] See the FDA News Release, "FDA Requests Boxed Warnings on Fluoroquinolone Antimicrobial Drugs", found at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116919.htm

changes were required and FDA issued a Drug Safety Communication regarding possibly permanent nerve damage on August 15, 2013.[5]

Myasthenia Gravis Exacerbation Warning

Cases of exacerbation of myasthenia gravis were observed in some premarketing clinical trials of fluoroquinolones, as well as postmarketing adverse reactions. An FDA review in 2010 identified serious adverse event cases of myasthenia gravis exacerbation associated with use of all fluoroquinolones, some resulting in a fatal outcome. Biological plausibility for such an effect was supported by in vitro data where fluoroquinolones were able to effectively block neurotransmission across synaptic endplate at clinically achievable concentrations, chemical similarity between the fluoroquinolones and other drugs associated with myasthenia exacerbations (quinine), and their calcium-chelating properties. A Boxed Warning was added to describe potential life-threatening consequences of exacerbation in patients with myasthenia gravis and to advise healthcare providers to avoid use of fluoroquinolones in such patients. The Warnings and Precautions section of the package insert and Medication Guide were also updated accordingly.

QT Prolongation and Torsades de Pointes (TdP) Warning

Drug-associated QT prolongation and TdP has been a topic of interest and research for the past 20-25 years. The propensity of fluoroquinolones to induce QT prolongation became apparent in 1990s, when several of the approved products included warning statements of their pro-arrhythmic potential in the label (sparfloxacin 1996, trovafloxacin and grepafloxacin 1997). In 1999, grepafloxacin became the first antibacterial drug removed from the market because of an increased risk of QT prolongation resulting in TdP. Cautionary statements in the Warnings Section were included in most fluoroquinolone labels. Based on an FDA review, precautionary statements for use in geriatric population were added to the labeling of all marketed fluoroquinolones in 2007. Additional review of the spontaneous reports in 2010-2011 prompted revisions of QT prolongation language to include risk factors for QT prolongation for all fluoroquinolones.

Phototoxicity Warning

The differences in the phototoxic potential among the fluoroquinolones appeared to be related to the differences in C8 substituent in the quinolone ring structure. Despite differences in photosensitizing potential among fluoroquinolones, review of FAERS found that phototoxicity reactions were reported in association with all fluoroquinolones. In 2007, phototoxicity was included in the Warnings and Precautions section.

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

Hypersensitivity Warning

The labels include a list of serious and sometimes fatal hypersensitivity reactions associated with use of fluoroquinolones. The fatal hypersensitivity reactions included in labeling continue to be updated based on review of postmarketing safety information.

b. Epidemiological Review of Specific Adverse Reactions

The Division of Epidemiology II in OSE conducted a literature review of observational epidemiologic studies that assess the absolute or relative risk of adverse reactions associated with fluoroquinolones. There were a large number of studies published in the literature, and we focused only on higher-quality assessments of three serious adverse reactions of interest: tendinitis/tendon rupture, cardiac arrhythmia, and peripheral neuropathy. More detailed information about the approaches to the epidemiological reviews can be found in Appendix E.

Tendinitis/Tendon Rupture

We limited our in-depth review for this briefing document to four studies that included clearly confirmed cases of tendinitis/tendon rupture. All four studies found a positive association between fluoroquinolones and tendinitis/tendon rupture, as shown in Table 1.

Table 1: Association between fluoroquinolones and tendinitis/tendon rupture across four selected studies

Study	Adjusted RR/ OR of tendinitis/tendon rupture	95% confidence interval
Seeger, West, et al, 2006	1.2	0.9-1.7
Wilton, Pearce, et al, 1996[α]	2.7	0.8-9.5
van der Linden, van de Lie, et al, 1999	2.1	0.8-5.1
van der Linden, Sturkenboom, et al, 2003[α]	11.0	5.8-20.8

OR, odds ratio; RR, rate ratio

[α] Crude relative risk estimates and 95% confidence intervals calculated by the FDA reviewer.

One study (Seeger, West, et al, 2006) found an association of fluoroquinolones with tendinitis/tendon rupture in elderly subjects using corticosteroids, but this was a subgroup analysis of a smaller population and thus led to a wide confidence interval (adjusted odds ratio = 5.8; 95% confidence interval [CI] 0.9-38.6). Another study (van der Linden, Sturkenboom, 2003) restricted the study population to elderly subjects and found a high risk associated with fluoroquinolone use relative to fluoroquinolone-associated risk observed in the other studies, suggesting an increased risk among elderly patients.

One of the most concerning outcomes assessed in the four studies was Achilles tendon rupture, a disabling, serious adverse event sometimes requiring surgery and found in the FAERS data. Because the incidence of Achilles tendon rupture is low, a moderately increased relative risk

among fluoroquinolone users would only result in a small increased absolute risk. That is, among the general population or among users of non-fluoroquinolone antibacterial drugs, the incidence density ranged from 0.5 to 1.0 per 10,000 person-years. In contrast, among fluoroquinolone-exposed persons, the incidence density appears to be increased and ranged from 1.3 to 5.6 per 10K person-years among the four studies.

Cardiac Arrhythmias

We included two studies in the in-depth review (Chou, Wang, et al, 2015; and Rao, Mann, et al, 2014) because they captured both fatal and non-fatal cardiac arrhythmias within the drug-exposure period. It is important to note that this epidemiological review focused on the clinical outcome of cardiac arrhythmia and did not focus on QT interval prolongation itself. The studies did not provide sufficient clinical granularity for us to adequately adjust for confounding due to the indication. The insufficient adjustment for confounding by indication was an important limitation for the cardiac arrhythmia outcome since respiratory tract infections can increase risk of the outcome. Table 2 summarizes the main findings from these two studies.

Table 2: Summary of the main findings on the relative risk of adverse cardiac events associated with fluoroquinolone use

Study	Outcomes	Antibacterial Groups	Incidence rate[β]	Crude OR/HR	Adj. OR/HR
Rao, Mann, et al, 2014	5-day all-cause mortality	Amoxicillin Levofloxacin	15 38	1.00 2.92[α] (2.00-4.26)	1.00 2.49[α] (1.70-3.64)
	5-day serious arrhythmia events	Amoxicillin Levofloxacin	9 28	1.00 2.43[α] (1.56-3.79)	1.00 3.13[α] (2.03-4.84)
Chou, Wang, et al, 2015	7-day serious arrhythmia	Amoxicillin-clavulanate Fluoroquinolones Moxifloxacin Ciprofloxacin Levofloxacin	12 23 57 15 26	1.00 1.97[α] (1.49-2.60) 4.92[α] (3.13-7.74) 1.27 (0.85-1.89) 2.22[α] (1.49-3.30)	1.00 2.07[α] (1.56-2.76) 3.30[α] (2.07-5.25) 1.07 (0.69-1.66) 1.41 (0.91-2.18)
	7-day cardiovascular death	Amoxicillin-clavulanate Fluoroquinolones Moxifloxacin Ciprofloxacin Levofloxacin	13 24 46 12 39	1.00 1.89[α] (1.45-2.49) 3.60[α] (2.20-5.88) 0.91 (0.59-1.40) 3.04[α] (2.18-4.25)	1.00 1.97[α] (1.49-2.59) 2.31[α] (1.39-3.84) 0.70 (0.44-1.12) 1.77[α] (1.22-2.59)

OR: odds ratio; HR: hazard ratio

[α]$p<0.05$

[β]Unit of Incidence rate was per 100,000 prescriptions in Rao, Mann, et al., 2014 study, and per 100,000 patients in Chou, Wang, et al., 2015 study.

