FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

JOINT MEETING OF THE ANTIMICROBIAL DRUGS ADVISORY COMMITTEE AND THE DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE

Thursday, November 5, 2015

8:01 a.m. to 6:05 p.m.

FDA White Oak Campus

Building 31, The Great Room

White Oak Conference Center

Silver Spring, Maryland

Meeting Roster

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C O N T E N T S

C O N T E N T S (continued)

C O N T E N T S (continued)

P R O C E E D I N G S

(8:00 a.m.)

Call to Order

Introduction of Committee

CAPT PARISE: Good morning, everyone. I'd first like to remind you to please silence your cell phones, smartphones, and any other devices if you have not already done so. I'd also like to identify the FDA press contact, Lyndsay Meyer. If you are present, please stand. Thank you.

My name is Captain Monica Parise. I'm the chairperson for the Antimicrobial Drugs Advisory Committee. I'll now call this joint meeting of the Antimicrobial Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee to order.

Just before we start, I wanted to mention, for those of you who may not have heard, that Dr. Alan Magill, who was a member of the Antimicrobial Drugs Advisory Committee, passed away recently unexpectedly and prematurely. So can we

just take a moment of silence just in his remembrance?

(Moment of silence.)

CAPT PARISE: We're going to start by going around the table and introducing yourself. And just in advance, this is a large group, and I will apologize if Jennifer and I are looking at our seating chart so we can get your names right, but we're going to do our best. So let's start on the right.

DR. KARTSONIS: Dr. Nicholas Kartsonis. I'm the industry representative from Merck Research Laboratories.

DR. STAUD: Roland Staud. I'm with the University of Florida, and my specialty is rheumatology.

DR. RUSSELL: Jon Russell, retired academic rheumatologist and recently doing research on fibromyalgia in the community in San Antonio.

DR. VITIELLO: Ben Vitiello. I'm a psychiatrist. I'm from the National Institute of

Mental Health in Bethesda.

DR. HOGANS: My name is Dr. Beth Hogans. I'm from Johns Hopkins. I'm a neurologist.

DR. FLOYD: I'm James Floyd from the University of Washington. I'm a general internist and epidemiologist.

DR. CHOUDHRY: Niteesh Choudhry from Harvard University and Brigham and Women's Hospital, where I'm a general internist and health services researcher.

MS. PHILLIPS: Marjorie Shaw Phillips from Georgia Regents Medical Center in Augusta and University of Georgia College of Pharmacy. I'm a clinical research pharmacist, pharmacy manager, and have an emphasis in medication safety.

DR. BESCO: Good morning. My name is Kelly Besco. I'm the medication safety officer for the Ohio Health Hospital System in Columbus, Ohio. I'm a pharmacist by background. Thank you.

DR. CORBETT: Hi. I'm Amanda Corbett. I'm a clinical associate professor at the University of

North Carolina Eshelman School of Pharmacy.

DR. SCHEETZ: Marc Scheetz, Midwestern University, clinical associate professor.

DR. GERHARD: Tobias Gerhard, pharmacoepidemiologist from Rutgers University.

DR. WINTERSTEIN: I'm Almut Winterstein. I'm professor for pharmaceutical outcomes and policy at the University of Florida. I'm a pharmacoepidemiologist.

CAPT PARISE: Dr. Monica Parise from the Centers for Disease Control, adult infectious disease specialist.

LCDR SHEPHERD: Jennifer Shepherd. I'm the designated federal officer.

DR. LO RE: My name is Vincent Lo Re. I'm in the Division of Infectious Diseases, the Center for Clinical Epidemiology and Biostatistics, and the Center for Pharmacoepidemiology Research and Training at the University of Pennsylvania.

MS. SCHWARTZOTT: I'm Jennifer Schwartzott. I'm the patient representative.

DR. ANDREWS: I'm Ellen Andrews from the Connecticut Health Policy Project, and I'm from the Connecticut Health Policy Project.

DR. BADEN: Lindsey Baden. I'm at Harvard Medical School, Brigham and Women's Hospital, Dana Farber Cancer Institute. I'm an infectious disease specialist.

DR. DASKALAKIS: Demetre Daskalakis. I'm an infectious disease specialist focusing on HIV prevention and treatment, and I'm the assistant commissioner for the Bureau of HIV/AIDS Prevention and Control, New York City Department of Health.

DR. ARRIETA: Antonio Arrieta. I do pediatric infectious diseases at Children's Hospital of Orange County, University of California Irvine.

DR. HONEGGER: Dr. Jonathan Honegger. I do pediatric infectious diseases at the Ohio State University.

DR. SCHMID: Chris Schmid. I'm a professor of biostatistics at Brown University.

DR. PROESTEL: Scott Proestel, director,

Division of Pharmacovigilance II, FDA.

DR. STAFFA: Judy Staffa, director, Division of Epidemiology II, FDA.

DR. TOERNER: Joe Toerner, deputy director for safety in the Division of Anti-Infective Products at FDA.

DR. NAMBIAR: Sumathi Nambiar, director, Division of Anti-Infective Products, CDER, FDA.

DR. COX: Good morning. Ed Cox, director, the Office of Antimicrobial Products, CDER, FDA.

DR. BALL: I'm Bob Ball, deputy director, Office of Surveillance and Epidemiology, FDA.

CAPT PARISE: Thank you, everyone.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record

only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion.

Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or during lunch. Thank you.

Now I'll pass it to Lieutenant Commander Jennifer Shepherd, who will read the conflict of interest statement.

Conflict of Interest Statement

LCDR SHEPHERD: Good morning. The Food and Drug Administration is convening today's joint

meeting of the Antimicrobial Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry representative, all members and temporary voting members of the committees are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of these committees' compliance with federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 USC Section 208 is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of these committees are in compliance with federal ethics and conflict of interest laws. Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special government employees

and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Related to the discussion of today's meeting, members and temporary voting members of these committees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 USC Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves the risks and benefits of the systemic fluoroquinolone antibacterial drugs for the treatment of acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis in patients who have chronic

obstructive pulmonary disease, and uncomplicated urinary tract infections in the context of available safety information and the treatment effect of antibacterial drugs in these clinical conditions.

This is a particular matters meeting during which general issues will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they may have made concerning the topic at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Nicholas Kartsonis is participating in this meeting as a nonvoting industry representative, acting on behalf of regulated industry. Dr. Kartsonis's role at this meeting is to represent

industry in general and not any particular company. Dr. Kartsonis is employed by Merck & Company.

We would like to remind members and temporary voting members that if the discussions involve any other topics not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committees of any financial relationships that they may have regarding the topic that could be affected by the committees' discussions. Thank you.

CAPT PARISE: Thank you. We will now proceed with Dr. Nambiar's introductory remarks.

FDA Introductory Remarks – Sumathi Nambiar

DR. NAMBIAR: Thank you, Dr. Parise, and good morning, everybody. I'll take this opportunity to welcome you to the joint meeting of the Antimicrobial Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee.

So why are we here today? We are here to discuss the benefits and the risks of the systemic fluoroquinolone antibacterial drugs for three specific indications. And we are doing this given that there have been recent scientific advances in clinical trials, and the safety profile that has emerged over the life cycle of these drugs.

So today, we will be discussing the following three indications: acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, and uncomplicated urinary tract infections.

This table provides a list of the currently available systemic fluoroquinolones and the year they were initially approved. Of the three indications that we're going to discuss today, this table summarizes the labeled indications for the various systemic fluoroquinolones that are currently in the market. I think it's worth noting that the indications may not be identical across the various drugs, given that these were approved over a fairly long period of time.

As in any other labeling, the labeling for systemic fluoroquinolones has specific sections that address the various safety concerns that have emerged. The products carry a boxed warning regarding the risk of tendinopathy and tendon rupture and the risk of exacerbation of myasthenia gravis.

The warnings and precautions section again across all labels is not identical, and this is not an all-inclusive list. But these are the more common ones, and they are seen across the various fluoroquinolones currently in the market: hypersensitivity reactions, hepatotoxicity, effects on the central nervous system, risk of peripheral neuropathy, prolongation of QT interval, blood glucose disturbances, and photosensitivity.

In addition, the adverse reactions section of the package insert lists the adverse reactions seen in clinical trials and postmarketing. In addition, all systemic fluoroquinolones have a medication guide, as required under 21 CFR 208.1. So with

every prescription of a fluoroquinolone, the patient is required to receive a medication guide.

I'll just provide a quick overview of some of the key safety labeling changes that have occurred over time. The first one is tendinitis and tendon rupture. For some of the initial fluoroquinolones, information was included in labeling about the nonclinical information that we had on joint pathology with these drugs.

Subsequently, once clinical information became available, it was included in labeling for all marketed fluoroquinolones. And then as new fluoroquinolones came along, a warning was included as part of a class effect, even though there were no instances of this particular adverse effect in clinical trials.

In 2004, the warning was expanded to include the at-risk populations, and in 2008, a boxed warning was added to describe the risk and the at-risk populations.

Again, from the very beginning, labeling for

some of the fluoroquinolones has included the potential for central nervous system adverse reactions. And the most recent update was in 2011, when pseudotumor cerebri was added.

In 2004, the labeling for the fluoroquinolones was updated to include a warning regarding peripheral neuropathy. And in 2013, this warning was revised to add the potential for neuropathy to be irreversible. At this time, the FDA had also issued a drug safety communication.

In 2010, myasthenia gravis was included in the boxed warning following review of cases that had a fatal outcome. And prior to this, it was already included in other sections of labeling.

QT prolongation and the risk for Torsade has also been in the labeling for fluoroquinolones since the '90s, and over the years there have been periodic updates further describing the risk. Phototoxicity was included in labeling in 2007. In addition, the labeling for these systemic fluoroquinolones includes a section on

hypersensitivity, which is regularly updated as new information become available.

Now, in the last few years, we've received an increasing number of reports from patients who describe signs and symptoms that involve different body sites and that often interfere with their activities of daily living, and in many instances persist for a fairly long period of time, and that will be discussed in greater detail today.

We are also aware of recent publications, which have described increased risk of other adverse reactions, such as retinal detachment and an aortic aneurysm rupture. We will not be discussing these at today's meeting.

So in preparation for today's meeting, we've looked at what the treatment benefit might be for these three indications, and then we've also done an overview of the safety information at hand for the systemic fluoroquinolones.

As many of you are aware, there have been several prior discussions regarding treatment

benefit of antibacterial drugs for acute bacterial exacerbation of chronic bronchitis and acute bacterial sinusitis.

Our recommendation and the advice we've received from previous advisory committee meetings is that placebo-controlled trials are acceptable for these two indications, specifically for acute bacterial sinusitis and mild acute bacterial exacerbation of chronic bronchitis. And this is reflected in our current guidance.

In 2006, there was a discussion about the risks and benefits of telithromycin at an advisory committee meeting. And subsequently, the indications for treatment of acute bacterial exacerbation of chronic bronchitis and acute bacterial sinusitis were removed from the labeling for telithromycin.

The treatment benefits of antibacterial drugs for uncomplicated UTI have not been previously discussed in an FDA public forum, and we will have a more detailed discussion of it today.

From a safety standpoint, we have looked at drug utilization data for the oral fluoroquinolones. A review of the epidemiologic studies have been performed, focusing on three labeled events: tendinopathy, cardiac arrhythmia, and peripheral neuropathy. We've also reviewed the FDA adverse event reporting system to characterize the constellations of signs and symptoms, which are associated with disability.

So the outline for the day is as follows. We have four FDA presentations. Dr. Toerner will discuss the antibacterial drug treatment effects for the three specific indications we are discussing today, ABS, ABECB, and uncomplicated UTI.

Dr. Ready will present the oral fluoroquinolone utilization patterns. Dr. Trinidad will discuss the epidemiology of selected fluoroquinolone-associated adverse reactions. And Dr. Boxwell will discuss the fluoroquinolone-associated disability cases, again focusing on these three specific indications.

We have a series of industry presentations, we'll break for lunch and come back for the open public hearing, and then move on to discussion and questions to the committee.

So we have three voting questions for the committee, one for each of the three indications. The first question would be, do the benefits and risks of the systemic fluoroquinolone antibacterial drugs support the current labeled indication for the treatment of acute bacterial sinusitis?

Following your vote, we request that the committee members provide specific recommendations, if any, concerning the indications for treatment of ABS and the safety information discussed today, including the constellation of adverse reactions that were characterized as fluoroquinolone-associated disability.

A second question will focus on the indication of ABECB. Do the benefits and risks of systemic fluoroquinolone antibacterial drugs support the current labeled indication for the treatment of

ABECB? Following your vote, please provide specific recommendations, if any, concerning this indication and the safety information discussed today, including the constellation of adverse reactions characterized as FQAD.

The last question pertains to the indication of uncomplicated urinary tract infections. We've also included acute uncomplicated cystitis because some products carry that indication rather than uncomplicated UTI.

Following your vote, please provide specific recommendations, if any, concerning the indications for treatment of ABS and safety information discussed today, including the constellation of adverse reactions characterized as FQAD.

With that, I'd invite Dr. Toerner to give his presentation. Thank you.

FDA Presentation - Joseph Toerner

DR. TOERNER: Thank you, Dr. Nambiar, and good morning.

Today I'll be reviewing the treatment effects

of antibacterial drugs for acute bacterial sinusitis, or ABS; acute bacterial exacerbation of chronic bronchitis, or ABECB; and uncomplicated urinary tract infection, or uncomplicated UTI. Before that, I'll provide a brief regulatory overview of the approaches to antibacterial drug development in the past.

In the 1980s and 1990s, there were advances in the pathophysiologic understanding of infectious diseases. And the concentrations of drug at the site of infection was identified as an important consideration for the treatment of certain infectious diseases. And the different clinical outcome assessments maybe be required, depending on the site of infection.

Also in the 1980s, new regulations were introduced that described the characteristics of adequate and well-controlled studies that FDA must use to establish efficacy for a new drug.

From this point forward, clinical trials of antibacterial drugs were designed to enroll patients

with a specific body site of infection, and these trials were generally equivalence trials that included an active control. Often these trials were smaller, and they were underpowered for an efficacy finding of noninferiority.

Now, as we move to the turn of the century and into the 21st century, there were advances in the scientific understanding of the noninferiority trial design, where the goal is to establish a degree of confidence that a new test drug is not worse than an active control drug by a prespecified amount. In order to have a clear finding of efficacy, the treatment effect of the control drug over placebo needs to be established.

In the Division of Anti-Infective Products, along with our colleagues in the Office of Biostatistics, we have done a lot of work to justify the noninferiority margin of the control drug to be used in noninferiority trials. This work has been included in many of our indication-specific guidance documents.

Often we do not have evidence from placebo-controlled trials for some of our other indications. However, in the setting of ABS, ABECB, and uncomplicated UTI, we do have evidence from placebo-controlled trials, which provide the best source of data to provide the treatment effect of an antibacterial drug.

As Dr. Nambiar had mentioned, we have discussed ABS and ABECB in previous advisory committee discussions, and we've taken the advice from the advisory committee discussions and worked on guidance documents. And in 2012, we issued final guidance documents for these two indications.

I will be providing a high-level overview of our findings of treatment effects in ABS and ABECB. For uncomplicated UTI, I will be going through in greater detail of our findings of the treatment effects of an antibacterial drug.

Our general approach here was to review trials that have been published in the medical literature and are therefore available in the public

domain. We selected only randomized, prospective, placebo-controlled or, in a few instances, a non-antibacterial control. And largely, these were double-blinded studies as well.

We also reviewed trials that used any antibacterial drug, and so therefore, our evaluation of treatment effects was across all antibacterial drugs. We did not focus on any one particular class of antibacterial drugs.

I'll first describe the treatment effects for ABS. We found 20 placebo-controlled trials that were published in the medical literature. Many of these trials tried to enrich for patients who were likely to have a bacterial etiology for their signs and symptoms of sinusitis. Only six of 20 trials showed a statistically significant difference over placebo on the prespecified primary outcome measure.

It's important to note that the outcome measures and the timing of assessments differed among all 20 trials, and also differed among the six trials that showed a statistically significant

difference. So we were unable to identify any one particular outcome measure and timing of assessment among these six trials that could be used to describe a treatment effect.

The Cochrane Collaboration has conducted a review of acute rhinosinusitis and found that there is no treatment effect on antibacterial drugs for acute rhinosinusitis and offered this conclusion statement, that there is no place for antibiotics for the patient with clinically diagnosed, uncomplicated acute rhinosinusitis.

The same group in 2014 took a different approach and evaluated trials that focused on patients who had signs and symptoms of sinusitis that were localized to the maxillary sinuses. And in this instance, there is some information that these patients have a greater likelihood of having a bacterial etiology for their signs and symptoms of sinusitis.

Here they found moderate evidence that antibacterial drugs provide a small treatment

benefit. But they noted that 80 percent, approximately, had improved within two weeks without receiving any antibacterial drug therapy.

The Infectious Diseases Society of America has issued clinical practice guidelines for bacterial rhinosinusitis and notes that a viral etiology accounts for the vast majority of patients who present with acute sinusitis, and that it's difficult to differentiate between viral and bacterial sinusitis.

The guidelines recommend reserving antibacterial drug treatment for patients with greater severity of symptoms, and the examples they give are patients who present with fever greater than 102 degrees Fahrenheit, or patients who have unrelenting symptoms of 10 days' duration or greater.

However, a group of investigators evaluated nine randomized trials, and they were unable to identify the symptoms and their severity for whom antibacterial drug therapy would be warranted.

In summary, only some trials show a treatment effect of antibacterial drugs over placebo for ABS. Even in trials that attempted to enrich for a bacterial etiology or a bacterial pathogen was actually identified, a large proportion of placebo recipients had favorable clinical outcomes.

It's very difficult to differentiate between a viral and bacterial etiology on the basis of clinical signs and symptoms alone. Current treatment guidelines recommend antibacterial drugs for patients with greater disease severity of ABS. Our 2012 final guidance document recommends the superiority clinical trial design to establish efficacy for the treatment of ABS, for example, the placebo control trial design.

Now I'll move on to ABECB. We found 15 placebo-controlled trials that were published in the literature. These trials enrolled patients with a wide variety of disease presentations and severity.

Six trials showed a statistically significant

difference over placebo. Two trials enrolled patients who were hospitalized for their ABECB and showed a benefit over placebo. One study, in fact, showed a reduction in mortality in patients who were randomized to receive an antibacterial drug.

The four other studies that showed a statistically significant difference enrolled outpatients with milder disease, and the common theme among these studies is that the outcome measure was from the perspective of the patient and was a symptom-based outcome measure.