Both studies found an increased risk of serious cardiac arrhythmias associated with fluoroquinolone use. The Rao, Mann, et al., 2014 study found a statistically significant three-fold risk of serious arrhythmias and a 2.5 fold risk of all-cause mortality over five days of levofloxacin use. The Chou, Wang, et al., 2015 study found a statistically significant two-fold

risk of serious cardiac arrhythmias or cardiovascular mortality over seven days of fluoroquinolone use (together including moxifloxacin, levofloxacin, and ciprofloxacin). Although these two studies showed a statistically significant increased risk, the absolute risks of serious cardiac arrhythmias associated with fluoroquinolone use show that these adverse reactions are infrequent and ranged from15 to 57 per 100,000 users of fluoroquinolones. However, this should be compared to absolute risk of 9-12 per 100,000 users of amoxicillin or amoxicillin-clavulanate. Fluoroquinolone users with underlying cardiovascular disease appeared to have a higher baseline risk for serious cardiac arrhythmias than those without cardiovascular disease. The absolute risk of serious cardiac arrhythmias ranged from 46-85 per 100,000 users with cardiovascular diseases versus 5-44 per 100,000 users without cardiovascular diseases.

Of note, the Rao and Chou studies were previously reviewed by DEPI in an earlier examination of arrhythmia and mortality with use of azithromycin. The reviewer, Dr. Mosholder, recommended moving the existing warning for QT prolongation to the boxed warning section in the fluoroquinolone labels. However, Dr. Mosholder's recommendation arose as an incidental finding, and he had not conducted a systematic review of the fluoroquinolone literature. Dr. Staffa, The Director of DEPI-II, determined that a complete review of the fluoroquinolone literature was warranted prior to recommending a boxed warning for the fluoroquinolone products, and wrote a memo recommending further study of the issue and discussion of Dr. Chen's review at this advisory committee meeting. We provide both Dr. Mosholder's review and Dr. Staffa's memo in Appendix F.

Peripheral Neuropathy

An observational analytic epidemiologic study of fluoroquinolones and peripheral neuropathy was found to contain sufficient information for the in-depth review (Etminan, Brophy, et al, 2014). The authors report a statistically significant two-fold risk (absolute RR = 2.07; 95% CI 1.56-2.74) of peripheral neuropathy with current new use (within the past 14 days) compared to no use of fluoroquinolones in a nested case-control study of older males. The results from this study are limited because of insufficient adjustment for confounders, lack of outcome validation, narrow patient population of older males, and lack of sample size justification.

Summary of Epidemiological Review

A review of higher-quality epidemiological studies published in the literature showed an increased relative risk for the adverse reactions of tendinitis/tendon rupture, cardiac arrhythmias, and peripheral neuropathy among users of fluoroquinolones. We found that the incidence of tendinitis/tendon rupture among fluoroquinolone-exposed persons ranged from 1.3 to 5.6 per 10,000 person-years and the incidence of cardiac arrhythmias ranged between 15-57 per 100,000 patients exposed to fluoroquinolones. Both adverse events are infrequent but appeared to be higher in comparison to unexposed persons or persons exposed to a different antibacterial drug. There appears to be a two-fold increase in the incidence of peripheral neuropathy, but the incidence rate is also likely to be similarly infrequent.

c. FDA Adverse Event Reporting System Review

A review of the FDA Adverse Event Reporting System (FAERS) was performed to characterize a constellation of symptoms leading to disability that had been observed during FDA monitoring of fluoroquinolone safety reports. This constellation of symptoms will be referred to in this review as "fluoroquinolone-associated disability" (FQAD). While most of the individual AEs that exist within FQAD are currently described in fluoroquinolone labeling, the particular constellation of symptoms across organ systems is not. Individuals with FQAD were defined as U.S. patients who were reported to be previously healthy and prescribed an oral fluoroquinolone antibacterial drug for the treatment of uncomplicated sinusitis, bronchitis, or urinary tract infection (UTI). To qualify, individuals had to have AEs reported in two or more of the following body systems: peripheral nervous system, neuropsychiatric, musculoskeletal, senses, cardiovascular, and skin. These body systems were chosen as they had been observed to be frequently involved with the fluoroquinolone reports describing disability. In addition, the AEs had to have been reported to last 30 days or longer after stopping the fluoroquinolone, and had to have a reported outcome of disability.

The regulatory definition of disability was used for this review, i.e., "a substantial disruption of a person's ability to conduct normal life functions," (21 CFR 314.80: Postmarketing reporting of adverse drug experiences). Whether a case report met a legal definition of disability was not a consideration for this review, and FQAD should not be construed to represent a legal definition of disability. A "healthy patient" was defined as a person able to perform all of the usual activities of daily living without significant restrictions prior to taking the fluoroquinolone. Patients were included if they had controlled disease states, such as hypertension, hypothyroidism, or hyperlipidemia.

The FAERS database was searched with the strategy described in Table 3.

Table 3. FAERS Search Strategy*	
Date of search	May 30, 2015
Time period of search	November 1, 1997† – May 30, 2015
Product Terms	Avelox (moxifloxacin), Cipro, Cipro XR, Proquin XR (ciprofloxacin), Factive (gemifloxacin), Levaquin (levofloxacin), Floxin (ofloxacin)
Indication	Sinusitis acute, Sinusitis bacterial, Sinusitis Bronchitis acute, Bronchitis, Bronchitis bacterial Cystitis, Acute cystitis, Cystitis bacterial Urinary tract infection, UTI-urinary tract infection, Urinary tract infection bacterial
MedDRA Search Terms	All PT terms searched
Other Criteria	US cases only Outcome: Disability only Oral dosage forms
* See Appendix G for a description of the FAERS database. † Date that AERS database went online.	

FAERS reports were excluded if they met any of the following criteria:

1. Events reported to have resolved within 30 days of stopping the fluoroquinolone.

2. Adverse events reported from only one or none of the following body systems: Peripheral Nervous System; Musculoskeletal; Neuropsychiatric; Senses (vision, hearing, etc.); Cardiovascular; or Dermatology.

3. Reported to be diagnosed with an indication other than uncomplicated acute bacterial sinusitis, bronchitis, or UTI.

4. Patient with a reported pre-existing medical history or taking medications that could confound the case. Examples include disease states such as fibromyalgia, rheumatoid arthritis, lupus, history of long-term steroid use, diabetes with complications, Lyme disease, multiple sclerosis, renal or hepatic impairment, cancer chemotherapy, HIV, joint replacement, or organ transplant.

5. Duplicate reports.

6. If more than one fluoroquinolone was described in the report, the case was selected for the fluoroquinolone most recently taken or being taken when the disability occurred (i.e., cases were not included twice).

7. Not enough information to properly evaluate the report.

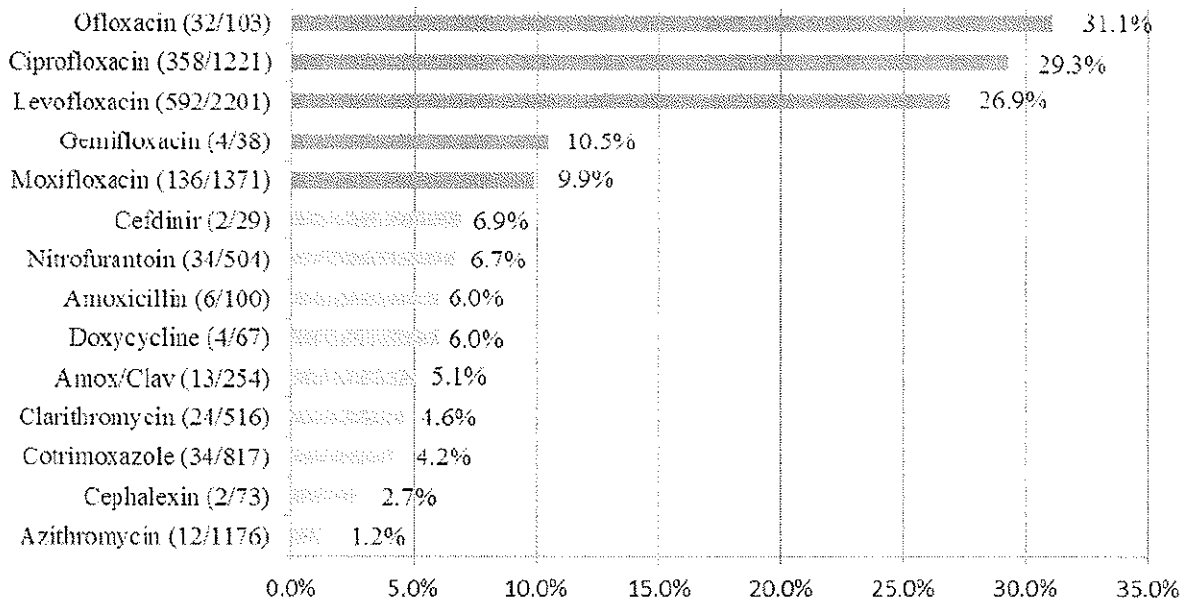
The FAERS search retrieved a total of 1,122 reports. Table 4 shows the number of disability reports for each fluoroquinolone in US patients who were being treated for the indications of uncomplicated sinusitis, bronchitis, or UTI.

Table 4: Number of Disability Reports in FAERS in US Patients Orally Treated for the Indication of Uncomplicated Cases of Sinusitis, Bronchitis, and/or UTI	
Fluoroquinolone	**Number of Reports***
Levofloxacin	592
Ciprofloxacin	358
Moxifloxacin	136
Ofloxacin	32
Gemifloxacin	4
TOTAL	1,122

* The numbers of reports listed are crude counts that may include duplicate reports.

The numbers of reports listed are crude counts that may include duplicate reports, and are presented without regard to causality assessment. The percentage of disability reports among all serious reports for each fluoroquinolone was also calculated (Figure 6). This was then compared to 9 other antibacterial drugs that have been, or are being used, for the treatment of these three uncomplicated infections. The search criteria for the other 9 antibacterial drugs were the same as for the fluoroquinolones.

Figure 6: Percentage of Disability Reports* Among all Serious Reports During Use for Uncomplicated Sinusitis, Bronchitis, and UTI (Oral and US only)

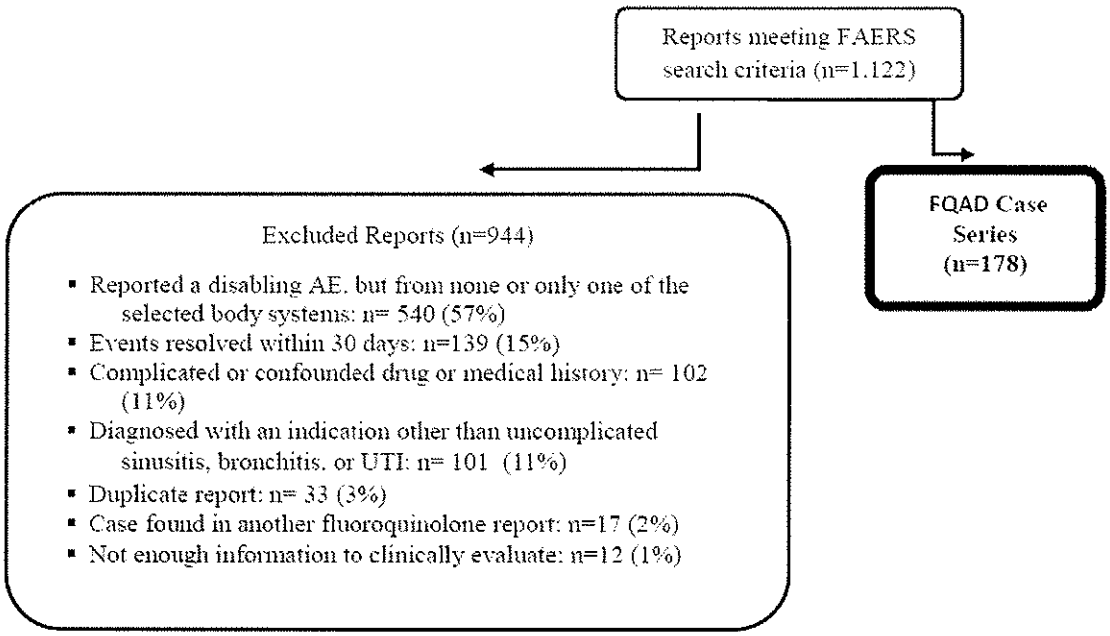


*Number of reports reporting disability divided by the total number of serious adverse event reports for oral dosage forms, from November 1, 1997 to May 30, 2015

Compared with the other 9 antibacterial drugs, all 5 fluoroquinolones had the highest percentages of disability reports for these uncomplicated infections, ranging from 9.9% to 31.1%.

After reviewing each of the 1,222 individual reports and applying the exclusion criteria described above, 178 cases were included in this case series of FQAD (Figure 7). See Appendix J for the FAERS case report information.

Figure 7: FAERS Case Selection



A majority of the reports that were excluded (57%) were patients who did not report an AE from two or more of the selected body systems. These reports, a total of 540, still described a disabling outcome, such as peripheral neuropathy or tendon rupture.

The percentage of FQAD cases identified among the total disability reports for each fluoroquinolone was similar (Table 5).

Table 5: US Disability Reports associated with Oral Fluoroquinolones and FQAD Cases			
	Total Disability Reports	**Total FQAD Cases**	**Percentage of Reports**
Levofloxacin	592	91	15%
Ciprofloxacin	358	65	18%
Moxifloxacin	136	19	15%
Ofloxacin	32	2	--*
Gemifloxacin	4	1	--*
TOTAL	1,122 reports	178 cases	

*Ofloxacin and gemifloxacin had too few cases for evaluation so a percentage is not calculated.

Although comparing reports to cases is not equivalent because reports in Table 5 were not de-duplicated, these data still provide a general idea of the percentages of FQAD among all disability reports.

Table 6 summarizes descriptive characteristics of the 178 FAERS cases of FQAD reported with all 5 currently marketed oral fluoroquinolones in the U.S.

Table 6: Descriptive Characteristics of FQAD Cases Reported to FDA from November 1, 1997-May 30, 2015 (n=178)		
Age (n=173)	Mean: 48.1 years Median: 48 years Range: 13-84 years	0-29 years: n=15 (9%) 30-59 years: n= 128 (74%) ≥ 60 years: n=30 (17%)
Report type	Direct: 152 (85%) Expedited: 18 (10%) Non-expedited: 8 (5%)	
Sex	All cases (n=178) Female: 138 (78%) Male: 40 (22%)	Non-UTI cases (n=93): Female: 74% Male: 26%
Reported Indication for FLUOROQUINOLONE Therapy	Cystitis/UTI—84 (47%) Sinusitis—59 (33%) Bronchitis—26 (15%) Sinusitis/bronchitis—7 (4%) Bronchitis/UTI—1 (<1%) Sinusitis/bronchitis/UTI—1 (<1%)	
Onset of AEs from start of FLUOROQUINOLONE therapy (n=102)	Mean: 5.4 days Median: 3 days Range: 1 hour-3 months Onset 1-2 days of starting FLUOROQUINOLONE: n=49 (48%) Onset 3-4 days of starting FLUOROQUINOLONE: n=20 (20%) Onset 5-10 days of starting FLUOROQUINOLONE: n=21 (20%) Onset >10 days of starting FLUOROQUINOLONE: n=12 (12%)	
Duration of AEs *at the time the report was sent to the FDA* (n=166)	Mean: 61.2 weeks (14 months) Median: 30 weeks (7 months) Range: 30 days—9 years ≥ 1 year: n=39 (23%)	

The mean and median age for the patients in this case series were 48.1 and 48 years, respectively. Although there was a wide range in age, from 13 to 84 years, nearly three-quarters of the cases (74%) occurred in patients 30-59 years of age.

There were also two characteristics of this case series that stood out. The first was that 85% of the cases were direct reports to FDA from the public, which is an unusually high number. Over the past 10 years, the percentage of direct reports overall in FAERS has ranged from 2.4 to 6.3%.