The Cochrane Collaboration also reviewed evidence in the literature for a treatment effect in ABECB, and they found support for antibiotics for patients who are moderately to severely ill.

Published treatment guidelines from the American Thoracic Society and the European Respiratory Society, as well as the American College of Physicians, who published these papers with a focus on patients who have chronic obstructive pulmonary disease, in their treatment guidelines

recommend antibacterial drug therapy for patients with moderate to severe disease.

A review article recently published, also focusing on patients with chronic obstructive pulmonary disease, recommended antibacterial drugs for patients with moderate to severe ABECB.

When evaluating these publications, clear definitions of moderate to severe versus mild disease were not provided, so we consider the following definitions: that patients who require hospitalization for treatment of ABECB have disease severity characterized as moderate to severe; and patients who are being treated as outpatients have disease severity characterized as mild.

So in summary, we found a treatment effect of antibacterial drugs for hospitalized patients with ABECB, and treatment guidelines in review articles recommend antibacterial drug treatment for patients with moderate to severe ABECB.

For patients with mild disease, we found a treatment effect from the perspective of the

patient, although the difference from placebo in many of these trials did not represent a large treatment difference. And it's for this reason that generally antibacterial drug therapy is not recommended for patients with mild ABECB.

Our guidance document for ABECB published in 2012 recommends the superiority trial design to demonstrate efficacy, and that trials should enroll outpatients with mild ABECB. The endpoint should be an outcome measure from the perspective of the patient -- for example, a patient-reported outcome instrument. And there are several trial design options to show superiority: a treatment delay approach, the placebo control, or superiority to an active control.

So the third clinical disease we're discussing today is uncomplicated UTI. We found five prospective, randomized, controlled trials in outpatients with signs and symptoms of uncomplicated UTI. Four used a placebo control. One used ibuprofen as the control drug.

Most of these trials enrolled young adult women with signs and symptoms of uncomplicated UTI. There were different price outcome measures among the five trials: the eradication of bacteria at a follow-up visit, and its eradication of the bacteria found at the trial entry; improvement or resolution of symptoms following treatment; or a responder endpoint where individual patients had to achieve both eradication of bacteria and resolution of symptoms.

On this slide are the results from three of the five trials and each of these three trials evaluated the endpoints separately. So table 1 shows the microbiologic eradication evaluation in patients in these trials.

You can see for each of the three trials, for patients who were randomized to receive the antibacterial drug, there was a much higher proportion of patients who had microbiologic eradication in comparison to the control drug, whether it was placebo or ibuprofen. The timing of

the follow-up urine culture was relatively uniform, approximately some amount of time following completion of antibacterial drug therapy.

Table 2 describes the findings from the clinical response evaluation in the same three trials. And for the two trials that used a placebo control, for patients who were randomized to receive the antibacterial drug, there is a much higher proportion of patients who achieved a clinical response of improvement or resolution of symptoms.

One trial that used ibuprofen as the control, there was a numerically higher proportion of patients who had symptom resolution in comparison to patients who were randomized to receive the antibacterial drug. Note that the timing of the assessment differed among the three trials.

On this slide, the results of the random effects meta-analysis is shown. And the treatment effect, based on the microbiologic eradication outcome assessment, is at least 13 percent.

A random effects meta-analysis of the

clinical symptom resolution outcome assessment showed that the treatment effect crossed zero. And this is due to the ibuprofen control, which had shown symptom resolution in a significant proportion of patients.

The remaining two trials used the responder endpoint, where individual patients had to experience both clinical symptom resolution and microbiologic eradication. So for these two trials for patients who were randomized to receive the antibacterial drug, there was a much higher proportion of patients who achieved this endpoint in comparison to the placebo control.

On this slide is the results of the random effects meta-analysis, and the treatment effect based on this responder endpoint was at least 9 percent.

In summary, from our review, we found a treatment effect versus control on the microbiologic eradication outcome assessment. We found a treatment effect over placebo on the responder

outcome assessment, where patients had to achieve both microbiologic eradication and symptom resolution.

We found a treatment effect over placebo on the resolution of symptoms endpoint. And then there's the trial versus ibuprofen, where it's uncertain whether there is a treatment effect versus ibuprofen on resolution of symptoms.

The strengths of our analysis are that clinical microbiology laboratory assessments for urine culture are standardized and well characterized and represent a highly reliable outcome measure. Symptom outcome assessments are also straightforward, where patients presenting with symptoms are expected to have resolution of those symptoms following treatment.

The limitations of our review, we found variability in the timing of the outcome assessments so that there was not one uniform timing of the outcome assessment following completion of therapy, and there is the trial that shows symptom relief

with ibuprofen.

Our other observations of these file trials, we noted approximately 34 percent to 44 percent of patients who were randomized to receive placebo actually achieved microbiologic eradication. There was only one trial that reported the proportion of patients who received rescue antibacterial drug therapy, and this was the trial that used ibuprofen as the control.

Thirty-three percent of patients who were randomized at the start of the study to ibuprofen received a rescue antibacterial drug during the course of the study. Eighteen percent who were randomized to antibacterial drug at the start of the study actually stopped that and received a different rescue antibacterial drug.

Among the five trials, three patients were treated for pyelonephritis. Two patients were randomized to receive placebo. One patient was randomized to receive the antibacterial drug.

Infectious complications of untreated

uncomplicated UTI remain a concern, and the clinical course of untreated uncomplicated UTI has not been well characterized. There are other populations in which infectious complications have been well characterized.

So the clinical course of untreated asymptomatic bacteriuria in women who are pregnant has been clearly characterized, and there is an increased risk of development of pyelonephritis if left untreated.

The Cochrane Collaboration also published a review, but the authors did not even question efficacy against placebo for this review. And essentially, their review is a comparative effectiveness of different antibacterial drug therapies for uncomplicated UTI.

The Infectious Diseases Society of America issued treatment guidelines and recommend treatment with antibacterial drugs for patients with uncomplicated UTI. There are no options for a non-antibacterial therapy in this setting.

My final slide is the overall summary. For ABS, only a small number of trials showed evidence of a treatment effect over placebo. For ABECB, there is a treatment effect of antibacterial drug therapy for hospitalized patients with moderate to severe disease. There is a treatment effect for patients with mild disease based on symptom improvement.

For uncomplicated UTI, there is a treatment effect of antibacterial drug therapy over a control on microbiologic eradication. There is a treatment effect versus placebo control for symptom resolution. And there is a treatment effect over placebo for the responder endpoint of both microbiologic eradication and symptom resolution.

That concludes my talk, and I'll invite Dr. Ready to begin his presentation.

FDA Presentation – Travis Ready

LT READY: Good morning. My name is Travis Ready, and I am from the Division of Epidemiology II in the Office of Surveillance and Epidemiology. I

will be providing utilization trends for selected oral fluoroquinolones during recent years. Please note for the remainder of this presentation, I will refer to the selected oral fluoroquinolones as the fluoroquinolone market.

An outline of my presentation is as follows. I will begin with sales data of the fluoroquinolones, followed by utilization patterns from the U.S. outpatient retail pharmacy setting, the limitations, and finally the key findings.

Sales distribution data were used to determine settings of care. Fluoroquinolones were distributed primarily through the retail pharmacy setting in 2014; therefore, we focused our analysis on the outpatient retail pharmacy settings only.

IMS Total Patient Tracker and National Prescription Audit databases were used to provide national estimates of dispensed prescriptions and patients who received prescriptions for the fluoroquinolones from the U.S. outpatient retail pharmacies in recent years.

The graph display shows the estimated number of patients who received prescriptions for the fluoroquinolones from U.S. outpatient retail pharmacies during recent years. From this graph, we see the total number of patients was steady at approximately 22 to 23 million unique patients each year. Ciprofloxacin accounted for the largest proportion, followed by levofloxacin, moxifloxacin, gemifloxacin, and ofloxacin.

The chart displayed shows that in the U.S. outpatient retail pharmacy settings, female patients accounted for nearly two-thirds of the total patients. The figure here shows that prescription trends were similar to the unique patient data. The total number of prescriptions dispensed was higher than the number of unique patients shown in the earlier graph, remaining steady at approximately 32 to 33 million prescriptions each year. The higher estimates of prescriptions compared to patients suggest that some patients receive more than one prescription per year.

The table displayed shows the nationally estimated number of prescriptions for the fluoroquinolones, stratified by prescriber specialty, dispensed from U.S. outpatient retail pharmacies in 2014. From this table, we see that primary care specialists and mid-level practitioners were the top prescribers of fluoroquinolones.

Next, I will present the diagnoses associated with the use of selected fluoroquinolones using the Encuity Research TreatmentAnswers database. These nationally projected data are based on surveys from a sample of 3,200 office-based physicians who report on patients encounters during one day per month. Diagnoses mentioned in association with a drug were captured using ICD-9 codes.

The term "drug use mention" refers to mentions of a drug and association with a diagnosis during a patient visit to an office-based physician. This term or expression may be duplicated by the number of diagnoses for which the drug is mentioned.

Importantly, drug use mentions do not

necessarily result in a prescription being generated. Rather, the term indicates the drug or product was mentioned during an office visit.

Due to the small sample size and wide confidence intervals, counts below 100,000 per year do not provide reliable national estimates of use. Therefore, these results were not shown.

According to the U.S. office-based physician survey data for 2014, ciprofloxacin was the most commonly mentioned fluoroquinolone, followed by levofloxacin, moxifloxacin, gemifloxacin, and ofloxacin.

For the ICD-9 codes associated with the fluoroquinolones, urinary tract infection or UTI not otherwise specified was the most common diagnosis associated with ciprofloxacin, followed by prostatitis not otherwise specified.

Pneumonia, followed by UTI, were the most common diagnoses associated with levofloxacin. Bronchitis, followed by pneumonia, were the most common diagnoses associated with moxifloxacin.

Acute bronchitis was the only diagnosis with a reliable national estimate associated with gemifloxacin, while no reliable national estimates of diagnoses associated with ofloxacin were available due to the low numbers.

In order to provide greater insight into prescribing patterns for drugs possibly used to treat the three indications of interest for this meeting, select ICD-9 codes from the same survey data source were used to define possible ABECB, uncomplicated UTI, and acute sinusitis.

Of note, because there are no specific ICD-9 codes for ABECB and uncomplicated UTI, we expanded these definitions to include multiple ICD-9 codes likely to encompass these disease states. We did not, however, expand the definition of acute sinusitis because an ICD-9 code was available. Thus, for broadly defined acute bacterial exacerbation of chronic bronchitis, we used the following ICD-9 diagnosis codes.

For broadly defined uncomplicated UTI, we

used the following ICD-9 diagnosis codes, and for acute sinusitis we used ICD-9 code 461. Of note, there are no ICD-9 codes described in the etiology of acute sinusitis such as viral or bacterial. Therefore, acute sinusitis ICD-9 code 461 may be considered broad as it relates to the etiology.

When antibiotics were mentioned in association with a patient encounter for broadly defined ABECB, the top antibiotics were azithromycin, with 27 percent of the drug use mentions, followed by levofloxacin, with 23 percent.

When antibiotics were mentioned in association with a patient encounter for acute sinusitis, the topic antibiotics were amoxicillin-clavulanic acid, with 28 percent of the drug use mentions, followed by amoxicillin, with 26 percent, azithromycin, with 20 percent, and levofloxacin with 6 percent.

Of note, this analysis focused only on antibiotics associated with ABECB and acute sinusitis, whereas other commonly used symptomatic

treatments such as pain relievers were not included.

When drugs were mentioned in association with a patient encounter for broadly defined uncomplicated UTI, the top molecules were ciprofloxacin, with 32 percent of the drug use mentions, followed by nitrofurantoin, with 23 percent, sulfamethoxazole-trimethoprim, with 22 percent, phenazopyridine, with 8 percent, and levofloxacin, with 5 percent.

My apologies. The slide did not advance. I'll give you a moment to look at that.

There are important limitations kind of the data I presented. Our analysis of patient dispensing data was focused only on the outpatient retail setting and may not apply to other settings of care such as clinics or mail-order settings.

Diagnosis data were based on Encuity's office-based physician survey database, and indicate that a given drug was mentioned during a patient encounter with an office-based physician and do not necessarily mean that a prescription was generated.

Further, because there are no specific ICD-9 codes for ABECB and uncomplicated UTI, we broadened the definitions by including multiple ICD-9 codes, which may have resulted in more severe states being included. However, these office-based survey data provide valuable insight into prescriber intent as these drugs were mentioned in association with the treatment of these diagnosis.

For my last slide, I will go over the key findings. In summary, as a class, fluoroquinolones are widely used, and use has remained unchanged over recent years. Ciprofloxacin is the most commonly used fluoroquinolone, followed by levofloxacin and moxifloxacin.

Female patients are the primary users of fluoroquinolones. Primary care and mid-level practitioners are the primary prescribers of fluoroquinolones. And according to an office-based physician survey database, fluoroquinolones were associated with possible acute sinusitis, broadly defined uncomplicated urinary tract infection, and

broadly defined acute bacterial exacerbation of chronic bronchitis.

That concludes my talk.

FDA Presentation - James Trinidad

LCDR TRINIDAD: Hello. I'm Lieutenant Commander James Trinidad, and I will be presenting on behalf of my colleagues in the Division of Epidemiology II.

Today, I will present the methods and results of our literature review to quantify the absolute or relative risk of three labeled adverse outcomes associated with fluoroquinolone exposure. The three adverse outcomes were tendinopathy, serious cardiac arrhythmia, and peripheral neuropathy.

We conducted a literature search in PubMed to identify epidemiological studies on fluoroquinolone exposure and adverse events in humans. We were interested in six fluoroquinolone-associated adverse events that OSE had reviewed previously.

These events were acute kidney injury, anaphylaxis, tendinopathy, peripheral neuropathy,

retinal detachment, and cardiac arrhythmia. We identified 722 articles published since 1986 that address these adverse events.

From those, we excluded publications that were not epidemiological studies, had no safety data, or studies that only assessed pediatric populations, non-systemic exposures, or exposures in inpatient settings.

We identified 25 published observational epidemiological studies in one poster that was part of an ongoing collaboration between the FDA and the Department of Defense. These studies focused on three labeled adverse events -- tendinopathy, cardiac arrhythmia, and peripheral neuropathy. These events are part of the constellation of fluoroquinolone-associated events that my colleague in the Division of Pharmacovigilance will discuss in the next presentation.

Tendinopathy was examined in 11 published manuscripts and the poster. Cardiac arrhythmia was examined in 12 studies. Peripheral neuropathy was

examined in two studies.

The next sections of this presentation are organized by adverse outcome. The first adverse outcome of interest is tendinopathy. All fluoroquinolones carry a boxed warning for tendinitis and tendon rupture. The boxed warning states that this risk is increased further among patients who are over 60 years of age, taking corticosteroids, or have kidney, heart, or lung transplants.

From the 12 epidemiological studies on fluoroquinolone-associated tendinopathy, we selected studies for in-depth review if they adjudicated cases of tendinopathy and did not only study transplant recipients. Failure to confirm cases may result in false positive cases, so we were concerned that fluoroquinolone users may be more likely to have rule-out diagnoses since tendinopathy is a labeled warning.

Studies of transplant recipients have limited generalizability and only focus on patients with

severe underlying conditions. The remaining four studies were selected for in-depth review.

Despite using different methods, the four studies found a consistently elevated risk of tendinopathy among patients exposed to fluoroquinolones. Their study types included case control or cohort designs.

The data were healthcare claims or prescription event monitoring data. The comparators were other antibiotics or no antibiotic exposures. The studies assessed different outcomes, including tendinopathy, Achilles tendon rupture, or tendinitis. The studies examined tendinopathy events occurring within one to six months of exposure.

Potential confounders for tendinopathy were addressed using different approaches. The associations ranged from an odds ratio of 1.2 to a relative risk of 11, but the confidence intervals were generally wide, and some confidence intervals were consistent, with no association.

The restriction to elderly subjects may help explain the strong association of 11 in the 2003 study by van der Linden and colleagues. Advanced age is a risk factor for fluoroquinolone-associated tendinopathy.

Although they did not meet the criteria for in-depth review, the other eight studies also found a consistently elevated risk of tendinopathy among fluoroquinolone users.

One of the most concerning tendinopathies is Achilles tendon rupture. This outcome is a disabling serious adverse event sometimes requiring surgery, and it is commonly seen in case series data on fluoroquinolone-associated tendinopathy.

The incidence rate of tendinopathy reported in two of the studies that we reviewed ranged from 13 to 56 ruptures for every 100,000 person-years of fluoroquinolone exposure, whereas the incidence rate in the general population was only 5 to 10 ruptures per 100,000 person-years. In context, the background incidence of Achilles tendon rupture

ranges from 2 to 37 ruptures for every 100,000 person-years, as shown in the grey box.

Two of the four studies assessed risk by age and use of corticosteroids. According to labeling, these factors magnify the risk of fluoroquinolone-associated tendinopathy.

The studies by Seeger and van der Linden found that elderly patients who use corticosteroids were at particularly high risk of tendinopathy associated with fluoroquinolones or with all quinolones, including nalidixic acid, plus fluoroquinolones. The study by van der Linden also found a strong association among the elderly, regardless of corticosteroid use.

None of the four studies assessed risk of tendinopathy by transplant recipient status, the other labeled factor that is thought to magnify fluoroquinolone-associated risk of tendinopathy. Transplant recipients may receive corticosteroids for immunosuppression, so they may have an increased risk of tendinopathy from the corticosteroids.

In conclusion, the epidemiological data support the boxed warning of an increased risk of tendinitis and tendon rupture. The epidemiological data also provide moderate support for further increased risk in the elderly and patients taking corticosteroids.

However, we cannot comment on where there is an increased risk among transplant recipients since the epidemiological studies were not designed to AEs this issue. Even so, there may be an elevated risk of tendinopathy in transplant patients because of the frequent corticosteroid use in this population.

Lastly, although there is a low absolute risk of tendon rupture associated with fluoroquinolones, events like Achilles tendon rupture are serious, disabling adverse events.

The next adverse outcome of interest is serious cardiac arrhythmia. With minor variations, all fluoroquinolone labeling warn of the known association with QT prolongation and infrequent cases of arrhythmia, or they warn of isolated care

cases of Torsade de Pointes.

The labeling also recommend avoidance or caution in use of fluoroquinolones among patients who have selected cardiovascular or proarrhythmic conditions, who use antiarrhythmic agents or other drugs that prolong the QT interval, or who are susceptible elderly patients.