The other characteristic was that 78% of the patients were female. Even when all UTI cases were removed (approximately 80% of the UTI cases were in women), 74% of the cases still occurred in women. Of note, 59% of FAERS reports for ciprofloxacin, levofloxacin, and moxifloxacin for all indications were for female patients. Assuming that a clinical entity such as FQAD exists, it is unclear whether women may be at increased risk, if they are more likely to submit a report, or if there may be another unidentified reason. The drug use data sheds some light on this imbalance

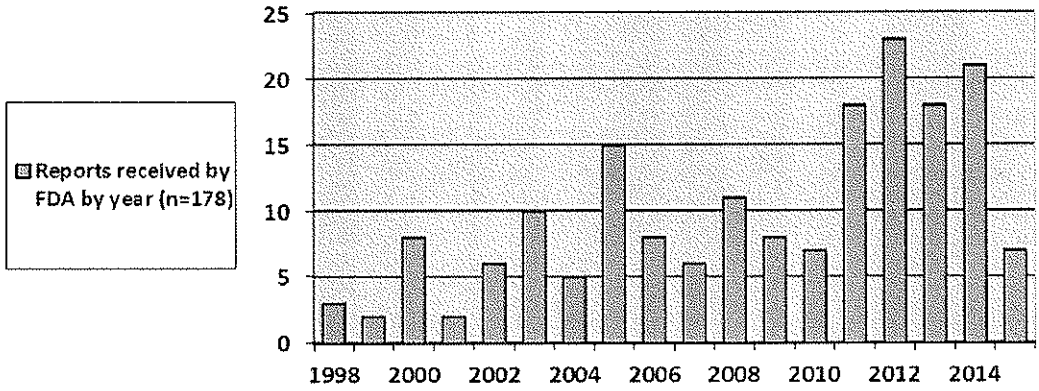
because women were more likely to be offered a prescription for a fluoroquinolone (see section IV on drug utilization patterns).

The mean and median time to onset of adverse events was 5.4 days and 3 days, respectively. However, the range was very wide, from 1 hour after taking the first dose to 90 days after the drug was discontinued. In almost half of the cases (48%), the onset was rapid, occurring after one or two doses of the drug. In 12% of the cases, the onset occurred more than 10 days after starting the fluoroquinolone, which in most cases would have been after fluoroquinolone therapy had ended.

The duration of the disabling adverse events was defined as the ongoing duration at the time the report was sent to FDA. The mean was 61.2 weeks (14 months), and the longest duration reported was 9 years after the events started. The actual duration cannot be determined without regular follow-up over a period of years, and it is possible that some symptoms may become permanent.

Figure 8 shows the years that FDA received the FQAD cases. Most notable is the increase in reporting over the last 5 years. Drug use data does not show an overall increase in fluoroquinolone prescribing over the same time period. This increase may be related to a general increase in reporting to FAERS or a focused effort by patients to report these AEs to the FDA. In addition, there was no U.S. geographic clustering of the cases.

Figure 8: FQAD Cases Received by Year from Nov 1, 1997 to May 30, 2015



For inclusion in this case series, each of the 178 cases had to have an AE in two or more of six body systems. Musculoskeletal events, which included tendon, joint, and/or muscle, were reported in 97% of the cases. This was followed by neuropsychiatric events in 68%, and

peripheral nervous system events in 63% (Table 8). These 3 body system events were reported much more frequently than the other 3 included body systems (senses, skin, and cardiovascular). The most commonly reported symptom across almost all cases was pain. Of note, if patients reported that their ongoing pain was causing insomnia, depression, or some other secondary AE, those secondary AEs were not included.

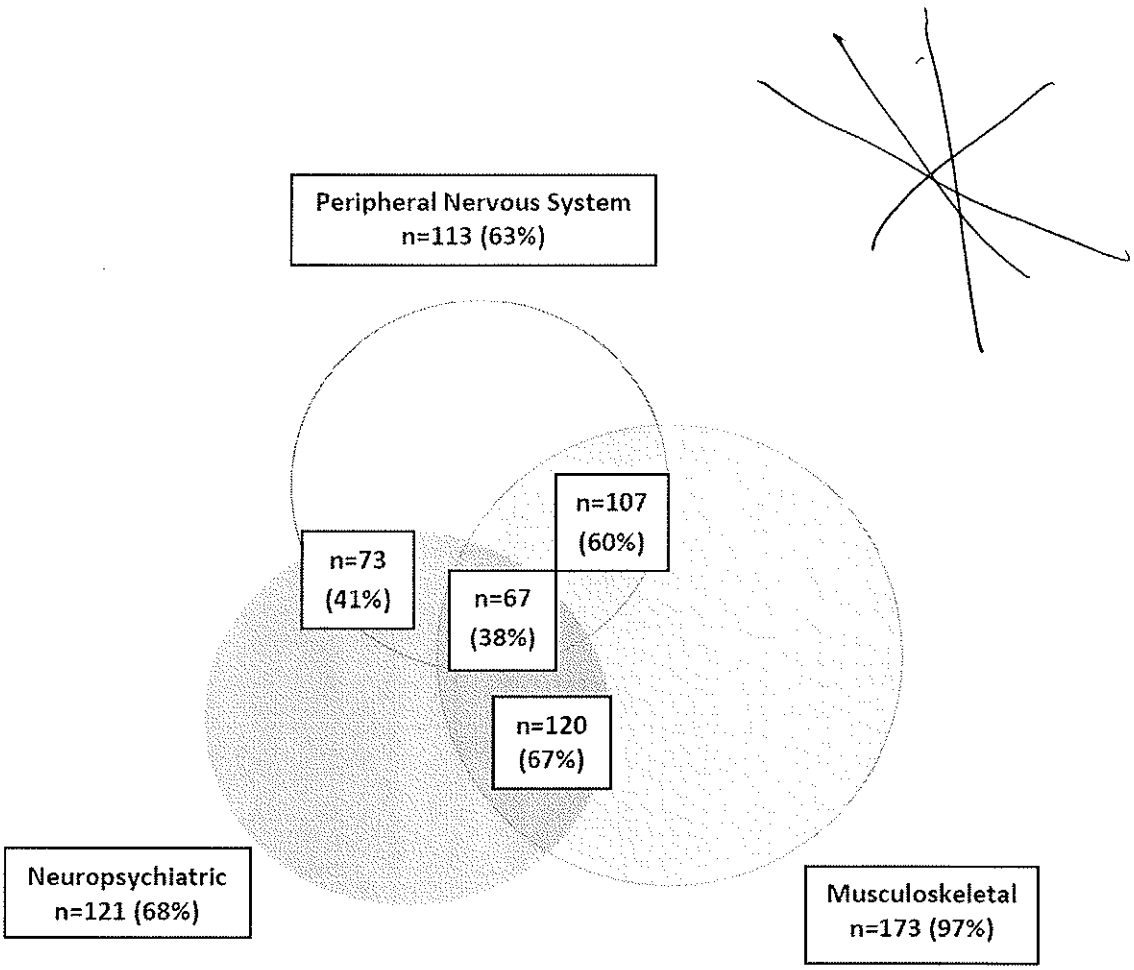
Table 8: Body Systems in FQAD Cases

Organ System	Percentage of Cases Involved (n = 178)
• Musculoskeletal (tendon/joint/muscle):	97%
• Neuropsychiatric:	68%
• Peripheral Nervous System:	63%
• Senses (vision, hearing, etc.):	32%
• Skin:	15%
• Cardiovascular:	12%

Most of the specific AE terms found in the FAERS database are already included in the labels for all fluoroquinolones.

Figure 10 is a Venn diagram showing the number of cases in the three body systems that had the highest number of reports (musculoskeletal, peripheral nervous system, and neuropsychiatric), as well as the overlap among these body systems.

Figure 10: Venn Diagram of FQAD Cases that Reported an Adverse Event from One of the Top 3 Body Systems (n=178)



There was considerable overlap among these three groups. Forty-one percent of patients who had a neuropsychiatric AE also experienced an AE from the peripheral nervous system; 60% of patients had AEs from both the musculoskeletal and peripheral nervous system; and 67% had both neuropsychiatric and musculoskeletal AEs. In addition, 38% of patients had AEs from all 3 body systems.

In Table 9, the percentage of AE cases that occurred with each individual fluoroquinolone was calculated by body system.

Table 9: Percentage of Adverse Events Cases for Each Fluoroquinolone by Body System

	Musculo-skeletal	Peripheral Nervous System	Neuropsychiatric	Senses	Cardio-vascular	Skin
Levofloxacin (n=91)	98%	52%	74%	30%	10%	10%
Ciprofloxacin (n=65)	94%	78%	66%	31%	12%	15%
Moxifloxacin (n=19)	95%	79%	65%	30%	10%	15%
Ofloxacin* (n=2)	--	--	--	--	--	--
Gemifloxacin* (n=1)	--	--	--	--	--	--

*Ofloxacin and gemifloxacin had too few cases for evaluation so a percentage is not calculated.

Overall, the musculoskeletal system was most commonly involved, followed by the peripheral nervous system and neuropsychiatric system.

The following direct report was illustrative of the case series:

Case #5699626, Direct report, 2004

This patient received a 10-day supply of levofloxacin 500 mg to treat a sinus infection. The onset of adverse reactions occurred 2 days after starting the drug.

"Prior to taking this drug, I was a healthy 49-year old, an advanced downhill skier, with NO medical problems. I could barely walk, had to crawl up my staircase. I had severe muscle weakness, muscle burning and joint pain in all my limbs...I ached and burned in what seemed every tendon and muscle in my body...I continue to suffer 22 months later with the following disabling conditions: Severe tendon/muscle pain and tightness, tendinitis, tingling, numbness, prickling, pins and needles sensations in my extremities. Electrical sensations. Feeling of worms crawling under my skin. Severe arm and leg weakness. Muscle twitching, spasms and contractions. Severe muscle tenderness. To poke my muscles feels like a bee sting! Inability to sleep due to pain 24 hours per day, 7 days per week. Inability to work due to pain and weakness. Difficulty thinking clearly, confusion. Chronic fatigue."

This FAERS review identified 178 previously healthy patients who took an oral fluoroquinolone for the treatment of uncomplicated sinusitis, bronchitis, or UTI, and developed FQAD. Although a wide age range was reported, the majority of cases (74%) were in patients 30 to 59 years of age. Quite a few reporters described how seriously the disability impacted their lives, including losing jobs, the resulting lack of health insurance, large medical bills, financial problems, and family tension or dissolution. In addition, the Boxed Warning states that fluoroquinolones "...are associated with an increased risk of tendinitis and tendon rupture in all ages. This risk is further increased in older patients usually over 60 years of age." In this case series, which included cases of tendon rupture, only 17% of patients were found to be 60 years of age or older.

The mean duration of the disabling adverse events at the time of the reports was 14 months, and the longest duration reported was 9 years. Several cases reported that selected adverse events either resolved or improved, but these cases also reported events that got worse or continued unchanged. It is possible that the symptoms may be permanent in patients who continue to have symptoms years after stopping the drug.

Long-term pain (of any kind) was the most commonly reported symptom across almost all cases, which is not surprising with 97% of all cases reporting one or more musculoskeletal (tendon/joint/muscle) symptoms. The impact of the neuropsychiatric events in these cases was also compelling. The ongoing AEs were reported to be quite distressing and affected employment and quality of life.

A potential limitation of this review is that the patient population in this case series was narrow in scope. These were patients who reported being previously healthy and were being treated for uncomplicated infections that developed FQAD. Other reports with patients who were being treated for more serious infections, had a pre-existing confounding medical history, or who were taking concomitant medications that could cause additive or synergistic AEs, were excluded from the definition of FQAD. Another limitation is that we are currently unaware of a plausible biological mechanism that could explain the pattern of involvement of multiple organ systems that were observed during this review. A final limitation is that all cases described as UTI were included in this case series. The focus on oral antibacterial drug use likely restricted cases to uUTI, but we acknowledge that oral fluoroquinolones may be used for the treatment of complicated UTI.

In conclusion, we find an association between oral fluoroquinolone use in previously healthy U.S. patients being treated for uncomplicated cases of sinusitis, bronchitis, or UTI, and the development of FQAD. While the individual components are included in fluoroquinolone labels, a description of the constellation of disabling adverse events is not currently described in the fluoroquinolone labels.

IV. DRUG UTILIZATION PATTERNS FOR ORAL FLUOROQUINOLONES

Proprietary drug utilization databases available to the Agency were used to conduct drug utilization analyses of the selected systemic oral fluoroquinolones (see Appendix H for full database descriptions and limitations).

IMS Health, IMS National Sales Perspectives™ was used to determine the various retail and non-retail channels of distribution for the oral forms of ciprofloxacin, levofloxacin, moxifloxacin, gemifloxacin, and ofloxacin. Sales data for 2014 indicated that approximately 82% of oral ciprofloxacin, levofloxacin, moxifloxacin, gemifloxacin, and ofloxacin bottles were distributed to outpatient retail pharmacy settings, followed by 17% to non-retail pharmacy settings, and 1% to mail-order/specialty pharmacies.[6] As a result of these distribution patterns and the nature of the questions being addressed, only U.S. outpatient retail pharmacy utilization data were analyzed. Data from mail-order/specialty and non-retail settings, including inpatient hospitals, were not included in this analysis.

The IMS, National Prescription Audit™ (NPA) database was used to provide the nationally estimated number of prescriptions for oral fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin, gemifloxacin, and ofloxacin) dispensed from outpatient retail pharmacy settings in the U.S., from 2010 through 2014. The database was also used to obtain prescriber specialty data for the selected oral fluoroquinolones for 2014.

The IMS Health, Vector One®: Total Patient Tracker (TPT) database was used to provide the nationally estimated number patients receiving dispensed prescriptions for oral fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin, and gemifloxacin) from outpatient retail pharmacies in the U.S., from 2010 through 2014, stratified by patient age and sex.

The Encuity Treatment Answers™ with Pain Panel was used to provide the most common diagnoses mentioned during visits to office-based physicians, associated with the use of ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin, and gemifloxacin for 2010 and 2014. This U.S. office-based physician survey database was also used to provide the most common drugs mentioned to be associated with selected ICD9 codes for possible acute sinusitis, ABECB, and uUTI, stratified by molecule, for 2010 and 2014. Acute sinusitis was broadly captured using ICD9 461.x. Possible ABECB was broadly defined using ICD9 codes for COPD with exacerbation [ICD9: 49121.2]; obstructive chronic bronchitis with exacerbation [ICD9: 49121.0]; and obstructive chronic bronchitis with acute bronchitis [ICD9: 49122.0]; and possible uUTI were broadly defined using the ICD9 codes for acute cystitis [ICD9: 59500.0]; cystitis NEC [ICD9: 59589.0]; cystitis NOS [ICD9: 59590.0]; and urinary tract infection NOS [ICD9: 59900.0]).

Drug Utilization Results

The results of the IMS NPA database showed that during each year approximately 32 million to 33 million total prescriptions for oral fluoroquinolone products were dispensed from outpatient

[6] IMS Health National Sales Perspective (NSP), Y2014, Extracted AUG2015, Source File: NSP_2015-896 FQ AC 2014