Among the 12 studies identified from the literature search, we selected studies for in-depth review if they met several quality criteria. We selected studies in the in-depth review -- we just asked a short risk window for arrhythmia following treatment with fluoroquinolones.

We selected studies that used active comparators and captured indications for antibiotic use. It was especially important to account for certain respiratory infections that are also independent risk factors for arrhythmia, such as pneumonia or exacerbation of COPD. Similarly, we only selected studies that adjusted for important risk factors of drug-induced arrhythmia.

We selected studies that provided evidence of the validity of the cardiac arrhythmia definition and those that captured serious clinical consequences of QT prolongation, such as death.

Out of the 12 studies, two met the quality criteria for in-depth review. The two studies included in the in-depth review are both retrospective cohort studies that used healthcare claims data. They both compared fluoroquinolones to similar active comparators, amoxicillin or Augmentin. They also examined the risk of serious arrhythmia and death shortly after fluoroquinolone exposure. Lastly, they both captured indications for antibiotic use and adjusted for a comprehensive list of risk factors for a drug-induced arrhythmia.

However, the two studies had similar limitations. First, they did not adequately control for indications for antibiotic use. The study by Rao defined the indications for the antibiotics using infection-related diagnoses within the past year. This lookback period is very long, so

fluoroquinolones may not have been used to treat these infections.

Although Chou and colleagues reported that they used diagnoses associated with the index prescription to determine indication, the source of this information is not clear. Furthermore, the indications examined were too broad to adequately control for specific infections that are risk factors for arrhythmia, like pneumonia.

The outcomes of these studies are also not specific to QT prolongation. For example, Rao examined all-cause mortality, whereas Chou assessed cardiovascular deaths. At least some of the events were likely not related to QT prolongation.

Furthermore, Chou included outpatient diagnoses of arrhythmia in addition to the events diagnosed in hospital or in emergency room settings. Arrhythmia diagnosed in outpatient settings may be of lower severity than ones diagnosed in acute care settings, and the validity of these outpatient diagnoses is unknown.

Because these studies had significant limitations, they cannot provide information on relative risk. However, these studies can provide information of absolute risk for serious cardiac arrhythmia. These estimates of absolute risk should be interpreted with caution.

They could underestimate the true risk because they do not include deaths related to cardiac arrhythmia. However, the estimates from the Chou study could also overestimate the risk because it included events diagnosed in outpatient settings. The studies by Rao and Chou found that that serious arrhythmia was a rare event.

Recall that the comparator antibiotics were amoxicillin or Augmentin, shown here as the far left columns for each study. For every 100,000 prescriptions in Rao or patients in Chou, 9 to 12 patients on these antibiotics experienced serious arrhythmia. The incidence of serious arrhythmia was higher among users of fluoroquinolones, ranging from 12 to 57 events per

100,000 prescriptions or patients.

The study by Chou conducted an analysis stratified by underlying cardiovascular disease. Patients had underlying cardiovascular disease if, prior to antibiotic exposure, they had any of the diagnosis codes listed here.

As would be expected, the study by Chou found that underlying cardiovascular disease greatly increases the absolute risk of serious arrhythmia. This was true regardless of exposure status. For every 100,000 patients without cardiovascular disease, 5 to 44 patients experienced serious arrhythmia. Meanwhile, among those who had a history of cardiovascular disease, 42 to 85 patients experienced serious arrhythmia.

Although the two studies selected for in-depth review met several quality criteria, the limitations in these studies preclude us from drawing conclusions on relative risk. To recap, these limitations included inadequate control for confounding by indication, as well as the inclusion

of less serious arrhythmia and events unrelated to QT prolongation and cardiac arrhythmia.

However, these studies can provide estimates of absolute risk for serious arrhythmia. Overall, the risk of serious arrhythmia was low. In addition, patients with underlying cardiovascular disease were at higher risk of serious arrhythmia, which is consistent with label warnings.

The final outcome of interest was peripheral neuropathy. With minor variations, fluoroquinolone labeling warn of the risks of peripheral neuropathy, its quick onset, and the possibility of it being irreversible.

The literature search identified two studies of fluoroquinolone-associated peripheral neuropathy. One was an analysis of data collected by the FDA Adverse Event Reporting System, also known as FAERS. This analysis was excluded from the in-depth review because it was based on data from a passive surveillance system. The other was a case control study. The case control study was selected for

in-depth review.

Etminan and colleagues conducted a retrospective case control study using the IMS LifeLink commercial healthcare claims database. The investigators used a cohort that was constructed for another study. The source population consisted of one million people randomly selected from the database. From this population, the study only included men between the ages of 45 to 80 who did not have diabetes.

Incident cases of idiopathic or drug-induced peripheral neuropathy were identified using health claims data, and these cases were matched on age, year of entry into the cohort, and follow-up, which was not defined.

The study compared past year or current exposure to oral fluoroquinolones between cases and controls. Analyses were adjusted for several conditions and drugs that may be risk factors for peripheral neuropathy, including hyperthyroidism, postherpetic neuralgia, and nitrofurantoin use.

Several limitations make the results of this study difficult to interpret. First, although estimates of relative risk are reported, the authors of the study did not provide information on the incidence of peripheral neuropathy within the study population.

It is also unclear whether the estimates of relative risk are accurate. First and foremost, the algorithms to detect outcomes were not validated. Diagnosis codes are used for billing purposes rather than for clinical records, so we recommend validation of algorithms used to detect outcomes in claims data. In addition, only a few risk factors were considered in analyses, and cases of Guillain-Barre syndrome were not identified.

The study results also have limited generalizability since this case control study was nested within a larger cohort study that examined drug use among men between the ages of 45 to 80 years old.

Keeping in mind the limitations mentioned in

the previous slide, the study found a positive associate between fluoroquinolones and peripheral neuropathy. The X-axis shows the exposure groups by frequency of fluoroquinolone use, and the Y-axis shows the adjusted ratios.

Compared to controls, cases of peripheral neuropathy were 30 percent more likely to have used any fluoroquinolones in the past year, and about 80 percent more likely to have an active prescription of fluoroquinolones at index date.

The results suggest that incident use of fluoroquinolone more than doubles the risk of peripheral neuropathy, and incident use has a higher risk than prevalent use. When examined individually, levofloxacin, moxifloxacin, and ciprofloxacin all had a similar risk of peripheral neuropathy.

Although it does not contradict the label warnings, the case control study provides weak support for an increased risk of peripheral neuropathy. Methods and results were unclear, so it

is difficult to interpret the results. For these reasons, it is unknown whether the associations observed in the study are accurate.

The case control study also does not provide any information on the timing of peripheral neuropathy relative to the start of fluoroquinolone exposure or whether the nerve damage became permanent.

In conclusion, we find that the epidemiological data support the current labeling of an increased risk of tendinitis and tendon rupture, particularly among the elderly and patients taking corticosteroids. However, we cannot make a definitive conclusion on the relative risk of cardiac arrhythmia, and the epidemiological data provide only weak support of a risk of peripheral neuropathy.

In context, tendinopathy, serious cardiac arrhythmia, and peripheral neuropathy are rare adverse events. Still, it is important to remember that these are severe and disabling outcomes.

FDA Presentation – Debra Boxwell

DR. BOXWELL: Good morning. My name is Debbie Boxwell, and I'm a safety evaluator with the Division of Pharmacovigilance. Today, I will be describing a case series from the FDA's Adverse Event Reporting System, also known as FAERS, titled, Fluoroquinolone-Associated Disability Cases in Patients Being Treated for Uncomplicated Sinusitis, Bronchitis, and/or Urinary Tract Infection.

As Dr. Nambiar mentioned, in 2013 the FDA did a review describing disabling peripheral neuropathy associated with fluoroquinolone use. This resulted in a labeling change in the warnings and precautions section, describing the potential for irreversible peripheral neuropathy.

In addition, while reviewing these FAERS cases, it was noted that 76 percent of patients with peripheral neuropathy also reported adverse events, or AEs, involving other body systems, including neuropsychiatric, vision, cardiac, and musculoskeletal events such as tendinitis, tendon

rupture, myalgia, and arthralgia. The duration of many of these other adverse events also appeared to be prolonged and disabling.

This review was done to try to characterize the constellation of symptoms leading to disability that was observed in the previous review, and we will be referring to this constellation as fluoroquinolone-associated disability, or FQAD.

The regulatory definition of disability was used, which is a substantial disruption in a person's ability to conduct normal life functions. It was determined that a patient must have adverse events reported from two or more of the following body systems -- musculoskeletal, neuropsychiatric, peripheral nervous system, senses like vision or hearing, skin, and cardiovascular.

In addition, these AEs had to last 30 days or longer after stopping the fluoroquinolone. Although a definition of what qualifies as a long-term disabling adverse event could not be found, for the purposes of this review, we chose to use 30 days as

a reasonable length of time for AE resolution.

There are many published articles in the literature on the individual adverse events associated with fluoroquinolones, but there are far fewer that describe this constellation of disabling symptoms.

One of the first, which was identified while researching the previously mentioned review, was an article by Dr. Jay Cohen, who described peripheral neuropathy associated with fluoroquinolone use. While reviewing these cases, he also collected additional information on severe long-term adverse effects that also affected other body systems.

Just last month Dr. Beatrice Golomb from UC San Diego published a case series of four previously healthy patients who developed serious, persistent, multi-system adverse effects after taking a fluoroquinolone. She is currently enrolling patients in the UCSD fluoroquinolone effect study, which is an online survey study that is trying to identify and describe AEs associated with

fluoroquinolones.

Reports consistent with FQAD were much more likely to be found in the lay press. Many patients who have experienced these multiple disabling events have told their stories in newspaper articles like the New York Times and the Washington Post, on TV news reports, on websites, and on social media like Facebook.

Before I describe what we found in the FAERS case series, I want to quickly go over the benefits and limitations of the FAERS database. The benefit is that FAERS is a spontaneous or voluntary reporting system. While clinical trials are usually done in hundreds or maybe thousands of people, once a product goes to market, it is often used by millions of people. Because of this, FAERS has the ability to detect rare and serious adverse events.

As for limitations, there is known underreporting. Causality may also be difficult to determine. Just because a specific drug was coded in a report, it doesn't mean that drug was

necessarily associated with the AE.

Individual reports must be reviewed and evaluated for concomitant drugs, medical history and comorbid conditions, and temporal relationship of the administered drug to the event. In addition, reports may be incomplete or not contain enough detail to properly evaluate an event.

So the goal of this review was to identify FQAD cases reported to FAERS in a very specific population, and that population was patients who were reported to be previously healthy before taking the prescribed oral fluoroquinolone and who were being treated for the uncomplicated indications that we are discussing today.

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 chronic diseases such as hypertension, hypothyroidism, or hyperlipidemia.

Reports were searched in FAERS using the

following criteria: oral dosage forms for the five available fluoroquinolones, U.S. cases only because we are reviewing indications in the U.S. label; the outcome was reported as disability; the indications were for three previously described uncomplicated infections; the search dates were from November 1, 1997 to May 30, 2015; and all MedDRA-preferred terms or adverse event terms were searched.

This table shows the search results. For all fluoroquinolones, there were a total of 1,122 disability reports. Levofloxacin and ciprofloxacin had the highest numbers. The numbers of reports seen here may include duplicate reports.

The outcome of disability falls into the category of being a serious outcome by regulatory definition. Other serious outcomes include death, life-threatening events, hospitalization, congenital anomaly, and other important medical events, which are based on the clinical judgment of the reporter.

The percentage of disability reports among all serious reports was calculated for each

fluoroquinolone as well as any other antibacterial drugs that have been or are being used for the treatment of these three infections. The FAERS search criteria was the same for all 14 antibiotics.

So as an example, for gemifloxacin, which is the fourth line down, there were a total of 38 reports with a serious outcome and 4, or 10.5 percent, reported an outcome of disability. As you can see, compared with the other nine antibacterial agents, all five of the fluoroquinolones had the highest percentage of disability reports, ranging from 9.9 to 31.1 percent.

After retrieving the 1100-plus reports, an individual hands-on review of each report was required to further identify cases of FQAD, first to identify that the patient had adverse events reported from two or more body systems, and second, that these AEs lasted 30 days or longer after stopping the fluoroquinolone.

In order to identify the FQAD cases with the

criteria that I just described in this particular population, we also needed to apply exclusion criteria, and these can be found in the large box.

The most common exclusion, at 57 percent, was patients who did not report an AE from two or more body systems. These reports, totaling 540, still reported a disabling outcome, but in most cases it was only one AE, such as peripheral neuropathy or tendon rupture, or two AEs within the same body system, like joint swelling or muscle pain. The second-highest exclusion at 15 percent was that the adverse event resolved in less than 30 days after stopping the fluoroquinolone. After all 1,122 reports were reviewed and exclusions were applied, 178 individual cases were identified.

This table shows the percentage of FQAD cases identified among the total disability reports for levofloxacin, ciprofloxacin, and moxifloxacin, that they were similar, ranging from 15 to 18 percent. Because ofloxacin and gemifloxacin had so few cases, a percentage was not calculated.

Although comparing reports to cases is not equivalent because reports have not been deduplicated, these data still provide a general idea of the percentage of FQAD cases among all disability reports. From this, it did not appear that any one fluoroquinolone in this case series had a greater association with FQAD than another.

This table summarizes the descriptive characteristics of the 178 cases for all five fluoroquinolones. Because there is so much information on this table, I put a box around the information that I will be highlighting at some point in my talk.

The mean and median age was 48 years old, with a wide range of 13 to 84 years. Nearly three-quarters or 74 percent of the cases were identified in patients 30 to 59 years of age. Seventy-eight percent of cases occurred in women. Even when all UTI cases were removed, 74 percent of the cases were still found to occur in women.

Of note, 59 percent of FAERS reports for

ciprofloxacin, levofloxacin, and moxifloxacin were of female patients for all indications. We do not know if women may be at increased risk, if they are more likely to submit a report, or if there is some other unidentified reason.

The other point of interest on this table was the unusually high number of direct reports at 85 percent. Direct reports are submitted directly to the FDA and not through a drug company. Reporters are typically the patient or family members and sometimes a healthcare provider.

The time to onset of the adverse events from the start of the therapy was a mean of 5.4 days and a median of 3 days. However, the range was very wide, from one hour after taking the first dose to three months after the drug was discontinued.

In nearly half the cases, the onset was very rapid, occurring within owner or two days after starting the drug. However, in 12 percent of the cases, the onset occurred after more than 10 days, which in most situation would have been after

fluoroquinolone therapy had been completed.

The duration of the disabling adverse event was defined as the ongoing duration at the time the report was received by the FDA. The mean was 61.2 weeks, or 14 months, and the longest duration reported was nine years after the event started. Actual duration cannot be determined without regular follow-up. However, 23 percent of patients reported disabling symptoms that lasted for a year or longer.

As stated earlier, each of the cases had to have an AE from two or more of these body systems. Musculoskeletal events, which included tendon, joint, and muscle, were reported in 97 percent of the cases. This was followed by neuropsychiatric events in 68 percent and peripheral nervous system events in 63 percent. In general, these adverse events all occurred within a few days to weeks of each other.

These next few slides show the reported adverse events for each of the six body systems. To identify if an event was unlabeled across the class

of fluoroquinolones, the term was underlined.

In the musculoskeletal group, joint pain was the most commonly reported event, followed by tendon pain or tendinitis, muscle pain, and muscle weakness. Pain was the most commonly reported symptom across almost all cases. The events on this slide are all labeled. In addition, patients may have reported more than one event in each body system.

The neuropsychiatric class had the least number of labeled events. Fatigue was the most commonly reported, followed by insomnia, anxiety, severe headaches, and dizziness. If a patient specifically said that their insomnia or depression was due to pain, those events were not included.

For the peripheral nervous system, peripheral neuropathy was the most commonly reported term, followed by descriptive terms for either paresthesias or peripheral neuropathy. These AEs are also all labeled.

This slide shows the different senses that

were affected. The highest number of reports was with eye pain, then diminished vision, tinnitus, and blurred vision. Palpitations and tachycardia were most commonly reported for the cardiovascular system, and skin rash, sweating, photosensitivity, and sensitivity to touch were the most common for skin.

This is a Venn diagram showing the number of cases for the musculoskeletal, neuropsychiatric, and peripheral nervous systems, which were the groups with the highest number of reports. Peripheral nervous system is the yellow circle, musculoskeletal is the pink circle, and the neuropsychiatric circle is blue.

As you can see, there was considerable overlap among these three groups. Forty-one percent of patients who had a neuropsychiatric adverse event also experienced an AE from the peripheral nervous system, 60 percent of patients had AEs from the musculoskeletal and peripheral nervous system, and 67 percent had neuropsychiatric and musculoskeletal

AES. In addition, 38 percent of patients had adverse events from all three body systems.

In this table, the percentage of disability cases that occurred with each individual fluoroquinolone was calculated by body system. With the exception of levofloxacin and peripheral nervous system at 52 percent, there's an interesting consistency across these three drugs for each body system.

Now, I would like to present an FQAD case report. This direct report was representative of what I found in the case series.

This report came from a 49-year-old woman who received a 10-day supply of levofloxacin, 500 milligrams, to treat a sinus infection. The symptoms began two days after starting the drug. The patient stated that:

"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 like every tendon and muscle in my body.

"I continue to suffer 22 months later with the following disabling conditions: severe tendon and muscle pain and tightness. Tendinitis. Tingling. Numbness. Prickling. Pins and needles sensations in my extremities. Electrical sensations. Feelings 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, seven days per week. Inability to work due to pain and weakness. Difficulty thinking clearly. Confusion. Chronic fatigue."

The patient did not report any test results, although she did state she saw five different medical specialists.

I would just like to finish up with some observations after reviewing these cases. The

first, again, is that based on these data, no one fluoroquinolone appeared to have a greater association with FQAD than another. Secondly, as I mentioned earlier, 85 percent of the cases were direct reports, which is an unusually high number.

Over the past 10 years, the percentage of direct reports received by FDA for all drugs has remained fairly consistent, ranging from approximately 2 to 6 percent. However, in this instance, the unusually large number of direct reports coming from patients who describe very similar experiences after taking a fluoroquinolone was very beneficial in describing these disability cases.

The current boxed warning states that tendinitis and tendon rupture can occur in all ages, but that there's an increased risk in older patients, usually over the age of 60. In this case series, which was looking at a constellation of disability symptoms, including tendinitis and tendon rupture, only 17 percent were found to be 60 years

of age and older.