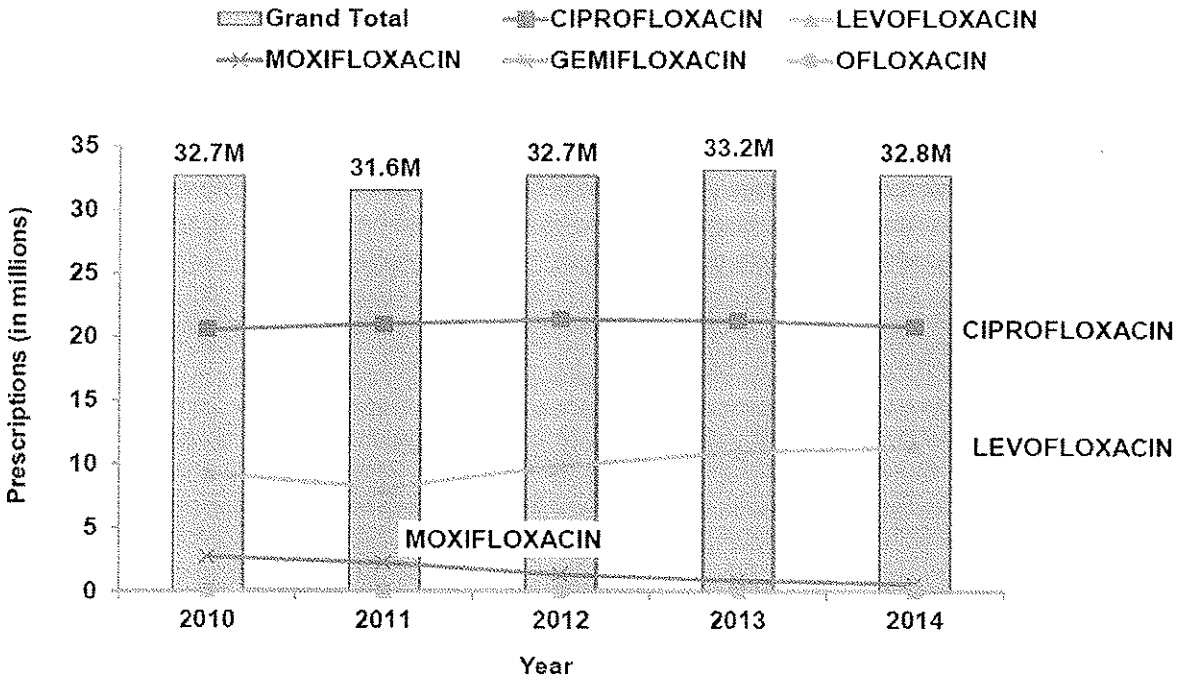
retail pharmacies in the U.S. Ciprofloxacin accounted for the majority of dispensed prescriptions each year with 63% to 66% of the total (approximately 21 million prescriptions) dispensed each year. Levofloxacin prescriptions dispensed increased from 9.3 million in 2010 to 11.3 million in 2014. The number of moxifloxacin prescriptions dispensed decreased by 78% from 2.7 million prescriptions in 2010 to 609,000 prescriptions in 2014. Gemifloxacin prescriptions dispensed decreased by 90% from 64,000 prescriptions in 2010 to 6,700 prescriptions in 2014. Ofloxacin prescriptions dispensed decreased by 74% from 37,000 prescriptions in 2010 to 9,500 prescriptions in 2014. Table 10 and Figure 11 show the number of dispensed oral fluoroquinolones from the years 2010 through 2014.

Table 10: Nationally estimated number of prescriptions for oral forms of selected fluoroquinolones dispensed from outpatient retail pharmacies in the U.S., stratified by molecule, from 2010 through 2014

	2010		2011		2012		2013		2014	
	TRx (N)	*Share%*	TRx (N)	*Share%*	TRx (N)	*Share%*	TRx (N)	*Share%*	TRx (N)	*Share%*
Total Prescriptions	32,666,213	*100%*	31,567,306	*100%*	32,712,846	*100%*	33,177,263	*100%*	32,768,680	*100%*
CIPROFLOXACIN	20,555,284	*62.9%*	21,033,382	*66.6%*	21,380,631	*65.4%*	21,286,243	*64.2%*	20,812,217	*63.5%*
LEVOFLOXACIN	9,263,006	*28.4%*	8,149,894	*25.8%*	9,903,630	*30.3%*	10,970,182	*33.1%*	11,331,292	*34.6%*
MOXIFLOXACIN	2,746,720	*8.4%*	2,282,053	*7.2%*	1,386,744	*4.2%*	893,422	*2.7%*	608,903	*1.9%*
GEMIFLOXACIN	64,307	*0.2%*	73,696	*0.2%*	22,869	*0.1%*	12,300	*0.0%*	6,733	*0.0%*
OFLOXACIN	36,896	*0.1%*	28,281	*0.1%*	18,972	*0.1%*	15,116	*0.1%*	9,535	*0.0%*

Source: IMS Health, National Prescription Audit (NPA), Y2010-2014, Extracted AUG2014

Figure 11: Nationally estimated number of prescriptions for oral forms of selected fluoroquinolones dispensed from U.S. outpatient retail pharmacies, stratified by drug, from 2010 through 2014



Source: IMS Health. National Prescription Audit (NPA), Y2010-2014. Extracted AUG2014

Of the estimated 33 million oral fluoroquinolone prescriptions dispensed in 2014, family practice was the top prescriber specialty with 20% (6.7 million prescriptions) of the total, followed by internal medicine with 19% (6.3 million prescriptions) and nurse practitioner with 10% (3.2 million prescriptions). Table 11 outlines the prescriber specialties from these data.

Table 11: Nationally estimated number of prescriptions dispensed for the oral forms of selected fluoroquinolones, stratified by prescriber specialties, from outpatient retail pharmacies in the U.S. in 2014

	TRx (N)	Share %
Grand Total	**32,768,680**	***100.0%***
Family Practice	6,706,881	*20.5%*
Internal Medicine	6,287,868	*19.2%*
Nurse Practitioner	3,209,545	*9.8%*
Osteopathic Medicine	3,172,033	*9.7%*
Physician Assistant	2,676,992	*8.2%*
Urology	2,186,872	*6.7%*
Emergency Medicine	1,685,179	*5.1%*
Specialty Unspecified	770,250	*2.4%*
Obstetrics/Gynecology	768,209	*2.3%*
General Surgery	487,293	*1.5%*
All Other Specialties	4,817,558	*14.7%*

Source: IMS Health National Prescription Audit (NPA), 2014, Extracted AUG 2014, Source File: NPA 2015-896 FQ AC 2014 by prescriber.xls

Next we describe the nationally estimated number of patients who received prescriptions for selected oral fluoroquinolones from U.S. outpatient retail pharmacies, stratified by the oral fluoroquinolone, from 2010 through 2014. The total number of patients who received a prescription for an oral fluoroquinolone remained stable with approximately 23 million patients in 2010 and 22 million patients in 2014. Unique patients who received ciprofloxacin dispensed prescription accounted for 64% (15 million patients) of the total patients in 2010, increasing slightly to 68% (15 million patients) of total patients in 2014. Unique patients who received levofloxacin dispensed prescription accounted for 33% of the total in 2010 (7.7 million patients) and increased slightly to 36% (8 million patients) of the total in 2014. Conversely, the number of unique patients who received a dispensed prescription for moxifloxacin, gemifloxacin, and ofloxacin declined overall from 2010 through 2014. Approximately 2.3 million unique patients received a dispensed prescription for moxifloxacin in 2010, decreasing to 479,000 patients in 2014. Unique patients who received a dispensed prescription for gemifloxacin increased slightly from 53,000 patients in 2010 to 62,000 patients in 2011, followed by a sharp decline to 4,900 patients in 2014. Unique patients who received dispensed prescription for ofloxacin declined steadily from 26,000 patients in 2010 to 6,000 patients in 2014.

In 2014, of the approximately 22 million unique patients who received a dispensed prescription for a selected oral fluoroquinolone, adult patients aged 18 years and older accounted for 98% of the total, while pediatric patients aged 0-17 years accounted for approximately 2% of the total patients. Female patients accounted for 65% of the total patients who received a dispensed prescription for oral fluoroquinolone in 2014. This is described in Table 12.

Table 12: Nationally estimated number of patients who received a dispensed prescription for a selected oral fluoroquinolone* from outpatient retail pharmacy in the U.S., stratified by patient age and sex, for year 2014

	Year 2014									
	Total Patients (N)	Share %	Male Patients (N)	Vert Share %	Horiz Share %	Female Patients (N)	Vert Share %	Horiz Share %	Unspecified Sex	Vert Share %	Horiz Share %
Total Patients	22,235,393	100%	7,739,277	100%	34.8%	14,469,902	100%	65.1%	26,501	100%	0.1%
0-17 years	379,773	1 7%	143,050	1 8%	37.7%	233,936	1.6%	61.6%	2,386	9.0%	0.6%
18+ years	21,801,950	98.1%	7,576,728	97.9%	34.8%	14,201,554	98.1%	65.1%	24,014	90.6%	0.1%
Unknown Age	82,949	0.4%	28,236	0.4%	34.0%	54,671	0.4%	65.9%	55	0 2%	0.1%

Unique patient counts may not be added across patient age subtotals due to patients aging during the study. Patients may be counted more than once in the individual age categories. Therefore, summing across patient age bands is not advisable and may result in overestimates of patient counts.

Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients 0-17 years of age include patients 17 years and 11 months

Source: IMS Health, Vector One®: Total Patient Tracker (TPT), Y2014, Extracted AUG2015, Source File: TPT 2015-896 FQ AC age sex 2014 AUG2015

We also evaluated the top diagnoses associated with the selected oral fluoroquinolones based on U.S. office-based physician surveys, stratified by molecule and ICD9 code (DX4), for 2010 and 2014. For 2010 and 2014, ciprofloxacin was the most commonly mentioned fluoroquinolone, followed by levofloxacin, moxifloxacin, gemifloxacin, and ofloxacin.

Urinary tract infection, not otherwise specified (ICD9 code 599.0) was the most common diagnosis associated with ciprofloxacin for each year, with 43% of drug use mentions[7] in 2014. Pneumonia, organism not otherwise specified (ICD9 code 486.0) was the top diagnosis associated with levofloxacin for each year with 17% of drug use mentions in 2010 and 22% in 2014. Chronic sinusitis, not otherwise specified (ICD9 473.9) was the top diagnosis associated with moxifloxacin with 21% of drug use mentions in 2010, whereas bronchitis, not otherwise specified (ICD9 code 499.0) was the top diagnosis in 2014, accounting for 22% of drug use mentions. Bronchitis, not otherwise specified (ICD9 490.0) was the top diagnosis associated with gemifloxacin with 49% of drug use mentions in 2010, whereas acute bronchitis (ICD9 466.0) was the top diagnosis in 2014, accounting for 90% of drug use mentions. Urinary tract infection,.not otherwise specified (ICD9 code 599.0) was the most common diagnosis associated with ofloxacin for each year; however, the number of drug use mentions was too low to provide reliable national estimates. See Appendix I for data table.

The following Tables 13 through 18 show the drug use mentions with the respective ICD9 codes for ABS, AEBCB-COPD and uUTI.

[7] The term "drug uses" refers to mentions of a drug in association with a diagnosis during a patient visit to an office-based physician. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in a prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

Tables 13 & 14: ABS: Top systemic antibiotics (oral forms only) by number of drug use mentions associated with acute sinusitis code ICD9 461.x, stratified by drug, as reported by U.S. office-based physician surveys for years 2010 and 2014

Table 13

2010	Uses (000)	*Share %*	95% C.I. (000)
Systemic Antibiotics	5,199	*100.0%*	4,859 - 5,539
amoxicillin/clav	1,223	*23.5%*	1,058 - 1,388
amoxicillin	1,015	*19.5%*	864 - 1,165
azithromycin	914	*17.6%*	771 - 1,057
cefdinir	569	*10.9%*	456 - 681
levofloxacin	393	*7.6%*	299 - 486
moxifloxacin	255	*4.9%*	179 - 330
cefuroxime	251	*4.8%*	176 - 326
sulfamethoxazole/tmp	129	*2.5%*	76 - 183
doxycycline	113	*2.2%*	63 - 163
clarithromycin	107	*2.1%*	58 - 155
cephalexin	72	*1.4%*	32 - 112
cefprozil	68	*1.3%*	29 - 107
gemifloxacin	30	*0.6%*	4 - 55
erythromycin	20	*0.4%*	< 0.5 - 41
cefuroxime	20	*0.4%*	< 0.5 - 41
All Others	21	*0.4%*	< 0.5 - 43

Table 14

2014	Uses (000)	*Share %*	95% C.I. (000)
Systemic Antibiotics	8,884	*100.0%*	8,412 - 9,356
amoxicillin/clav	2,515	*28.3%*	2,264 - 2,766
amoxicillin	2,274	*25.6%*	2,035 - 2,512
azithromycin	1,784	*20.1%*	1,573 - 1,996
levofloxacin	551	*6.2%*	434 - 669
cefdinir	545	*6.1%*	428 - 662
sulfamethoxazole/tmp	314	*3.5%*	225 - 402
moxifloxacin	244	*2.7%*	166 - 322
cephalexin	163	*1.8%*	99 - 226
cefuroxime	117	*1.3%*	63 - 171
clarithromycin	116	*1.3%*	62 - 170
cefixime	99	*1.1%*	49 - 149
cefprozil	52	*0.6%*	16 - 88
doxycycline	47	*0.5%*	13 - 82
cefuroxime	47	*0.5%*	13 - 81
penicillin	16	*0.2%*	0 - 36

Source: Encuity Treatment Answers™ with Pain, 2010&2014, Extracted AUG2014, Source File(s): PDDA 2015-896 FQ AC AUG2015

Tables 15 & 16: ABECB-COPD: Top systemic antibiotics (oral forms only) by number of drug use mentions associated with broadly defined acute bacterial exacerbation of chronic bronchitis (ABECB)* as reported by U.S. office-based physician surveys, stratified by drug, for years 2010 and 2014

Table 15

2010	Uses (000)	*Share %*	95% C.I. (000)
Systemic Antibiotics	510	*100%*	403 - 617
levofloxacin	158	*30.9%*	98 - 217
moxifloxacin	136	*26.7%*	81 - 191
doxycycline	94	*18.5%*	48 - 140
azithromycin	71	*14.0%*	31 - 111
clarithromycin	12	*2.5%*	< 0.5 - 29
tetracycline	12	*2.3%*	< 0.5 - 28
ciprofloxacin	9	*1.8%*	< 0.5 - 23
amoxicillin	6	*1.2%*	< 0.5 - 18
amoxicillin/clav	6	*1.2%*	< 0.5 - 18
cefuroxime	5	*1.0%*	< 0.5 - 16

Table 16

2014	Uses (000)	*Share %*	95% C.I. (000)
Systemic Antibiotics	594	*100%*	472 - 716
azithromycin	162	*27.3%*	98 - 226
levofloxacin	138	*23.3%*	79 - 197
doxycycline	98	*16.6%*	49 - 148
amoxicillin/clav	43	*7.2%*	10 - 75
ciprofloxacin	39	*6.6%*	8 - 70
moxifloxacin	39	*6.6%*	8 - 70
cefuroxime	35	*5.9%*	5 - 64
amoxicillin	20	*3.4%*	< 0.5 - 42
clarithromycin	13	*2.1%*	< 0.5 - 30
amoxicillin	7	*1.2%*	< 0.5 - 20

**ABECB definition was expanded to include COPD with exacerbation (ICD9: 49121.2), obstructive chronic bronchitis with exacerbation*
(ICD9: 49121.0), and obstructive chronic bronchitis with acute bronchitis (ICD9: 49122.0)
Source: Encuity Treatment Answers™ with Pain, 2010&2014, Extracted AUG2014, Source File(s): PDDA 2015-896 FQ AC AUG2015

Tables 17 & 18: uUTI: Top drug molecules (oral forms only) by number of drug use mentions associated with broadly defined uncomplicated urinary tract infection* (uUTI) as reported by U.S. office-based physician surveys, stratified by drug, for years 2010 and 2014

Table 17

2010	Uses (000)	Share %	95% C.I. (000)
Total Market	22,338	100.0%	21,632 - 23,043
ciprofloxacin	7,773	34.8%	7,357 - 8,189
sulfamethoxazole/tmp	5,550	24.8%	5,198 - 5,901
nitrofurantoin	4,534	20.3%	4,217 - 4,852
phenazopyridine	1,524	6.8%	1,340 - 1,709
levofloxacin	1,155	5.2%	994 - 1,315
cephalexin	502	2.3%	396 - 608
doxycycline	128	0.6%	74 - 181
cefdinir	96	0.4%	49 - 142
meth/me bl/salicy/na phos/hyos	93	0.4%	48 - 139
ampicillin	89	0.4%	44 - 133
All Others	894	4.0%	753 - 1,035