In addition, when tendinitis and tendon rupture were calculated in patients less than 60 years of age and those 60 and older, the percentage of tendinitis or tendon rupture cases were the same in both the younger and older age groups.

A majority of the cases, 74 percent, were identified in patients who were 30 to 59 years old, or young to middle aged. Patients of all ages, but especially this group, made a point of describing how seriously their disability impacted their lives, including losing jobs, the resulting lack of health insurance, large medical bills, serious financial problems like losing their house, and family tension or dissolution.

Many of the patients' clinicians were reported to be at a loss as to what was causing these symptoms, and quite a few patients visited many medical specialists. Some patients reported extensive and very expensive medical testing to try

to diagnose the cause of their disability symptoms.

Some of the reported tests included routine blood work, blood tests for autoimmune diseases, CT scans, MRIs, EMGs, nerve conduction studies, skin biopsies to identify small fiber neuropathy, and lumbar puncture.

A majority of these tests came back negative. MRIs did identify tendon rupture, but many EMGs and nerve conduction studies did not reveal abnormalities. A few of the diseases that were commonly tested for included lupus, Lyme disease, multiple sclerosis, and ALS.

Effective treatments were also not identified in this case series. Patients reported taking drugs like opiates, nonsteroidal anti-inflammatory agents, corticosteroids, muscle relaxants, gabapentin, and amitriptyline, and tried other therapies including cold laser therapy, acupuncture, and transcutaneous electrical nerve stimulation, with no relief. One patient was told she had a psychological condition and was prescribed psychotropic drugs.

Most of the individual AEs that exist within FQAD currently described in the fluoroquinolone labels, primarily the boxed warning or the warning and precautions section. However, the constellation of disabling symptoms described here is not in the label.

My last comment is that based on these reviewed cases, the described decrease in quality of life was very profound for both the patient and his or her family. Thank you.

Clarifying Questions to the Presenters

CAPT PARISE: Thank you.

Are there any clarifying questions from the committee for the FDA?

DR. WINTERSTEIN: Yes. I have one question about the efficacy review. From what I understand, this was a review of all antibiotic regimens, not specifically fluoroquinolones. Is that correct? So that would be for Dr. Toerner, I believe.

DR. TOERNER: Yes. Hi. This is Dr. Toerner. That's correct. It was a review of any

antibacterial drug. There was not a focus on the fluoroquinolone antibacterial drugs. It was any antibacterial drug used in the studies.

DR. WINTERSTEIN: Could you comment -- were there any placebo-controlled --

DR. TOERNER: They were all placebo-controlled trials.

DR. WINTERSTEIN: -- quinolone-based regimen? So what's the proportion that actually involved the quinolone compared to macrolides or whatever else? Or let me rephrase that because you probably wouldn't be able to pull it out of your hat. But is there a difference whatsoever? Should we care, or does it really not matter?

DR. TOERNER: We chose to broadly look at the treatment effect of an antibacterial drug and made an assumption that the antibacterial drugs would have a treatment effect that would be similar across all classes of antibacterial drugs. We did not single out one particular antibacterial drug.

The fluoroquinolones did represent a very

small minority of all the trials that we reviewed. But in each of the three indications, there was at least one trial that used a fluoroquinolone. But again, we did not want to focus or highlight that. We were interested in your general approach for treatment effects of an antibacterial drug.

DR. WINTERSTEIN: Obviously, in most instances the message was that there really is not superior efficacy except for that definition of severe ABECB. So there it might be interesting to know what the quinolones are doing there.

DR. TOERNER: And we found a treatment effect for uncomplicated UTI.

CAPT PARISE: Committee members, since we do have a large group, if I'm not seeing you, wave to Jennifer, and then you'll get on the list.

Next we have Dr. Gerhard, had a question.

DR. GERHARD: Dr. Winterstein just asked the questions I had as well.

CAPT PARISE: Dr. Baden?

DR. BADEN: For the FAERS reporting system,

do you know if there is any temporal relationship with the quinolone reports of adverse events and the changing of the label over the years? And might that reflect increasing awareness of the individual issues that were being highlighted over time?

The question is, do you know if, as the label had changes with different fluoroquinolones having different issues being raised, did that impact the kinetics of the reports via the FAERS system so that the label change may have precipitated increased reporting of these types of issues more broadly? So is there a temporal relationship?

DR. BOXWELL: There is thought to be. The more its publicly available, information, that it stimulates reporting. I've also seen studies that say that, no, the Weber effect does not actually occur. But I would think that from what we see, it does increase after an event's been --

DR. BADEN: So that if you were to do a time trend on the reports for the quinolones, there would likely be more of these reports recently than in

1997 to 2000?

DR. BOXWELL: Yes. There's been a big increase in the last five years.

DR. BADEN: Thank you.

CAPT PARISE: Dr. Choudhry?

DR. CHOUDHRY: I'm just curious about the current labels for sinusitis and acute exacerbation of chronic bronchitis, and whether or not they currently indicate anything about disease severity.

DR. TOERNER: The indications in the labels are for treatment of ABECB, and they do not describe disease severity.

CAPT PARISE: Just one reminder. If the FDA could also, when you're going to answer, state your name for the record so that we have that. Thank you.

Next, Dr. Hogans?

DR. HOGANS: My question is for Dr. Boxwell regarding the FAERS, and it's a two-part question. One is, when you look at other medications for drugs that have musculoskeletal side effect profile -- for

example, the statins, where people report a lot of myalgias -- is there a similar sort of distribution pattern where there might be a gender different or there might be a particular age group that tends to report those kinds of symptoms? And then I have a second part to my question.

DR. BOXWELL: Let me answer the first one first because I'll forget. I didn't drill down that low, into that much detail, to really know what they were taking in age group and gender. So I can't really answer that.

DR. HOGANS: It goes to whether or not there's a reporting bias in terms of whether there are particular populations or genders that might be more prone to report symptomatologies. So if it's not an established phenomenon, I just wanted to posit that question. And then I have another question.

DR. BOXWELL: Honestly, I didn't see that. But I don't know.

DR. HOGANS: Then my other question is, if I

understand correctly, the percentage of direct reports was really very exceptional compared to what usually occurs. And if I understood you, it sounds like a lot of these reports could be coming from patients and families.

If you were to segregate out the reports that come from providers, whether that's physicians, nurse practitioners, pharmacists, would they be considered direct reports? If you were to segregate those, is that number still truly exceptional compared to what's ordinarily seen?

DR. BOXWELL: Most of these were from patients. We had direct reports from healthcare providers, but a majority of these direct reports were from patients or their families, which is exceptional.

DR. HOGANS: Yes. I understand that. But if you were to then make the numerator providers, does it really still stand out? So if you were to compare the provider-generated reports for fluoroquinolones to provider-generated reports for

other drugs or drug classes, would it still be really a standout?

DR. BOXWELL: Probably it would not. I think that because these patients could get a diagnosis from their doctors and had no treatments and tests were coming back negative, physicians, I think, are less likely to report something they don't even know what's wrong. So at that point, the patient reported what was going on, and that's how we described it.

CAPT PARISE: Dr. Arrieta?

DR. ARRIETA: Yes. This question is also for Debra Boxwell. I want to make sure that I am understanding your conclusions appropriately. You indicated that no one fluoroquinolone appeared to have a greater association with FQAD than another.

I presume that is based on the percent of reports for a particular quinolone. They all seem very similar. But if we go through the presentation by Dr. Ready -- I hope I am pronouncing that correctly -- ofloxacin is hardly ever prescribed.

It is the most common fluoroquinolone associated with a severe, debilitating adverse effect of 31 percent, while it really represented an unusual amount of prescriptions, suggesting to me that if we look at the incidence per quinolone, it would appear that there seems to be a significantly higher risk with ofloxacin than with the oral ones as a ratio of utilization and the incidence of side effects.

DR. BOXWELL: Well, we can't calculate incidence with FAERS data. So this was just what we observed in the spontaneous reports, that they all appeared to be very similar.

DR. ARRIETA: But you have the data. Right? You have the number over prescriptions that have been written for each of the quinolones, and you have the incidence of adverse events that have been reported.

DR. BOXWELL: Travis?

DR. ARRIETA: I don't know if I'm making sense.

DR. PROESTEL: Scott Proestel, FDA. I'm looking on page 20 of the briefing package. I just want to make sure that we're clear on this table. The 31 percent is, of the ofloxacin reports, 31 percent were disability reports.

So that could be a very small number of reports, but 31 percent of them were disability reports. So there's not more disability reports. It's a higher proportion.

DR. ARRIETA: Of all the reports of disability, of all the collective reports of disability, 31 percent were assigned to ofloxacin.

DR. PROESTEL: For all SAE reports for ofloxacin, 31 percent were disability reports, which isn't to say that there were more disability reports for ofloxacin.

DR. ARRIETA: So 31 --

DR. PROESTEL: This is -- I'm sorry. This is a way of adjusting for the point you were bringing up. So instead of looking at total numbers of reports, what we're showing here, or trying to show,

is the differences in proportion of disability reports, so that we don't -- I mean, there's a lot of ways to look at data.

But because of the significant differences in total prescriptions, one way is to look at proportions of disability for all reports for that drug. And in fact, this is not for all reports, but within the SAEs, say for ofloxacin, 31 percent were disabling.

DR. ARRIETA: Okay.

DR. PROESTEL: Okay.

CAPT PARISE: Dr. Scheetz?

DR. SCHEETZ: My question is also for Dr. Boxwell. Can you comment on, is the granularity of the FAERS database able to help us calculate sensitivity for the entity that has been termed fluoroquinolone-associated disability? How good is the current label at predicting those that would end up with fluoroquinolone-associated disability?

You gave some great data on age. So I think you've already shown that age is outside of what's

on the current label. So younger patients are ending up with fluoroquinolone-associated disability that's not on the current label.

Does the database contain any information on corticosteroid use? Does it contain any information on whether or not these patients had transplants, kidney heart, or lung, as has been suggested on the label?

DR. BOXWELL: Within this specific narrow population, which was just healthy people, there were seven people who received a corticosteroid, usually at the time they were being prescribed the fluoroquinolone, for bronchitis or something like that. And there were a few that were using nasal steroids.

But again, this is a very narrow population. It's incomplete. I really restricted this extensively. So it's really hard to make any predictions about percentages or likelihood. We can just observe what we're seeing in this group.

DR. SCHEETZ: Right. Thank you. I guess my

clarifying point is for the clinician that's thinking about prescribing a fluoroquinolone, does the current label provide them the information to help prevent them from having a patient that ends up with FQAD?

DR. BOXWELL: The current label?

DR. SCHEETZ: The current collective labels?

DR. BOXWELL: I believe that they're all individual, separate things. The box has the tendon rupture, and there's a long list of stuff in the warnings and precautions. So no, I don't think that physicians are really aware that this constellation of symptoms of disability can happen to patients the way it's labeled now.

CAPT PARISE: Dr. Andrews?

DR. ANDREWS: Dr. Boxwell is really popular today. My question -- well, I have several questions. But one is just explain to me why you chose to require that they have problems in two different systems because they could be moderate problems as opposed to someone who has a very

serious disability in musculoskeletal system, which might be, to a consumer, more salient and more important than two small things.

Some of the things that you talked about were like fatigue. I'm sorry, I feel fatigue all the time. So how did you decide that it had to cross two systems as opposed to dealing with severity problem?

DR. BOXWELL: When I did the peripheral neuropathy review two years ago, it really jumped out at me that a lot of these people were suffering not just from peripheral neuropathy but from other body system problems.

So because the single things are labeled, I wanted to look at things, the AEs, as groups of two or more AEs because they seemed to be occurring this way in this population of reports that I was looking at. And it seemed different than someone reporting tendinitis as opposed to somebody who was a marathon runner and could never get out of bed again type of thing.

So I wanted it to be two body systems that's -- and they seemed to all fit into place. They all seemed to be very similar, what everybody had.

DR. ANDREWS: But it excluded half of your sample, almost half.

DR. BOXWELL: It did.

DR. ANDREWS: Another question, just going back to the age question, especially that you're finding it more often in women -- I know women are 65 percent of prescriptions, but they were 78 percent or 74 percent in your database.

But elderly people are also at higher risk, and among the elderly, there are more women. It would be interesting to see if you could sort that out because we'd want to know if women are at higher risk. That would drive some questions for science.

Also, did you look at athletes as well? Because that was something that came up in the briefing documents. And people don't necessarily tell you, but you talk about a downhill skier and

marathon runners. And if people go back to their normal activities right afterwards and that causes a problem, that's something that could be included in a label.

DR. BOXWELL: There were a few that mentioned they were athletes or worked out regularly. This was not a group of people who were all training for the Olympics. These were your average healthy people. And a few of them did mention workouts and training.

DR. ANDREWS: And just one other comment is I get the question about whether the prevalence would be different or the incidence would be different if it was the direct consumer reports as opposed to provider reports. But many consumers are suggested to report things by their provider, and their provider might have reported that anyway.

I don't know that that's a reason to suggest that because it was organized -- there's obviously a lot of publicity around it -- that that's changing, that we should necessarily dismiss that or think

less of the incidence of -- concern about disability.

CAPT PARISE: Dr. Kartsonis?

DR. KARTSONIS: I'm going to let Dr. Boxwell sit down for just a few seconds. Actually, I have a few questions for Dr. Toerner.

Dr. Toerner, the first question I had was your analysis of the uncomplicated urinary tract infections obviously included a study from Bleidorn with ibuprofen and what have you. Clearly, one of the issues with that study is that the symptoms that were evaluated for within a day of when therapy had ended. And clearly, with NSAIDs, there could be a masking effect that's undertaken.

Do you know if there's any data in that study that would look at the symptoms a little bit later in the course of treatment?

DR. TOERNER: Joe Toerner from FDA. We did note that the timing of the assessment was different, and I chose the prespecified primary outcome evaluation for the studies. That particular

trial did look at later time points, and there was a similar proportion that remained symptom-free between the ibuprofen control and the antibacterial control at later time points.

But you're right that the one day following treatment was the largest difference between the two groups. It was noted in that trial.

DR. KARTSONIS: And the second question I had was -- obviously, I think the analysis you've done with the placebo-controlled studies is very helpful to the committee and what have you. But obviously, a lot of the studies that have been done in the last two decades have been noninferiority-based studies.

Has there been any look at these particular indications to see if there are any treatment effect differences between classes of drugs, particularly, for example, urinary tract infections or chronic bronchitis, or one versus the other, that might provide some further evidence that there is a treatment effect?

DR. TOERNER: We did not undertake a

comparative effectiveness evaluation in our work in this area. But your point is well-taken. There may be information from clinical trials that are conducted that can help us understand treatment effect in certain populations.

CAPT PARISE: Dr. Schmid?

DR. SCHMID: Yes. First, Dr. Boxwell, I've got a couple more questions. I'm just trying to understand the age effect a little bit better and going back to Dr. Hogans' reporting bias question.

So the 30 to 59 age group, they're likely to be more healthy than in the older people. So I'm wondering if part of what you're finding is that the older people were just excluded because they already have comorbidities and so they weren't in your sample.

Then second question would be, I want to get a better sense of how these direct reports are received. So, for example, if these are on the internet, younger people are more likely to use them. So I'm wondering whether older people are

less likely to have access.

DR. BOXWELL: As for the age, it's true that older people may have been excluded for various reasons. But I actually found something similar with the peripheral neuropathy paper that I did two years ago, where the middle age was the bigger age group rather than older, and I'm not sure why that is. But for older people, as long as they were functional, traveled, they were considered to be healthy.

Your other question was how direct reports --

DR. SCHMID: Yes. Do you get most of them through the internet? How do people report them?

DR. BOXWELL: No. Directly to the FDA through MedWatch.

DR. SCHMID: But do they need any kind of technological equipment to do that? If somebody's an older person, or any person that doesn't have internet access, would they call on the phone? Would they write a letter?

DR. BOXWELL: They can call. They can fill out a form. They can do it on the internet. There is a phone number.

DR. SCHMID: So I'm just wondering whether people like that would be less likely to report because they would -- people who have the internet access are more likely to just turn on the internet and do it.

DR. BOXWELL: That's true.

CAPT PARISE: Dr. Daskalakis?

DR. DASKALAKIS: I do have one question for Dr. Boxwell, and it's actually a question for Dr. Boxwell and maybe Mr. Trinidad as well. One of the things that I see absent in the list of people who've been reporting these adverse events, or even the data around the adverse events in some of the studies, is any commentary on race.

Is there any information about race and ethnicity around these adverse events?

DR. BOXWELL: I have no information on that.

DR. DASKALAKIS: I bring that up just because

of sometimes differential pharmacokinetics. Just thinking that there may be a signal there, something that is worth looking at. Thank you.

My other question is for Dr. Toerner, specifically around the definition of moderate to severe and mild. What is the process for getting to those definitions? I'm thinking there may be other clinical criteria such as home oxygen use, et cetera, that may make one person's mild or moderate be another person's severe. So just curious how that definition came up and if there's any sort of idea of exploring that definition further.

DR. TOERNER: We chose that definition mainly because our review had identified a treatment effect in patients who had outpatient or mild disease. And we did find -- and there were a total of eight of the 16 trials -- a total of eight of them enrolled only outpatients. And four of the trials had shown a treatment effect based on an outcome measure from the perspective of the patient.

The other four trials that did not show a treatment effect evaluated pulmonary function testing or had a physician global assessment, and those were trials that did not show a treatment effect. So that was our rationale for why we define mild as outpatient. And that just left us as what else? So anyone who's not an outpatient then would be moderate to severe. So hospitalized patients would be moderate to severe.

CAPT PARISE: We're going to do one more. I want to keep this on track, on schedule, for this morning, so we're going to do one more question this morning.

Then just a reminder to the committee that we do have a three-hour block this afternoon, and we'll start that where -- we still have people that had some clarifying questions. You'll get to ask your question and have a response.

Dr. Baden?

DR. BADEN: Mr. Ready or Ms. Boxwell. From the data presented, it seems that dose and duration

do not come out as a meaningful factor. Is that correct?

DR. BOXWELL: That's correct.

CAPT PARISE: So we're going to take a break. First, just a couple of requests.

When you come back, please fill in empty chairs in the middle when you return because we do have people that are standing and limited seating. So we want to maximize the ability for people to have seats. Also, a reminder that the first row is for the press only.

So we'll now take a 15-minute break. Panel members, please remember there should be no discussion of the meeting topic during the break among yourselves or with any member of the audience. And we'll resume at 10:15. Thank you.