Table 18

2014	Uses (000)	Share %	95% C.I. (000)
Total Market	25,177	100%	24,383 - 25,971
ciprofloxacin	8,100	32.2%	7,649 - 8,550
nitrofurantoin	5,822	23.1%	5,440 - 6,204
sulfamethoxazole/tmp	5,610	22.3%	5,235 - 5,985
phenazopyridine	1,980	7.9%	1,758 - 2,203
levofloxacin	1,223	4.9%	1,048 - 1,399
cephalexin	968	3.8%	812 - 1,124
amoxicillin	226	0.9%	151 - 301
amoxicillin/clav	165	0.7%	100 - 229
cefdinir	113	0.5%	60 - 166
cefuroxime	80	0.3%	35 - 124
All Others	890	3.5%	741 - 1,040

Source: Encuity Treatment Answers™ with Pain, 2010&2014, Extracted AUG2014, Source File(s): PDDA 2015-896 FQ AC AUG2015

**uUTI definition was expanded to include acute cystitis (ICD9: 59500.0), cystitis NEC (ICD9: 59589.0), cystitis NOS (ICD9: 59590.0), and urinary tract infection NOS (ICD9 59900.0)*

In summary, the results of the drug utilization analyses show that oral fluoroquinolones are widely used in the U.S. outpatient retail pharmacy settings with approximately 33 million prescriptions dispensed to approximately 22 million patients in year 2014. Ciprofloxacin was the most commonly used fluoroquinolone during the study period, followed by levofloxacin. The vast majority of use was observed in adult patients aged 18 years and older. Females accounted for approximately two-thirds of the total patients who received a dispensed prescription for an oral fluoroquinolone in 2014.

According to office-based physician survey database in 2014, the most common diagnosis associated with ciprofloxacin was urinary tract infection NOS. Pneumonia organism NOS was the most commonly mentioned diagnosis for levofloxacin. For the diagnoses of interest (e.g. ABS, ABECB-COPD, and uUTI) we were unable to search on specific ICD9 codes for ABECB-COPD and uUTI in our search criteria because the terms "ABECB" and "uUTI" may be considered colloquial; therefore, we broadened the definitions of ABECB and uUTI to include ICD9 diagnosis codes likely to encompass ABECB and uUTI. As a result of our broadening the definitions of ABECB and uUTI using ICD-9 codes, we increased the potential for misclassification by possibly including more severe diagnoses. The degree of misclassification, if any, is not known.

We utilized the Encuity database's predefined market categories for the drugs most commonly associated with one of the three diagnoses of interest. Specifically, "systemic antibiotics" mentioned to be associated with selected ICD9 codes for ABS and ABECB-COPD were assessed and any drug mentioned to be associated with the ICD9 codes for uUTI were assessed.

This step was conducted to capture use of other drugs possible used to treat uUTIs such as nitrofurantoin and fosfomycin products which are approved for treating uUTI but were not included in this database's definition of "systemic antibiotics" category. As a result, we found that other non-antibiotic treatments, such as phenazopyridine, were commonly associated with uUTI. Also, we analyzed other drugs mentioned for acute sinusitis and ABECB and found that "systemic antibiotics" was the most common drug category or "class" associated with acute sinusitis in 2010 and 2014; whereas for ABECB, "systemic antibiotics" was the most common category mentioned in 2010, but "corticosteroids plain oral" was the top category reported for 2014. And, although the data from the "total market" category for acute sinusitis and ABECB are not shown, these results were included to show that other non-antibiotic treatments were commonly associated with acute sinusitis and ABECB.[8]

Indications for use were obtained using a monthly survey of 3,200 office-based physicians. Although these data are helpful to understand how drug products are prescribed by physicians, the small sample size and the relatively low usage of some of these products limits the ability to identify trends in the data. In general, physician survey data are best used to identify the typical uses for the products in clinical practice, and outpatient prescription data are best used to evaluate utilization trends over time. Results should not be overstated when nationally projected estimates of annual uses or mentions fall below 100,000 as the sample size is very small with correspondingly large confidence intervals.

From our analyses we observed that oral fluoroquinolones are a widely used class of antibacterial drugs, with ciprofloxacin and levofloxacin accounting for the majority of use. Adult female patients accounted for the largest proportion of patients for oral fluoroquinolones, nearly double the number of male patients. According to an office-based physician survey database, fluoroquinolones were among the most common antibacterial drugs associated with possible acute sinusitis, uUTI (broadly defined), and ABECB-COPD (broadly defined). However, due the limitations in the use of ICD9 codes to characterize drug use for these diseases and other limitations discussed, these results should be interpreted with caution.

V. OVERALL SUMMARY

An evaluation of placebo-controlled trials in ABS or mild ABECB-COPD show that a large proportion of patients randomized to receive placebo recovered and thus these illnesses appear to be self-limited for many patients. Indeed some of these trials showed no differences in outcome measures when comparing the antibacterial drug to placebo. There appears to be strong evidence for the benefit of antibacterial drug therapy for patients hospitalized for moderate or severe ABECB-COPD. The evaluation of trials in uUTI using a placebo or a non-antibacterial control showed a treatment benefit of antibacterial drug therapy on the outcome measure of microbiologic eradication on follow-up urine culture. On the outcome measure of symptom resolution, the placebo-controlled trials showed a treatment benefit but the ibuprofen-controlled trial showed similar outcome findings between treatment groups. A random effects meta-

[8] Source: Encuity Treatment Answers with Pain, Y2014, Extracted AUG2015

analysis of all five trials including the ibuprofen controlled trial showed an overall treatment benefit on both outcome measures.

When considering the potentially modest treatment benefits of antibacterial drugs for these three indications, the risks of the fluoroquinolone antibacterial drugs should be taken into consideration. Over the life-cycle of these drugs, several adverse reactions have been reported, and most of them were not evident in the pre-approval safety databases. While the actual incidence of each adverse reaction is difficult to ascertain, the seriousness of certain uncommon adverse reactions deserves attention, such as tendinitis/tendon rupture, peripheral neuropathy, or cardiac arrhythmias. The identification of constellations of adverse reactions that appear to be long-term or permanently disabling is also a particular concern.

The use of fluoroquinolone antibacterial drugs has not shown an overall change in the past several years. This is particularly notable in light of the introduction of Boxed Warnings for tendinitis and tendon rupture in 2008 and the enhancement of Warnings and Precautions for the potential irreversibility of peripheral neuropathy in 2013.

VI. ISSUES FOR DISCUSSION

1. Consider the risks and benefits of the systemic fluoroquinolone antibacterial drugs for the indication for the treatment of acute bacterial sinusitis (ABS), in the context of available safety information on fluoroquinolone antibacterial drugs and the treatment effects of antibacterial drugs for ABS. Discuss any specific recommendations concerning labeling, if any, including the safety information regarding the constellation of adverse reactions that were characterized as FQAD.

2. Consider the risks and benefits of the systemic fluoroquinolone antibacterial drugs for the indication for the treatment of acute bacterial exacerbation of chronic bronchitis in patients with chronic obstructive pulmonary disease (ABECB-COPD), in the context of available safety information on fluoroquinolone antibacterial drugs and the treatment effects of antibacterial drugs for ABECB-COPD. Discuss any specific recommendations concerning labeling, if any, including the safety information regarding the constellation of adverse reactions that were characterized as FQAD.

3. Consider the risks and benefits of the systemic fluoroquinolone antibacterial drugs for the indication for the treatment of uncomplicated urinary tract infection (uUTI), in the context of available safety information on fluoroquinolone antibacterial drugs and the treatment effects of antibacterial drugs for uUTI. Discuss any specific recommendations concerning labeling, if any, including the safety information regarding the constellation of adverse reactions that were characterized as FQAD.

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