(Whereupon, at 10:02 a.m., a brief recess was taken.)

CAPT PARISE: We're going to resume.

Both the Food and Drug Administration, the FDA, and the public believe in a transparent process

for information-gathering and decision-making. To ensure such transparency at the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the industry's non-employee presenters, to advise the committee of any financial relationships that they may have with the firm at issue, such as consulting fees, travel expenses, honoraria, and interests in the industry, including equity interests and those based upon the outcome of this meeting.

Likewise, FDA encourages you at the beginning of your presentation to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We will now proceed with industry's presentations.

Industry Presentation - Melissa Tokosh

MS. TOKOSH: Good morning, Madam Chairman, members of the advisory committee, and FDA. My name is Melissa Tokosh, and I'm the global regulatory leader with Janssen Research and Development.

On behalf of the manufacturers of systemic fluoroquinolones, we welcome the opportunity to address the advisory committee today on the benefits and risks of systemic fluoroquinolones in the treatment of acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis in patients with COPD, and in uncomplicated urinary tract infections.

Our participation represents a collaborative effort between both branded and generic companies, with Bayer and Janssen leading the preparation of the background documents and presentation based on data from our products. Apotex and Lupin also communicated a commitment to this matter, and they, along with approximately 30 generic companies, have a shared stake in the discussions today.

We appreciate the opportunity to participate in this very important dialogue to assure the availability of important therapeutic options for appropriate patients, to address the safety topics of interest, to discuss labeling that ensures the understanding of the benefits and the risks of fluoroquinolones, while also ensuring that society benefits optimally from the use of fluoroquinolones.

Fluoroquinolones have accumulated close to 30 years of clinical experience. There are over 1 billion treatment courses of oral fluoroquinolones administers globally, with 33 million administered in the U.S. yearly. Of the 10 million yearly treatment courses utilized for the treatment of the three indications of interest today, you can see that the majority of the usage is in urinary tract infections.

All fluoroquinolones are now available as generics, which make up approximately 98 percent of the market share. While individual company safety databases adequately capture the safety of

individual products, other databases, such as FDA's AERS database and health claims databases include all fluoroquinolones and may be considered for analyses as well.

Fluoroquinolones are an important class of antibiotics that represent a major advancement in clinical medicine. The oral and IV formulations are interchangeable in bioavailability, and this allows the physicians the ability to transition easily from IV administration in an inpatient setting to oral administration in an outpatient setting.

Fluoroquinolones possess a broad spectrum of gram-negative and gram-positive pathogen activity and are approved for a wide range of treatment indications, including some serious infections such as pneumonia, intra-abdominal infections, anthrax, and plague. The indications were approved based on comparative trials with active comparators that had been approved by FDA and were done in accordance with FDA regulatory standards at the time.

Of the fluoroquinolones of interest today,

ciprofloxacin was first approved in 1987, and that was followed by the approval of ofloxacin in 1990. Levofloxacin and then moxifloxacin followed, and finally gemifloxacin was recently approved in 2003, the most recent.

Both ciprofloxacin and levofloxacin are approved for the three indications of interest, where moxifloxacin and gemifloxacin are not approved for urinary tract infections because they are not excreted in the urine at therapeutic levels.

Fluoroquinolones work effectively, and they remain an important choice for the appropriate patients in the three indications based on established and well-characterized safety and efficacy. They need to remain as treatment options for physicians.

Labeling reflects our current understanding of the science with respect to the risks and benefits, but additional investigation of FDA's defined criteria for the fluoroquinolone-associated constellation of symptoms is required. But industry

is committed to working with FDA to better understand the nature of these series of reports. We look forward to getting the perspective of the advisory committee and FDA to ensure the safe and appropriate use of our medicines.

I'd like to briefly just recollection through our agenda for our presentation. Following my introduction, Dr. Mandell will discuss the landscape of antibiotic treatment selection along with the medical needs of the fluoroquinolones for the three indications.

Dr. Alder will discuss the proper role of fluoroquinolones, along with the identification of appropriate patients likely to benefit from fluoroquinolone therapy. He will also discuss treatment usage patterns.

Dr. Nicholson will present an overall safety profile of the fluoroquinolones, the adequacy of the current labeling, along with providing an assessment of FDA's criteria for the constellation of symptoms.

Dr. Zinner will discuss the benefit/risk of

fluoroquinolones before concluding remarks are made by Dr. Alder.

Thank you for your attention, and I'd like to now introduce Dr. Mandell, who will discuss the medical needs of fluoroquinolones.

Industry Presentation - Lionel Mandell

DR. MANDELL: Good morning and thank you for the opportunity to address this group. By way of background and I guess qualifications for this task, I have been involved to some extent in looking at data and trying to interpret data on various trials.

I was co-chair of the guideline committee for pneumonia for the American Thoracic Society and the IDSA, Infectious Disease Society of America, for community-acquired pneumonia, and previously for hospital-acquired pneumonia, and did the same in Canada. And I've written chapters in Harrison's and Cecil's textbook on respiratory infections in several editions.

I think much more importantly, however, I'm a physician, and like many of you, I try to do my best

in an imperfect world to take care of patients and to try to do the best I can in terms of getting them better with a minimum of any risk.

I just want to point out that I've received consulting honoraria for my time. I don't have any financial interest in the companies or in the outcome of this meeting financially, but certainly as a physician I have tremendous interest. I've been a physician for 45 years. I've been doing infectious disease for 39. And the quinolones have made a huge difference in the management of patients.

I'm going to cover three entities: acute bacterial sinusitis, the acute bacterial exacerbation of COPD, and uncomplicated UTIs. And for each of them, I'll use the same format, definition, impact, etiology, and treatment.

Now, in terms of acute bacterial sinusitis, I think it's first important to define what we're talking about. The overarching term is acute rhinosinusitis, and it refers to inflammation of the

mucosal lining of the paranasal sinuses. It can be caused by a variety of things, including allergies, environmental irritants, and infections.

If we look at acute rhinosinusitis, 90 percent-plus are viral, and the bacterial, or acute bacterial rhinosinusitis, ABRS, is about 10 percent or less. But in terms of impact, that's over 3 million cases a year in the United States every year.

Now, once you've made a diagnosis of acute rhinosinusitis, the question then is, can you make a diagnosis of acute bacterial sinusitis? Because nobody is recommending that we treat viral sinusitis.

So the following are the recommendations from the IDSA guidelines. If the patient has an onset of persistent symptoms -- and this refers to a purulent nasal discharge, nasal congestion or obstruction, or facial pain or pressure -- if they have persistent symptoms and signs that are compatible with ARS for 10 days or longer, then there's a very good

correlation with it being bacterial.

Another possibility is that the onset is with severe symptoms right at the start, like severe pain, higher temperature such as 39 degrees Centigrade, lasting three to four consecutive days, but at the outset of the illness.

Then finally, this term double-sickening, where the person initially presents with what seems like a typical viral presentation, starts to get better, and then sudden gets ill again. And that correlates strongly with a secondary bacterial superinfection.

So those are the criteria that are recommended in order to make the diagnosis of acute bacterial sinusitis.

Now, in terms of potential complications, it can progress in some cases to a recurrent situation or to chronic sinusitis. There can at times be local extension into bone or soft tissue, and of course, CNS complications. And there was recently a paper in the New England Journal about this. This

isn't common, but when it occurs, it's serious, things like meningitis, brain abscess, et cetera.

Now, what are the pathogens? Well, if you look at data from sinus aspirates or aspirates from the middle meatus done endoscopically, the pneumococcus is still an important player, Haemophilus influenzae and Moraxella catarrhalis. And they're represented in the percentages here. And again, these are data taken from the IDSA.

Now, what I think is absolutely critical here is the problems with the clinical trials. Often you'll hear figures thrown out like, well, why bother treating this person with acute sinusitis when the data show that placebo has a 60, 70, 80 percent response?

Often you'll hear people trivialize these things by saying, well, somebody had the sniffles, and we all know it's a cold. In a lot of cases, it is a cold. But we're talking about the diagnosis made according to the criteria, of the 10 days or the severe onset or the double-sickening.

The problem with the data are as follows. If you look at most of the randomized, controlled trials carefully, you'll see that the diagnosis of so-called acute bacterial sinusitis was made on the basis of signs and symptoms, which were not as clearly defined as the IDSA has, and also on radiologic confirmation. And these in no way correlate with the presence of bacteria.

Also, many only had seven days of symptoms, and there was no indication as to whether the patient was getting better or worse. And according to the current guidelines, seven days with somebody just sort of carrying on would count as viral.

So these, I think, are two very important quotes. One is again from the IDSA guidelines. "There is good reason to believe that many patients enrolled in these studies had uncomplicated viral sinusitis rather than bacterial sinusitis." And that would dilute out any treatment effect and make the placebo effect obviously look much better.

Ellen Wald, who is a well-known investigator

in this area, she did a study with much more stringent criteria trying to make the diagnosis, and her quote from the paper in Pediatrics was, "With more stringent criteria, spontaneous improvement dropped to 32 percent versus 64 percent for the comparator," which in her study was amox-clav.

Now, again I can't emphasize enough that no one is recommending antibiotics for the viral, and certainly not a quinolone. But whenever we make a decision about an antibiotic, we have to try and decide, A, do they need an antibiotic, and B, if so, which one.

So I think you have to consider the following: the disease and its acuity, the patient, and the pathogen. In terms of the acuity, are we dealing with something that's mild or moderate or severe?

In terms of the patient, have they recently been on a course of antibiotics that might change their flora? Do they have allergies or other obvious contraindications? Are they going to be

compliant? And obviously, what's their immune status?

In terms of the pathogen, we obviously too have to consider are we dealing with, say, a pneumococcus that might be resistant, or an H. flu? Or is it an unusual pathogen, for example, a fungus, which could occur.

Now, these are the suggested treatment guidelines for antibiotics for acute bacterial sinusitis. And again, let me emphasize, this is assuming you have used the criteria and made the diagnosis of what you think is acute bacterial sinusitis, not someone with sniffles.

Initial therapy, either amox-clav or possibly doxycycline. If the person has a beta-lactam allergy, then the fluoroquinolones, then doxycycline. If there is a risk of resistance or they failed initial therapy, the fluoroquinolones or amox-clav. And finally, in severe cases, some of those may have to go to a hospital, fluoroquinolones or something like a third generation cephalosporin

given intravenously.

The IDSA no longer recommends as first line macrolides, trimethoprim-sulfa, doxy, or amoxicillin, although in 2012, doxy was put in the one line if you couldn't use the amox-clav because of a potential for greater failure, because of risks of resistance.

In conclusion, for sinusitis, considerable patient burden. If there is insufficient or delayed treatment, this can lead to prolonged illness and can result in chronic disease as well as potentially serious complications.

Antibacterial therapy is definitely appropriate for acute bacterial sinusitis when it's properly diagnosed. Things like severity, patient issues, and resistance patterns have to be considered in treatment choices. And we're getting to the point of a perfect storm, and this is true for all infections, where we've got increasing resistance and decreasing options, with few drugs in the pipeline. So we have to keep that in mind

always.

Next, I'd like to talk about acute bacterial exacerbations of chronic bronchitis in the setting of patients with COPD.

Now, COPD -- I'm sure you all know this -- is a problem with limitation of air flow because of structural changes in lung tissue, and it includes three entities: bronchiectasis, chronic bronchitis, and emphysema. But by far, the most important entity is chronic bronchitis.

Now, if there is a flareup of this or an acute exacerbation of the chronic bronchitis in the setting of COPD, typically that's defined as an acute increase in symptoms beyond the normal day-to-day variation. But it also includes one, two, or three of these cardinal symptoms that are listed below.

Now, I think again, like sinusitis, sometimes or oftentimes COPD tends to be dismissed by physicians who don't deal with it. I've bounced some of these figures, and I'll show you on the next

slide as well, off physician colleagues that don't follow this literature closely or deal with these patients, and they're blown away when they actually see the data.

In terms of COPD worldwide, in 2020, which is just over four years, it will be the third leading cause of mortality. It already is the third leading cause of death in the United States, and worldwide it will be the fifth leading cause of disease burden.

Now, the impact of exacerbations of chronic bronchitis in people with COPD, it definitely negatively affects their quality of life. Things like the increased symptoms and the decrease in lung function acutely, they don't recover in three or four or five or six days. They can take weeks to recover.

Also, there are now very good data to show that these repeated attacks lead to a long-term decline in lung function. There is considerable mortality associated with this, and I'll show you

that in a second, and very high direct and indirect socioeconomic costs.

Again, this figure, when I show it at meetings or to physicians who don't deal with it, they're always blown away by it. These are people who have an exacerbation. If they are sick enough to go to the ICU, 1 in 4 will die. That's much higher than a heart attack. If they are hospitalized, the hospital mortality is 6 to 12 percent.

I'd also like to point out that if you go to an ICU because of your exacerbation and you need mechanical ventilation, your three-year all-cause mortality is 49 percent.

Let's say you just go to an ER, so you're not necessarily admitted to the hospital or put in an ICU. Your relapse rate is 22 to 32 percent. And just the outpatients alone, their treatment failure rate is 13 to 33 percent.

So I would respectfully disagree with what was posited earlier. Moderate to severe is not just

for those admitted to hospital. You definitely see moderate in the outpatients, no question. And because it's harder and harder now to get patients into hospital and we do more and more outpatient treatment, we're seeing more and more patients who are approaching severe, and yet we try to treat them on the outside.

This is a representation trying to show you what the pathogens are, or potential pathogens, in relation to the disease. So the vertical axis is the FEV1 percent predicted because COPD, the diagnosis, is FEV1 over FVC, and it has to be less than .7.

On the left is acute bronchitis, which is usually viral, and don't give them any antibiotics. And as you move to the right, you're getting more and more serious problems -- chronic bronchitis, COPD, that's either simple or complicated, or complicated with risks.

You can see the organisms listed above that. Sometimes the atypicals, like mycoplasma, chlamydia,

may play a role. Then you start getting into more common pathogens with the AECB, organisms like H. flu, pneumococcus, Moraxella.

Then in people who have more severe underlying structural lung disease, and especially if there's bronchiectasis, you start running into pathogens like Pseudomonas and some of the Enterobacteriaceae.

If you have Pseudomonas exacerbation, you end up in the ICU, your three-year mortality is 59 percent. We see these people all the time, and we try and treat them on the outside when they get their flareups. So again, to the point that not everybody who is moderate to severe is in the hospital.

Now, in terms of what are we trying to accomplish when we treat these people, number one, we would like to get them back to baseline. We would like to prevent bad things from happening, like morbidity, hospitalization, and mortality. But also, one of the most important things we can do is

extend the interval to the next episode.

Now, this slide illustrates this, I think, very nicely. The vertical axis is the probability of survival, and the horizontal axis is time in months going out to five years. And what you see represented on the three curves are no flareups or exacerbations, one to two a year, and three or more a year. And I think the p-values speak for themselves. So in other words, the more frequently you have a flareup, the less likely you are to stay alive. And that's now been extremely well documented.

This leads, then, to the next question. If we say, okay, I think Mr. Smith needs an antibiotic for his acute exacerbation, which one am I going to pick? Is there something, some property among the various drugs, that would help us with that? And I think there is.

Again, this is where the quinolones come into play because there are good data to show that the quinolones, unlike comparator agents, can extend the

interval to the next episode. And that's absolutely critical.

So this is the MOSAIC study. The vertical axis is the percent of patients not experiencing a next event. Horizontal axis is time. And what they did was they entered patients, waited till the first flareup, then randomized them to quinolone or a comparator, which was a macrolide or a beta-lactam; it was left up to the physician, and then they followed them.

They stratified them into two groups, those who were frequent exacerbators -- in other words, more than every six months -- and those who were less frequent exacerbators. And there was definitely an improvement with the quinolones in terms of extending the interval to the next episode in those who were the more frequent exacerbators.

Now, again, just like with sinusitis or any other infection, we consider the acuity of the illness, the patient, and the pathogen. And someone earlier alluded to the fact that what's moderate for

one person might be severe for someone else. So FEV1 comes into play and what their baseline FEV1 was, what their age is, comorbidities, et cetera.

Now, virtually all the guidelines, and there are several, recommend antibiotics here for the moderate to severe. I chose the Canadian ones because they actually had a pictorial representation.

Again, on the left you've got simple chronic, which generally isn't too bad in terms of how seriously ill they become. Then as you move to the right, you're getting more and more seriously ill patients.

You can look at some of the associated things, like on the left it could be any age, less than 4 flareups a year, an FEV1 over 50 percent. As you're moving to the right, people are getting older. They're having more frequent exacerbations. FEV1 is going down.

So on the left, again, no one is recommending a quinolone. As you get to the complicated or the

chronic suppurative, the quinolones have a very important role to play.

Now, in terms of conclusion, I think there's no question that there's a considerable burden of illness with this, these exacerbations. Insufficient or delayed treatment can lead to severe complications such as pneumonia, respiratory failure, or hospitalization.

You can also have, with ineffective treatment, less time to the next flareup and more frequent flareups. Antibacterial therapy definitely has a benefit in appropriate patients. Patient risk factors and resistance patterns have to be taken into account when you're selecting antibiotics. And once again, this perfect storm that we see every day in clinics of increasing resistance and fewer options.

Finally, uncomplicated urinary tract infections. From a clinical point of view, the way we deal with uncomplicated UTI is they're either upper, kidney, like acute pyelo, or lower, acute

cystitis. And in each case, they can be either complicated or uncomplicated. Here we're dealing strictly with the uncomplicated, and the focus will be on the cystitis.

Now, in terms of symptom duration, it's 6.1 symptomatic days and 2.4 days of restricted activity. Again, as a male physician, in talking to male physician colleagues, they're often very dismissive of this. When you talk to your female patients or female physicians, they are not at all dismissive of this. This is a very real problem.

In terms of recurrence, 20 to 30 percent of women who have an episode will experience a recurrence within about three or four months after the previous episode. And this leads to additional morbidity and need for more antibiotics.

Again, the same approach. You consider what's the type of infection, the patient, and the bugs. In terms of type of infection, is it lower, like cystitis? And if so, is this a first episode or are we dealing with recurrent episodes? If it's

upper, acute pyelo as opposed to an uncomplicated pyelo, the patient and pathogen issues I won't go through at this point.

Now, these are the recommendations from the IDSA, which are actually combined guidelines from the IDSA and the European Society for Clin Micro and ID. And it's for uncomplicated cystitis. And again, if you look at the recommendation, the quinolones are not recommended as first line. They recommend something like nitrofurantoin, trimethoprim-sulfa, or fosfomycin.

The caveats would be that if there is any question of pyelo, then not to use nitrofurantoin or fosfomycin. An alternative agent, obviously, is the fluoroquinolones work very well in this area.

Now, in terms of conclusions, uncomplicated urinary tract infections can definitely cause substantial morbidity. A rapid reduction in symptoms is important. Short course therapy is preferred, and this is the classic use of three days of trimethoprim-sulfa as opposed to, years ago, when

it was seven, 10, to 14 days sometimes, which seems incredible in retrospect.

Patient factors and resistance patterns must be considered for treatment choice. Quinolones are definitely an alternative, but no one is recommending them as first line for the uncomplicated cases. And once again, we're starting to run out of options. Thank you.

Industry Presentation – Jeff Alder

DR. ALDER: Jeff Alder, senior director, global clinical development at Bayer HealthCare.

Fluoroquinolones do have a role in the treatment of acute bacterial sinusitis, exacerbations in COPD patients, and in uncomplicated UTI when used in the appropriate patient. The presentation will focus on the appropriate and proper role for fluoroquinolones in treatment of these three indications.

Fluoroquinolones were approved in all three of these indications based on trials with active comparators. Well, in fact, all antibiotics were

approved based on trials versus an active comparator. None were approved based on placebo-controlled trials in these indications.

The treatment guidelines, and we'll cite two by the Infectious Disease Society of America and one from the American Thoracic Society, recommend fluoroquinolones as second-line therapy or alternative therapy, depending on the language in the guideline. You'll see that the majority of fluoroquinolone usage in these three indications is in fact in uncomplicated UTI.

Now, if you take those three treatment guidelines and boil them down into what type of patient is most likely to benefit from a fluoroquinolone or alternative therapy, well, it's a patient that should have a bacterial infection. And we've heard much commentary on appropriate diagnosis.

A patient can't possibly benefit from bacterial therapy if they don't have a bacterial infection. So clinical diagnosis by signs and

symptoms is critical.

Very few of these patients are diagnosed based on a bacterial culture. They're based on physician assessment; patients who have allergies or who have experienced an adverse reaction to primary therapy; and patients who have experienced a therapeutic failure to primary therapy, or drug-resistant pathogens, and that's often suspected rather than known, again because of the lack of culture data.

Those three guidelines can be consolidated into a single table to see where the fluoroquinolones stack up. That's shown here. For example, on the left-hand side is the treatment guidelines from the IDSA for treatment of ABS.

You can see a beta-lactam such as amoxicillin-clavulanic acid or doxycycline as primary therapy, although doxycycline has been demoted recently. Respiratory fluoroquinolones are considered second-line therapy for ABS, and alternative therapy for exacerbations in COPD

patients and in uncomplicated UTI.

As was said a couple of times, the majority of fluoroquinolone use in these three indications is in uncomplicated UTI. Some of the reasons for that might be that in fosfomycin's label, it indicates that it was more than 20 percentage points less effective in clinical success than ciprofloxacin in a head-to-head trial, which gained approval for fosfomycin. Trimethoprim-sulfa has cautionary notes about drug resistance, and nitrofurantoin also has cautionary notes about acute pyelonephritis.

The figure here is consolidated from tables 14, 16, and 18 from the FDA briefing document so you can see the usage data all presented together. So the darker blue bars are showing total drug use in each of the three indications, the lighter blue bars are the fluoroquinolone use, in other words, the amount of that bar which is due to fluoroquinolone.

Immediately apparent that most of the use is an uncomplicated UTI. That's 9.3 million uses per year out of a total fluoroquinolone use in these

three indications of about 10.2. So 91 percent of the fluoroquinolone use that we're talking about and considering today is in uncomplicated UTI.

The fluoroquinolones were approved in these three indications based on trials versus an active comparator. As we said, all antibacterials were. We consolidate all of the trials that supported the NDA approvals; we'll be showing these on the next figure.

This is a forest plot, and there's several components. On the far right side is the clinical response of the fluoroquinolone versus the active approved comparator. Those active approved comparators were things such as azithromycin in the respiratory, cefuroxime, trimethoprim-sulfa in the UTIs. They were all active and approved comparators.

The fluoroquinolone clinical success rate is bolded in each of the trials. These trials span decades. They go back from the late 1980s through some that are about 15 years old.

You should see overall that the fluoroquinolones showed high clinical success rate, from 87 percent to virtually 100 percent, and so did the comparators. Comparators also showed high clinical success rate.

The vertical line in the middle is showing the demarcation between clinical response rates that favor the fluoroquinolone on the right and the comparator on the left. So it's simply subtracting the two clinical response rates for the point estimate. You can see that in 8 out of 10 times, the point estimate is on the side favoring fluoroquinolones, although none of those were statistically significant.

The error bars are all clearly within the noninferiority margins for each of these trials in all noninferiority. This was the basis for the approval of the fluoroquinolones in these three indications. None of these drugs squeaked through by just barely making a noninferiority margin. They all showed solid efficacy relative to an active

comparator.

For each of the three indications, we will have the same pattern. First we'll look at the guidelines. That will be followed up with looking at the guidelines versus the usage pattern to see if physicians appear to be following the guidelines or not, followed by efficacy data with placebo-controlled trials, and a summation. So we'll have the same pattern for each of these three: guidelines, usage, placebo, summation.

Guidelines for ABS. The guidelines indicate that treatment, based on clinical signs and symptoms, should be if one of three criteria are met. And it's based on signs and symptoms, duration, severity, or worsening.

Duration of 10 or more days is likely to indicate a bacterial infection, or severity or worsening for three or more days. If any one of those three events occurs, the decision is to treat with an antibacterial agent. Whether to initiate first-line or second-line therapy is one that's

dependent upon patient factors such as risk of resistance and the allergies, adverse reactions, or failure to primary therapy.

So looking at this guideline versus how are the drugs actually being used, on the left-hand side is the IDSA guidelines for treatment of ABS. You can see that the top two recommended agents, beta-lactam, amox, amox-clavulanic acid, are indeed the top two agents, comprising a little over 50 percent of the usage.

The fluoroquinolones are recommended as second-line therapy for patients with all those characteristics we just discussed. Together they comprise a little less than 9 percent of the overall usage in ABS, and that amounts to about 795,000 courses annually; keeping that in mind, 795,000 versus a total usage of about 10.2 million in these three indications.

So we don't conflate two different issues, this doesn't indicate if the antibacterials are being used appropriately or inappropriately, all

appropriate, all inappropriate. What we do know is that fluoroquinolones are clearly not being used as first-line therapy in ABS because they have less than 9 percent of the overall usages.

Placebo data is shown here, and this meta-analysis comes directly from the IDSA guidelines in their extended guidelines. So a total of 20 placebo-controlled trials were analyzed. In this particular analysis, none of these are fluoroquinolones. They're all some other drug.

In the 17 adults studies, you can see the clinical response rates of basically 73 percent versus 65 percent; an odds ratio of 1.4 -- that's positive. It certainly isn't impressively positive, but there is positivity.

Then if we look at the number of patients that would need to be treated to benefit one, it's 13. That's basically looking at a differential of 8 percent and how many in a population would you have to treat to benefit one based on that 8 percent difference from a placebo to actively treated, and

you get 13.

The pediatric data is a little more impressive, odds ratios of 2.52. You can see the clinical response rates, 78 and a half versus basically 60 percent for placebo. Odds ratio higher, 2.52. And number of patients to treat to benefit one is reduced all the way down to five.

Part of the reason the pediatric data looks a little more impressive was one study that was highlighted by Dr. Mandell. That was a study by Wald in which the diagnostic criteria were tightened up considerably, in which there were both signs and symptoms and radiographic data.

When more strict criteria were employed for the enrollment of patients, the placebo response rate dropped all the way to 32 percent in that study. And that's why the overall placebo response rate for the three studies is 60 percent. It also shows the wide range that we can get in placebo-controlled studies based on criteria.

There's two comments from the authors of the

IDSA guidelines. One is that there's good reason to believe many patients enrolled in these studies had uncomplicated viral URI, uncomplicated rhino infection, rather than ABRS, and that was based on the signs and symptoms. Many patients were enrolled based on seven or even fewer days of signs and symptoms, not 10 days.

The authors also concluded that one can only surmise that the benefit of antimicrobial therapy would have been substantially magnified if more of the study patients had actually had acute bacterial rhinosinusitis.

So overall, I think the agency and we are in basic agreement. There is modest treatment benefit. We're talking about alleviation of signs and symptoms and returning a patient to normal. This is not a case of ICUs or imminent mortality, but it is a case of clinical response based on defined signs and symptoms.

So overall, for ABS, the appropriate patient and the proper role for fluoroquinolones is based on

antibacterial treatment based on clinical signs and symptoms. The top three pathogens that you heard from Dr. Mandell, Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis, have virtually no resistance to fluoroquinolones.

The IDSA guidelines recommend fluoroquinolones as second-line therapy in ABS for patients that have these characteristics: allergies, adverse reactions, therapeutic failure, et cetera. Importantly, the usage pattern, i.e., a little less than 9 percent of the overall usage, would seem to indicate that the fluoroquinolones are being used as second-line therapy in treatment of ABS.

For the COPD patients, same thing, guidelines, usage, placebo, summary; so the guidelines. These types of patients are those most likely to benefit, i.e., these are those that would be considered for alternative therapy: patients with a higher risk of serious complications, and you heard in the medical landscape talk a bit about

that; patients that are on oxygen; patients that might be the type 1 or type 2, with more signs and symptoms; those with allergies or adverse reactions; pathogens resistant to initial therapy; and/or therapeutic failure.

Looking at the guidelines, and these are from the American Thoracic Society -- on the left, you see many choices for first-line therapy, and then the alternative therapy are respiratory fluoroquinolones.

The pattern's immediately apparent. The fluoroquinolones here have 36.5 percent of the total uses, obviously a much bigger share in the COPD patients. However, the COPD patients were not categorized in the usage based on their severity.

All we know is that they got oral therapy. We don't know if they were mild or moderate. You would suspect not severe. But the fact that a patient got oral therapy does not mean they were mild. So we suspect that there's at least some moderates included in this data.

So overall, the fluoroquinolones had a bigger share of utilization in COPD patients. But since the piece of pie is much smaller, the overall usage is only 216,000 uses annually, again compared to 10.2 million total in these three indications.

Shown here are 14 different placebo-controlled studies in COPD patients utilizing a drug versus placebo. And if one really went through the table, what it would describe is the great difficulty in doing placebo-controlled studies in COPD patients.

Many of these are really not placebo-controlled; I would call them delayed therapy. A patient started on a placebo and then was switched, clearly at the first signs of infection. Many of them are small. We see some of them are from the 1950s. They span more than 50 years.

Despite all of that, overall, seven of the trials showed p-values less than .05 of drug versus placebo, even if that was placebo meaning delayed therapy. Four of them the authors claimed advantage

for drug, but either the trials were too small, they couldn't calculate the p-values, or if they did, they were greater than 0.05. And then three, drug equaled the placebo.

Again, a whole variety of diagnostic criteria, some hospitalized, some outpatient. Overall, the FDA has concluded that there is a modest treatment benefit in the milder COPD patients and more substantial in moderate to severe patients.

So in summarizing the COPD patients, again, appropriate clinical diagnosis to make sure the patient actually has a bacterial infection, and the key diagnostic criteria there is sputum, purulence, and color. That is the most characteristic feature of a patient that actually has a bacterial infection.

The pathogens were listed. They are similar to those for acute bacterial sinusitis, with the addition of some gram-negatives Enterobacteraceae, and in the most severe patients, Pseudomonas.

ATS guidelines recommend fluoroquinolones as

alternative therapy in patients especially that have high risk of serious complications. And you heard what happens with treatment failure leading to a cascading cycle of additional exacerbations: allergies or adverse reactions; pathogens resistant to initial therapy; or, in fact, overall therapeutic failure.

Finally, for UTI, the treatment guidelines. Here, when a patient presents with characteristic signs and symptoms -- pain, burning, urgency, et cetera -- the decision is typically to treat. The big consideration is acute pyelonephritis, which is depicted in the orange-colored box off to the right, to rule in or rule out acute pyelonephritis.

Obviously, it's not always as clear-cut. But for the purposes of today's presentation, we'll consider that this is uncomplicated urinary tract infection down in the bottom blue box, although many clinicians would consider acute pyelonephritis to be part of uncomplicated urinary tract infection. The FDA considers them separately.

Once the decision is to treat, the choice of therapy, based on patient allergy, compliance history, local practice patterns, local resistance in your community, drug availability, drug cost.

Looking at the IDSA guidelines on the left, we see three main therapies recommended, nitrofurantoin, trimethoprim-sulfa, and fosfomycin, an alternative therapy fluoroquinolone.

Immediately apparent on the table on the right is ciprofloxacin, the most used drug. Now, bear in mind that the definition of uncomplicated UTI for the purposes of this table, which is table 18 in the FDA briefing document, was expanded somewhat. It included terms such as urinary tract infection, which clearly could include acute pyelonephritis.

So ciprofloxacin was the number one used drug, and of course that was mostly generic ciprofloxacin. Overall, a bit over 37 percent of the usages were due to fluoroquinolones, and that translates into 9.3 million uses annually.

So by far, this is the biggest piece of the pie when it comes to fluoroquinolone use in the three indications under consideration today. Looking at the evidence for drug use, the FDA concluded that there is treatment benefit in UTI, and we agree.

This is highlighting four of the studies. At the very top you see that oflox is on top. And this is one of the placebo studies where there is in fact a fluoroquinolone. There was also one in the ABS. I think there was only two in the overall analyses, at least what we're presenting here today.

Overall, placebo effect is considered to be roughly 25 to 50 percent. You see here 26 to 51 percent, depending on the trial, the inclusion criteria, et cetera. Effective drug therapy is typically considered in the 80-plus percent range. You see in fact here oflox at 89 percent.

If we remember back to that forest chart that was shown early in the presentation, the two fluoroquinolones under approved for treatment of

UTI, ciprofloxacin and levofloxacin, both had clinical response rates of 95 percent or greater, again in different trials, not in placebo-controlled versus an active comparator.

Here the placebo effect, 26 to 51 percent, and you see the drug effect, including one fluoroquinolone on the top, oflox, at basically 89 percent. The one drug that failed to show a differentiation is the small study from Dubai, amoxicillin alone at 45 percent, placebo at 44. Amoxicillin is not recommended as therapy as a stand-alone for uncomplicated UTI.

So summarizing the UTIs, antibacterial treatment decision is based on clinical signs and symptoms. The patient is rarely cultured for an active bacterial pathogen. E. coli is the predominate pathogen; approximately 70 percent of the cases are caused by E. coli, the rest by a variety of Enterobacteriaceae, and on the gram-positive side, Staphylococcus saprophyticus.

The IDSA treatment guidelines recommend

fluoroquinolones as alternative therapy in uncomplicated UTI based on patient allergy, their adverse reactions, their history, their compliance, drug availability, and drug cost.

Conclusions overall. The fluoroquinolones do have a role in treatment of these three infections. The fluoroquinolones were approved and, in fact, all other antibacterials, based on trials versus an active comparator, they all demonstrated high clinical success rates, for example, 95-plus percent in the UTI trials.

The treatment guidelines recommend fluoroquinolones as second-line therapy for ABS and alternative therapy for exacerbations in COPD patients and an uncomplicated UTI. We saw that the majority, the vast majority, of fluoroquinolone usage in these three indications is in fact in uncomplicated UTI.

Overall, the fluoroquinolones are an important drug class. They have a proven role in the treatment of these three infections.

I'd like to introduce Dr. Susan Nicholson, who will be giving the safety presentation.

Industry Presentation - Susan Nicholson

DR. NICHOLSON: Hello. My name is Susan Nicholson, representing Janssen Pharmaceuticals and the other industry partners. I'm the vice president of safety, surveillance, and risk management for the Johnson and Johnson Family of Companies.

Formerly, I was the therapeutic area lead for anti-infectives at Ortho-McNeil Pharmaceuticals, which is now Janssen Pharmaceuticals. I'm a board-certified infectious disease physician and a fellow in the Infectious Disease Society of America.

We've heard presentations by FDA and industry colleagues about the utility of fluoroquinolone antibiotics in several infection types. Fluoroquinolones are an important antibiotic treatment option for some infections in certain clinical scenarios.

Key in the selection of antibiotic therapy is consideration of risk/benefit. I'll be presenting a

perspective on the three adverse events, which have been identified to occur concurrently in some patients. I want to acknowledge that in no way are my comments meant to diminish the experiences of individuals who have taken a fluoroquinolone and experienced an adverse clinical outcome.

Fluoroquinolone safety has been well-characterized. Fluoroquinolones have been available for almost three decades. Thirty-three million oral treatment courses are prescribed each year in the United States across five marketed drugs in the class.

The safety profile has been well characterized through a large clinical trial database, including more than 60,000 patients. There is extensive description in the published literature, and the postmarket surveillance includes experiences in more than 1.1 billion treatment courses globally.

Fluoroquinolone class labeling reflects the current safety profile. Specifically, class

labeling updates have been made in close collaboration with the FDA and industry to address emerging safety issues. Cardiac arrhythmia was originally added in 1999, and updates to the labels were made three times subsequently.

Tendon rupture was initially added in 1996, and updated twice thereafter. Peripheral neuropathy was initially added in 2004, and updated in 2013 to include a comment, "May be irreversible." Individual components within the FDA-described constellation of symptoms are included in the label.

When any potential safety concern is raised, characterization of this event includes review of all available data sources. Each data source has its strengths and its weaknesses. As such, it's important to consider all sources to determine the best interpretation of events and guide any needed action.

Sources of data include mechanism of action and preclinical data; clinical trials database; published literature, which may include perspectives

not previously considered; focused observational studies; and postmarketing surveillance.

When I'm speaking of adverse events of interest, these include the adverse events identified by FDA in their analysis of the constellation of symptoms referred to in the briefing book. These events include cardiac arrhythmia, tendinitis and tendon rupture, and peripheral neuropathy.

As mentioned, all these adverse events are currently described in the fluoroquinolone label. Overall event incidences in clinical trials support the conclusion that these serious adverse events of interest are rare.

The companies have ongoing processes to determine if new safety information is available. These processes include real-time analysis of individual case safety reports, meaning when a case is called in to the company, it's evaluated for reportability to health authorities, and also a determination is made if additional action is

needed.

Aggregate reports are done not only to meet regulatory reporting requirements, but are an opportunity to look at all the available sources of data in their totality and determine if the risk/benefit profile of the drug has changed, and if so, what mitigating actions are appropriate for that circumstance.

Aggregate data analyses include periodic adverse drug experience reports, PADERs, and periodic benefit/risk evaluation reports, PBERs. In addition, ongoing scheduled product signal detection reviews are conducted.

Signal detection and management is ongoing. For signal detection, a source of a signal may come from various sources, including a meeting such as this. When a significant comes in to the company, a process called signal validation takes place. That's a process to determine if further evaluation of that potential signal is needed.

It's important to know that this process is

not perfect and there's often missing or incomplete data in the spontaneously reported adverse events. Therefore, signal evaluation and assessment is needed, looking at in-depth analysis of all other sources of data, as I mentioned previously, including literature reviews, trending analyses, preclinical data, et cetera.

In the final analysis, a discussion is had whether or not there's a recommendation for further action, which could include potential label changes, "Dear Healthcare Provider" letters, et cetera.

Cardiac arrhythmias. It's been known for some time that fluoroquinolones as a class prolong the QT interval by blocking the hERG channel. This results in increased ventricular repolarization and can result in serious cardiac arrhythmias, particularly Torsade de Pointes, in susceptible patients.

Not all individuals with a QT prolongation will experience an event, an arrhythmia, and generally one or more additional factors are present

in individuals who do have QT prolongation-related clinical events. This risk varies by patient population and must be considered when assessing risk/benefit for fluoroquinolones.

Risk for serious cardiac arrhythmias is not unique to the fluoroquinolones in the antibiotic class, and of note, other antibiotics such as macrolides also carry a QT prolonging risk.

Fluoroquinolones carry a low risk of serious cardiac arrhythmias. According to the Chou paper, the risk is between .15 and .57 per thousand patients exposed. Importantly, the Chou data shown here includes patients with all infection types. This is relevant, as serious respiratory infections independently carry a risk of cardiac events.

Further, the data was not controlled for all other risk factors such as serious underlying conditions, which may have selected patients for certain classes of antimicrobial therapy, the more complex infections being given fluoroquinolones. Consequently, this analysis will not be

representative of patients discussed for the infection types under discussion at this advisory committee, where event rates would be expected to be lower.

Risk factors are described in the labeling for cardiac arrhythmia, including known prolongation of the QT; electrolyte imbalance; cardiac disease; class 1A or 3 antiarrhythmics; other drugs that prolong QT, including erythromycin, antipsychotics, tricyclic antidepressants, for instance; and elderly patients may also be more susceptible.

The class label is here, representing the quinolones. "Warning: Prolongation of the QT interval. Some fluoroquinolones have been associated with the prolongation of QT interval in the electrocardiogram in cases of arrhythmia. Cases of Torsade de Pointes have been reported during postmarket surveillance in patients receiving fluoroquinolones, including trade name." And you'll see in the label it lists the risk factors that I mentioned earlier for increased risk of cardiac

arrhythmias with quinolones.

For tendinopathy and tendon rupture, there are a number of mechanisms discussed in the literature with regard to fluoroquinolones and tendinopathy. The pathogenesis is considered to be multifactorial, and hypothesized mechanisms include ischemic effects on tendon tissue, degradation of tendon matrix, and cytotoxic effect on tendon cells.

As described in the FDA briefing book, tendon ruptures are rare in fluoroquinolone-exposed patients, occurring at a rate of 1.2 to 1.6 per 10,000 treatment courses. As you can see, the calculated rate varies by study.

Risk factors are included in the labels for fluoroquinolones for tendon rupture. These include greater than 60 years of age; concomitant corticosteroid use; kidney, heart, or lung transplant; renal failure; previous tendon disorders, for example, rheumatoid arthritis; and strenuous physical exercise.

Tendinitis and tendon rupture is addressed in

a class label, a boxed warning. "Fluoroquinolones, including trade name, are associated with an increased risk of tendinitis and tendon rupture for all ages. The risk is further increased in older patients," and so forth, covering the risk factors I mentioned previously.

With regard to peripheral neuropathy, and this was discussed in the FDA presentation, a single epidemiologic study reports an increased ratio of peripheral neuropathy among nondiabetic men ages 40 to 85 years, which is doubled in the two weeks after exposure to a fluoroquinolone.

It is difficult to assess the significance of this observation due to some methodologic limitations and missing key information that has already been reviewed. There is no direct clinical or experimental evidence linking specific cellular abnormalities to the pathology of peripheral nerves in fluoroquinolone-treated patients. Nonetheless, peripheral neuropathy was added to the label in 2004, and the label updated, including "may be

irreversible," in 2013.

Here's the current class labeling for peripheral neuropathy in the warnings section. "Cases of sensory or sensorimotor axonal polyneuropathy affecting small and large axons resulting in paresthesias, hypoesthesias, dysesthesias, and weakness have been reported in patients receiving fluoroquinolones, including trade name." And a listing of the possible symptoms that might occur in patients is delineated here in detail. In addition, there's information in the adverse reaction section in the patient counseling information.

With regard to the FDA cases of interest, we reviewed the FDA cases of interest, as outlined in the briefing book. There were 178 total reports from FDA, received over a period of 17 and a half years. The reports were in three event categories: peripheral neuropathy-related events, tendon rupture and injury-related events, ventricular arrhythmia-related events.

These were further characterized for peripheral neuropathy-related events, including the listed signs and symptoms, nerve injury, burning sensation, numbness, tingling, severe muscle and nerve pain, prickling, pins and needles. Neuropsychiatric-related events were also included: insomnia, anxiety, confusion, depression. Tendon rupture and injury were included, and ventricular-related events were included.

This slide shows the FDA's search strategy used to identify the 178 cases. Earlier in my presentation I reviewed the typical process for evaluating new safety concerns.

The usual process is to combine cases of similar clinical symptoms and determine possible cause and effect by reviewing all available data. Outcomes become important in determining the appropriate actions to mitigate any identified risk.

For this analysis, the FDA took an unusual approach to selecting cases. The cases were first selected based on the outcome of disability, an

outcome which could result from any number or combination of circumstances. Then among the disability cases, cases were selected, which included two or more adverse events from categories outlined on the previous slide.

Another notable aspect to the series, which was mentioned before, is the high proportion of cases reported directly from the public, 84 percent. Of note, only 12 percent of the cases were reported from healthcare professionals.

Over the past 10 years, the percentage of direct reports overall in the FAERS database has ranged from 2.4 to 6.3 percent. Importantly, reports from the public may not include important clinical information needed to assess causality and determine what medical assessment was performed to rule out alternative diagnoses.

Specifically, primary data such as biopsies, imaging studies, et cetera, are not available. Medical history not reported or not documented, as in 60 cases in this series, does not necessarily

mean healthy with no previous illness.

Companies seek to gain more information about reported events by having follow-up conversations with healthcare providers. Often, patients do not give healthcare provider information, contact information, when they report the event, and this limits the ability to clarify any data, which is collected when the report is taken.

This graph shows the FDA cases reported over time. Although it looks like the numbers are increasing over time, a higher proportion of the later reports are older than one and in many cases older than two years from the first occurrence.

You can see in the red and gold, hopefully, that the red are cases that the initial case or signs and symptoms started more than two years prior to the report being received, and the gold are cases that started between one and two years before the report was received.

If we push them back to first occurrence, sort of smushing them off to the left from when they

were reported, the reporting rate flattens out. On average, there are about 10 cases received each year, with approximately 10 million courses of treatment for the three infection types. So per year, that comes to a reporting rate of about one in one million treatment courses.

This type of increased reporting pattern is consistent with stimulated reporting. Adverse event reporting is said to be stimulated when there's an increase in the number of reports caused by factors unrelated to the true event frequency, such as recent product approvals, media coverage, litigation, direct-to-consumer marketing, or release of new safety information.

With stimulated reporting, it becomes very difficult to interpret postmarketing safety data. Seeking other sources of data to evaluate this constellation of clinical events is necessary.

For instance, to consider a pair of symptoms to be associated, they should occur more often together than they would independently. Further, in

this constellation, the pairs should occur more often in fluoroquinolone-treated individuals than in a comparable population. These analyses can be tested, but not in the spontaneous reported postmarket database we've been discussing. A health services database would be an alternative consideration.

The current class fluoroquinolone labeling contains information on all the clinical conditions in the case series. There are proposed or proven mechanism for each category of adverse event, none of which tie together the constellation of symptoms.

The purpose of the safety section of the label is to provide healthcare professionals with information that informs their treatment choices. It's not apparent how this constellation would aid the clinician or how it would contribute to the improvement of the well-being of patients. We look forward to hearing the perspective of the advisory committee on the proposed constellation of adverse events.

In conclusion, serious adverse events of interest are rare in fluoroquinolone-treated individuals. No new information has come to light pertaining to these three adverse events of interest beyond what's in the current class labeling.

The current label reflects our present understanding of the potential risks of fluoroquinolones and guides physicians to make informed treatment decisions. At this time, evidence of the FDA-identified constellation of symptoms associated with the events of interest is inconclusive and needs to be explored. There's no plausible unifying biological mechanism.

We look forward to hearing the advisory committee's perspectives, and we're committed to working with the agency to further understand and characterize this constellation of symptoms.

Dr. Zinner?

Industry Presentation - Stephen Zinner

DR. ZINNER: Thank you very much, and I'm happy to be here today. Good morning. I'm Steve

Zimmer, and in addition to what's listed on here as my credentials from Mount Auburn Hospital and Harvard Medical School, I've been a board-certified infectious disease consultant for over 40 years, and I'm still seeing patients. I have received a consulting honorarium for my time, but I do not have any financial interest in the companies or in the outcome of this meeting.

I have two other disclosures. I survived childhood without antibiotics, because they weren't available, and I remember the practice of infectious diseases before fluoroquinolones became available.

I'd like to offer some clinical observations about benefit/risk of the fluoroquinolones, but first I just want to have some general considerations about the appropriate use of antibiotics.

All oral antibiotics are overused, especially in respiratory tract infections, many of which are viral. And this applies to the macrolides, beta-lactams, as well as the fluoroquinolones.

What we need are better and faster point-of-care diagnostics to help us distinguish between bacterial infections, which require antibiotic therapy, and nonbacterial or viral infections, which are usually self-limited.

Infectious disease physicians and the guidelines support the appropriate use of antibiotics to treat proven or highly suspected bacterial infections. We also support antibiotic stewardship programs, which were initially devised to increase appropriate use in hospitals, but are currently expanding into the outpatient arena, with some early success.

I certainly remember when the fluoroquinolones became available, and I recall the ability to treat patients who used to be hospitalized, such as with pyelonephritis, as outpatients, reducing the need for hospitalizations, and certainly shortening the course of those patients who could be treated in the hospital.

The unique pharmacokinetics of this class of

drugs, as we've heard, allows oral medication, oral therapy, to achieve similar drug exposures to that achieved with intravenous doses, allowing for the ability to treat many of these infections outside the hospital. And you've heard an enormous number of courses of therapy with these drugs has been used globally.

So the fluoroquinolones remain an important charge class. They demonstrate bactericidal activity against prevalent gram-positive and gram-negative pathogens, albeit resistance occurs, as it does with all the antibiotics. And these drugs are also active against atypical respiratory pathogens. And they've recommended as alternative or second-line therapy in the major treatment guidelines for all three indications.

Let's think about the medical need for antibiotics overall in respiratory infections. Acute bacterial exacerbation of chronic bronchitis in the setting of COPD and acute bacterial sinusitis are bacterial infections when appropriately

diagnosed and should be treated. There is considerable patient morbidity. There are risks of complications and sequelae. And as we've heard, in COPD exacerbations contribute to long-term lung function decline.

Unfortunately, most diagnosis is empiric and often is evaluated by telephone consultations with healthcare providers. And sometimes patients are treated with antibiotics just in case.

That said, the treatment environment is complex, and we need to have choices to treat these patients because the patients may differ with respect to their recent use of antibiotics. There may be a recent primary failure of the first therapy.

Recurrent infection can occur frequently in these patients. A lot of underlying and concomitant diseases, lots of additional medications, allergies to and intolerances to other antibiotics, as well as local resistance patterns, play on the choice of physicians. These are some of the strategies where

the fluoroquinolones can play an important role.

At the end of the day, for most physicians, whether to use an antibiotic or not often comes down to a determination, is this patient sick or not sick?

With respect to the medical need for antibiotics in urinary tract infections, these should be treated with antibiotics if appropriately diagnosed because the clinical morbidity is not negligible. Rapid bacterial eradication is important. Short courses of antibiotics are effective in reducing symptoms and in eradicating bacteria, and recurrences are frequent.

Cultures are no longer routinely obtained in the first episode of acute urinary tract infections, but they may be useful in properly managing patients with recurrent uncomplicated urinary infections. And bacterial resistance, of course, is an issue with all major antibiotic classes, including the fluoroquinolones, but it's important for us to have treatment choices.

With respect to the established safety profile, we've heard that in detail just recently, and that the serious adverse events of interest are rare. With regard to each of the new FAERS symptom constellation reports, I've read each of the case reports, and I understand and acknowledge the pain and suffering represented by the patients who submitted those cases.

I'm not sure we have a plausible biological mechanism to link the symptoms in this constellation, but we do need additional analyses of the possible clusters and their potential overlap with other well-known clinical syndromes such as fibromyalgia, chronic fatigue syndrome, which is also known as the systemic exertion and tolerance disease, which might be an alternative explanation for some of these symptoms.

Looking at the benefit/risk of these drugs in the three indications, the benefits include their activity against important bacterial pathogens, resolution of clinical signs and symptoms, regaining

functional status and improving the quality of life, reducing complications and hospitalizations; and the treatment of patients with allergies or adverse reactions to other antibacterials, or who have failed primary therapy, or who are infected with drug-resistant pathogens provide an arena where the fluoroquinolones can be used appropriately.

Fluoroquinolones have a favorable benefit/risk in appropriate patients in these indications, and we need these drugs as available choices to treat these infections when appropriately diagnosed. Thank you.

Industry Presentation - Jeff Adler

DR. ALDER: Before I give concluding remarks, I'd like to take a moment to recognize the people in the room who will be sharing their personal stories at approximately 1:00 p.m. today. Your stories, your participation in the meeting, is very important to us.

As clinicians, as researchers, as investigators, the safety of our drugs and the

safety of our patients is our top priority. We appreciate your being here today to share your stories, and we look forward to your participation.

For concluding remarks, the fluoroquinolones are an important choice in the treatment of these three indications. They have proven safety and proven efficacy over decades of use. The fluoroquinolones remain an important choice for patients and for physicians in these three indications.

The fluoroquinolones have been approved in these three indications based on solid efficacy data in multiple phase 3 clinical trials, first as an active and approved comparator.

The treatment guidelines endorse fluoroquinolones as alternative for a second-line therapy in each of these three indications. Those guidelines also indicate what is an appropriate and what's an inappropriate patient in each of the three indications.

There is an established and well-

characterized safety database, which is reflected in the label, and efficacy, which is also reflected in the label, for each of the fluoroquinolones.

The industry is committed to working with the FDA to better analyze, better characterize, and to evaluate this newly identified FDA constellation of events.

Dr. Parise, that concludes the industry presentation.

Clarifying Questions to Presenters

CAPT PARISE: Thank you.

Are there clarifying questions for the industry? Please remember to state your name for the record before you speak. And if you can, please direct questions to a specific presenter.

Dr. Vitiello?

DR. VITIELLO: I didn't really signal. You probably saw someone else.

CAPT PARISE: Sorry.

Dr. Choudhry?

DR. CHOUDHRY: Thanks. Niteesh Choudhry.

This is a question probably for Dr. Alder and Dr. Mandell. I'm trying to reconcile for COPD exacerbation the interpretation of the data.

Notwithstanding our commentary before about what constitutes mild, moderate, and severe, which I'd love some feedback on, frankly, but the FDA's briefing document talks about a variety of guidelines, not only the ATS guidelines.

Neither of the documents really talk about goals, but debate about mild disease, and the comments that Dr. Toerner made in patients with milder exacerbations, the evidence of benefit is small as opposed to I think Dr. Alder's comments were that they were moderate.

So there's seemingly some difference in interpretation of the quantity of the data. So I've got three questions related to that.

Number one, any comments on the thoughts of which guidelines we should look to, given the numerous ones that are out there? Number two, if you could help us reconcile the interpretation of

the data. And number three, if you had to propose a definition of what might constitute mild or not mild, or sick or not sick, what would that be?

DR. ALDER: The statement was that the efficacy in the milder COPDs was modest. So modest, I believe, was the FDA wording, though we concur, and more substantial in moderate to severe COPD patients.

As far as differentiating clinically a mild COPD, a moderate COPD, and a severe COPD patient, I would invite Dr. Mandell for his views.

DR. MANDELL: Thanks for your questions. You've raised a number of points. I'm sorry, I had terrible hearing, but one of the questions was which guidelines.

There are a number of guidelines that are very good. I don't want to sound like I'm supporting my home team, but I think the Canadian guidelines are great because they really focused in on it and expanded on the antibacterial treatment as opposed to some of the other treatments, which

definitely play a role, like bronchodilators, steroids, et cetera.

But there was a lot of work and effort that went into that document. And also, the Canadian guidelines for pneumonia, for example, were the first ones out there, and then subsequently the ATS and IDSA jumped on board.

So I would say you can read whichever ones you want because they all recommend treatment. The greatest detail, though, is in the Canadian document.

In terms of the interpretation of the data, I would agree. The initial study was the Anthonisen study a number of years ago, and for the mild, there really wasn't an effect. And I would agree, and so would most clinicians. If it's a mild flareup, you don't treat it.

So I guess the question is, what's mild? What's moderate? What's severe? Generally, we go by what are called the Anthonisen criteria. For COPD, we use the GOLD criteria. But for the

flareups, the Anthonisen are usually used to a general extent. And that means one, two, or three of increased sputum volume, sputum purulence, or shortness of breath.

So if someone came in -- and keep in mind, these patients are like athletes. They're very attuned to their bodies because they sense right away if sputum volume has gone up or they're short of breath. So if they came in with just one of those, I would probably say to them, just wait. Let's see what happens over the next few days. If they came in with two or certainly three, I would start to treat them. And the data support that.

I think where we may be at odds a little bit in terms of interpretation is, are the moderate and severe only in the hospital? Absolutely not. They are out there in the community. They walk among us.

Did you have another question? Okay.

CAPT PARISE: Dr. Winterstein?

DR. WINTERSTEIN: Actually, this came up twice. There was this reference to no unique

plausible mechanism. I'm struggling with, number one, why there would have to be a unique, plausible -- or unified, I think was the term -- plausible mechanism.

So if you're looking at the more severe events, we have our cardiac arrhythmias and sudden cardiac death and ventricular arrhythmia. And that goes through QT prolongation, and that seems to be a fairly clear mechanism. And one would expect that this is not the same mechanism that causes tendon ruptures.

So for the tendon rupture piece, I think there is a fairly good body of literature now that looks at collagen tissue. And to me, that seems to be also a plausible mechanism for neuropathy.

So I guess my question is, number one, why does it have to be a unified mechanism or what exactly did that refer to? And then number two, does the sponsor disagree, number one, that quinolones cause tendon ruptures, number two, that quinolones cause severe arrhythmia, and then number

three, that quinolones cause neuropathy?

Because there were a lot of references throughout that, well, there may be confounding here, and there may be something there. And maybe we can just establish whether we think that this is actually a causal association, and then next we can talk about how rare that is or not.

DR. ALDER: Dr. Nicholson?

DR. NICHOLSON: Sorry. I can't see over the screen here.

DR. WINTERSTEIN: I cannot see you, either.

(Laughter.)

DR. NICHOLSON: I'm here. So for each of the three adverse events, absolutely, there is an association with fluoroquinolone use, and I think that is adequately reflected in the label.

I think the issue is the constellation itself. When we looked at the 178 cases and tried to understand the aggregation of those cases, it was difficult, frankly, to understand why those cases would be put together and analyzed based on an

outcome of disability.

In order to really understand if there is in fact an increased frequency with the exposure to fluoroquinolones, I think we need a good case definition and probably a more comprehensive database, such as a health systems database, to really evaluate is there an increased frequency of this aggregation of adverse events in fluoroquinolone-treated patients?

I don't disagree that each of the individual adverse events, which are well labeled currently, can be associated with fluoroquinolones. I think what's at issue is this constellation as something that is unique. So that would be my comment.

DR. WINTERSTEIN: Well, but there's a summary of cases as it was presented. It had cardiovascular cases in there, and it has musculoskeletal issues there, so we have the same issue.

Nobody makes the inference that this is one specific phenomenon or syndrome. And quite frankly, the case reports to me are not that important as the

solid controlled epidemiological data that gives us controlled comparisons of, as you call them, association.

So I'm just trying to get my arms around what the issue is here. But it seems like we agree that there is a causal association with these three outcomes that we were discussing. Yes?

DR. NICHOLSON: Yes. We do agree.

DR. WINTERSTEIN: Thank you.

CAPT PARISE: Dr. Gerhard?

DR. GERHARD: Tobias Gerhard, Rutgers. I guess this is for Dr. Alder as well. Clearly, the majority of the use is in uncomplicated UTI. And in all the presentations and the guidelines, there was agreement that the quinolones would be considered alternative treatments.

However, it seems that when we look at the actual utilization, that cipro is the number one drug used for uncomplicated UTI. Could you comment where that is coming from and how you interpret that, what to me looks like a mismatch?

DR. ALDER: Sure. I would invite Dr. Abrahamian to comment on this, please.

DR. ABRAHAMIAN: Thank you. I'm Fred Abrahamian. I'm a board-certified emergency physician, practicing emergency physician, with academic and research interest in infectious diseases.

Your question as far as the higher utilization of ciprofloxacin in the context of uncomplicated urinary tract infection, well, we have two issues. One is that the definition of our uncomplicated urinary tract infection, our definition encompassed not only acute cystitis but also included urinary tract infection.

That can include also acute pyelonephritis because urinary tract infections, as they're divided from lower to upper, they both can be categorized as uncomplicated as well. So it is conceivable that many patients, or some patients within that category, had acute pyelonephritis, where fluoroquinolones are considered to be the right

choice for that disease.

Another thing that comes up as well is that it is very hard from that data to understand appropriate use of the agent or inappropriate use of the agent. In clinical practice also, many patients also come in not always falling truly into acute cystitis or acute pyelonephritis.

Many patients come in with symptoms that fall kind of in between. And oftentimes, physicians and healthcare providers want to make sure they're treating adequately for patients that fall in the category, in the middle category, where we oftentimes call them they have subclinical pyelonephritis. We treat them as pyelonephritis, and oftentimes they're designated as urinary tract infection as well.

CAPT PARISE: Dr. Baden?

DR. BADEN: Along those lines, a similar question. What is the proper definition then for uncomplicated cystitis or lower tract in a way that we can operationalize in practice since the use of

agents in that setting really drives the antibiotic use equation in today's discussion?

DR. ABRAHAMIAN: Thank you. It's not very clear in general in clinical practice. Like I said, many patients can present with symptoms that overlap both conditions. As far as terminology, even in clinical trials or articles or research articles or review articles, you see this mislabeling of various forms of urinary tract infection.

The best way to do it -- slide up, please. The best way to do it is -- obviously there are many forms of classification system. But one of the easier ways to do it is to consider the infection to be in the lower aspect of the genitourinary system, specifically within the bladder, or anything that's above that that involves the kidney.

We go by symptoms. If the symptoms are mainly concentrated or related to the bladder area, we call that cystitis. If anything that's more systemic -- flank pain, cross over to ankle tenderness, fever, and so forth -- more likely

pyelo.

In each category you can have uncomplicated and complicated infections. Uncomplicated infections are basically -- the way we like to think about it are infections that occur in premenopausal nonpregnant women without any genitourinary abnormalities and comorbidities. And that's what defines uncomplicated. Everything else becomes complicated infection.

So as far as terminology, I think it's best for us -- what we're talking about here is acute uncomplicated cystitis. That's the best way to define that. I believe that's the point of our discussion. When you say acute uncomplicated urinary tract infection, that broadens the infection to include upper tract infections as well.

DR. BADEN: Agreed. So help me understand, then, what are the medical risks, health risks, with undertreating -- can you leave that slide up, please -- undertreating uncomplicated cystitis with antibiotics?

DR. ABRAHAMIAN: Undertreating uncomplicated cystitis?

DR. BADEN: Correct. What you said is our discussion now is uncomplicated lower UTI.

DR. ABRAHAMIAN: Right.

DR. BADEN: If that is undertreated with antibiotics, what are the significant medical risks at play that we should be considering?

DR. ABRAHAMIAN: Well, may I ask you to define undertreatment? Can you give me an example of that, please?

DR. BADEN: Since the treatment is antibiotics, what if antibiotics are delayed as one tries to sort out the clinical scenario? As Dr. Zinner and Dr. Mandell have mentioned, a lot of treatment may go on over the phone or in the outpatient, and that often leads to antibiotic use in that setting.

What is there were more thought prior to triggering antibiotics? And then what would the potential health risks be to the patients?

DR. ABRAHAMIAN: Well, I think the best way to answer that question is that first we have to look at, I guess -- the best way you can say undertreatment is we have to compare it to placebo trials. I mean, that's the best way you can answer that question.

It is very clear with the evidence that's available that antibiotics do affect symptom resolution, both acutely and somewhat of a longer term as well, meaning three days versus seven days. They both affect symptoms resolution and, most importantly, they also have an effect on bacterial eradication.

Another way to think about undertreatment is to utilize drugs that we know are ineffective on the specific organisms we're talking about, where there is resistance to those antibiotics. And we know when there is resistance, the clinical failure rate and microbiologic eradication rates are not high, either.

I'm not aware of any studies that has taken

the approach of wait and see approach. These infections have their morbidities. Certainly uncomplicated cystitis does not have a mortality associated with it. However, there's significant morbidity associated with it in terms of days lost from work, school, pain and suffering, and so forth. So as much as possible, you like to treat this infection appropriately.

Now, another aspect that comes in here is that we always think about risks to benefits. The new Infectious Disease Society of America guidelines recommends nitrofurantoin as the first choice of therapy for cystitis.

When you look at the efficacy of nitrofurantoin compared to ciprofloxacin, it's not as good. However, considering all the things we talked about, risks and benefits and disease burden and so forth, it appears that to minimize the consequences that broader spectrum agents can do, we stick with nitrofurantoin as first choice and move on to -- later on if there is a worsening of

infection or recurring infections.

CAPT PARISE: Dr. Hogans?

DR. HOGANS: Thank you. To stay on the theme, it looks as though the utilization of fluoroquinolones in the COPD exacerbation and the UTI are in the high 30s. But it also seems plausible that with the COPD exacerbation, as was nicely explained, there is a compromise in the host, and oftentimes there's a pattern in the bacterial pathogen that would lend itself to explaining why fluoroquinolones are chosen.

In the UTI scenario, though, it's pretty clear that these are community-dwelling, healthy, otherwise uncompromised patients who are getting very frequent exposure to fluoroquinolones. And I understand the discussion about upper versus lower, cystitis, whatnot.

Are there strategies that could be adopted to lead to more appropriate antibiotic selection in the event of uncomplicated cystitis? Because it does appear from the data -- and I understand what's been

explained -- but it does appear from the data that there is an over-reliance on ciprofloxacin for uncomplicated cystitis. I understand that we can't sort it all out perfectly.

DR. ALDER: Thank you. I'd like to share a couple pieces of data first, and we can potentially look at the label for fosfomycin. This is the FDA-approved label, where they have the overall clinical success rates. Slide up, please.

This is some of the points that were discussed a moment ago by Dr. Abrahamian. So this is actually from the FDA label. Fosfomycin, clinical success rate 70 percent. Ciprofloxacin was the positive control, so this was not a ciprofloxacin trial; this was a fosfomycin trial. Ninety-six percent, and the little footnote basically says that fosfomycin failed the noninferiority test to cipro.

Trimethoprim-sulfa is another primary therapy checked in at 94 percent, very high success. Nitrofurantoin, 77 percent. So this gives one

perspective of the three primary therapies compared to a fluoroquinolone for their overall success.

As far as strategies to optimize these four agents, I would invite Dr. Abrahamian to return and offer some comments, please.

DR. ABRAHAMIAN: Thank you. Well, this is a question that has been discussed for many, many years. I think one of the best things that have been done compared to previous edition of guidelines is that the Infectious Disease Society of America clearly states what should be the first choice. And I think as this information gets disseminated and physicians are aware, our physicians are using nitrofurantoin more and more.

Nitrofurantoin wasn't used many years ago, and now we see it oftentimes now as the second choice. And I think that's a reflection of the guidelines and understanding what drugs you should be using as first.

CAPT PARISE: Dr. Honegger?

DR. HONEGGER: I also had a question about

the utilization of cipro for UTIs. In the analysis, the ICD-9 strategy could not distinguish very well upper and lower urinary tract infections. Is there a narrower ICD-9 code that you can look at in a subset of patients to know the frequency at which cipro is used?

DR. ABRAHAMIAN: By no means I want to come across as an expert as ICD-9. This is what happens. The bottom line is that these codings are not precise, and oftentimes what happens in real world, you'll try to go to the most likely diagnosis that you can find in the ICD-9 coding.

Oftentimes, when you diagnose this infection as a urinary tract infection, that's what you're going to go to. You most likely are not going to go in detail to find out as far as the location or severity or anything like that.

I think that's how it goes. The coding in general are not precise. And I guess that's one limitations of ICD-9. From what I hear, ICD-10 is not like that. It's far more complex. And we'll

see how that goes.

CAPT PARISE: We will now break for lunch. Just a note to the committee that I know there are some of you who do still have clarifying questions, and we'll also do that in our session this afternoon. We'll have time to do that.

So we will convene again in this room at 1:00. Please remember to take any personal belongings you may want with you at this time. Committee members, please remember there should be no discussion of the meeting during lunch among yourself, with the press, or with any member of the audience. Thank you.

(Whereupon, at 12:04 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:02 p.m.)

Open Public Hearing

CAPT PARISE: Just before we start the open public hearing, there has been some interest from the media. So I wanted to reintroduce Lyndsay Meyer. If you could just show people who you are, the FDA press contact, if she can be assistance to you.

Both the FDA and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with the industry, its product, and if known, its direct

competitors. For example, this financial information may include the industry's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance on the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect.

Therefore, speak only when recognized by the chair. Thank you for your cooperation.

Will speaker number 1 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MR. RHUDY: My name is Tim Rhudy. I represent people who have been injured by fluoroquinolones. No financial interest.

I was on staff at the Cleveland Clinic for six years until my career was effectively ended there by cipro. Quinolones don't just cause a list of side effects. They can cause a long-term to permanent, multi-systemic, debilitating to disabling syndrome.

Doctors are not aware of fluoroquinolone toxicity syndrome. It's not even in their sphere of awareness for most of them. In fact, most of the time that you would ask a doctor about fluoroquinolone toxicity syndrome, they'll deny that it even exists.

The claim that doctors know about fluoroquinolone adverse effects is fiction. The intimation that fluoroquinolone adverse disability or fluoroquinolone-associated disability might not be a legitimate consequence of fluoroquinolones is offensive and needs to stop now.

Today I'm speaking on behalf of former Deputy Sheriff Gail Orth Aikmus, who was injured by Avelox. Her story, her words.

"In February of 2011, I was prescribed Avelox and prednisone. Within 24 hours of taking the meds, I had pain all over my body, had panic attacks, and felt like I had been hit by a bus. I called my doctor's office and told them something was wrong. I was told prednisone was a horrible med and side effects were bad, but to keep taking all the drugs. I would feel better.

"I kept taking it all. Two days later I was worse and called them again. Now I could barely walk. The pain in my arms and legs was tremendous. I had to use the wall to keep from falling over. I

felt like my heart was going to pound out of my chest. Once again, my doctor's office said they understood, but keep taking everything. You'll feel better.

"I completed the course of Avelox and continued on the prednisone and was getting worse, not better. It became so bad one night I couldn't breathe. My son took me to the emergency room, where I was admitted and placed in the critical care unit.

"For the next nine days, I was pumped with massive doses of steroid and more antibiotic, and was released, barely walking on my own. I got home and laid in my bed for the next two weeks, only getting out of bed to use the restroom.

"I saw my primary care doc. His diagnosis, severe adverse reaction to Avelox. The reaction was made worse by all the steroids. I was bedridden for the next two months, then went to using a wheelchair to a walker to a cane, which I still use four and a half years later.

"I have chronic tendinitis, peripheral neuropathy, skin sensation disturbance, muscle issues, joint issues, balance issues, ongoing cognitive issues. My insurance company spent hundreds of thousands of dollars in hospitalizations, testing, doctor after doctor, specialist after specialist, trying to find a cure to help me."

As for myself, I'd just like to add, after working at the Cleveland Clinic, this is not even on doctors' radar. We just want full disclosure. If you're prescribing or dispensing or consuming, you need to know what kind of Russian roulette you're playing.

(Applause.)

CAPT PARISE: Will speaker number 2 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. BENNETT: Hi. I'm Dr. Charles Bennett. I'm an endowed professor at the University of South

Carolina School of Pharmacy, and I run the safety program for the University of South Carolina Center of Excellence. I have no financial conflicts of interest to report, and I do not represent any organization.

I will be giving two parts, just like the first speaker. The second part will be representing and speaking for Linda Martin, a PhD who's in Phoenix, who could not come today because she's too ill to make the trip.

So the first part. I run a program called the Southern Network on Adverse Reactions, SONAR, which is about $8 million in funding from the federal government and the state. It's the only state-sponsored drug safety program in the country.

What SONAR does and what we do is we look and try to understand safety side effects. We've done 50 so far, and we've done many that have been drugs on the market for 10, 20 years, just like we're talking about today.

The important point we do is to understand

both basic science and clinical science and preclinical science. The issues that we've been looking at for fluoroquinolone-associated toxicity, we've started to develop and look through mice studies.

We treated increasing doses of mice, 10 mice per panel, each half women, half men -- half male. And what we were able to do is increasing doses, is generate the same symptomatology that we talked about today in terms of neuropsychiatric findings.

This would be -- the mice would be unable to hold themselves. They could not get through a maze. They were depressed, you could see in the mice physiologic study. We also used a dosing in the mice that would be comparable to dosing that we use in humans to make sure it was not overly toxic. What we did with the mice is to find and replicate the neuropsychiatric findings.

Secondly, after we did that, we've done a sample of outreach, and we've identified 54 cases, much like the 178 that the FDA talked about this

morning. The symptomatology that we see is not necessarily FQAD. We find the symptoms that we've identified, that about 95 percent of the patients who report these symptoms during the time they're on drug, 5 percent after the drug is discontinued.

In terms of male/female, 85 percent female, as reported also. The interesting, important differentiation is that when you look at the time of disability, we have people disabled on mean over one year. And the difference between us and the FDA is because we have longitudinal follow-up, which was reported this morning as very difficult to get.

So finally, where we are. I have filed two citizen petitions personally to try to get the product label to be updated. This is a real finding. We've seen that in the findings that were associated with neuropsychiatric syndromes as opposed to the FQAD. Thank you.

(Applause.)

CAPT PARISE: Will speaker number 3 step up to the podium and introduce yourself? And please

state your name and any organization you are representing for the record.

MS. KING: My name is Teresa King. I reside in Mechanicsville, Virginia. I appreciate this opportunity to be able to come and speak to this panel. I have been severely injured since 2006, just connecting March of 2014.

I have seen many specialists, five orthopedic groups. My first adverse drug reaction was a torn glute; substantial tendinopathy in 2007. Another done in 2009. I have been to every specialist imagined from these fluoroquinolones.

I am only 56 years old, and they have taken eight years of my life. I have severe central nervous system damage, autonomic, five years of nausea, and the gastroenterologist, every gastro test they make; an esophageal manometry last Monday, my second endoscopy the 10th of this month.

I beg you, panel, to please strengthen the warnings of these fluoroquinolones. I was on NSAIDs before 2006, every one they make. Diclofenac,

methocarbam [indiscernible], and there are two other ones on here. I could not even do a speech. I am not mentally capable of putting eight years on paper. I called my husband. He said, "Wing it, girl."

But if you would just please strengthen the warnings for tendon ruptures, psychiatric issues. I saw a psychiatrist for three years. Cried for nothing. But also could laugh. And he couldn't understand. You are not clinically depressed if you can laugh.

Like I said, I just connected a year, a little over a year. And I have been to ophthalmologists, gastro, neuropsychiatrists, four orthopedic groups in Richmond, seeing six different doctors. No one would help me for torn glutes.

I have muscle contractions. My shoulders pull 24/7. My legs pull together. My feet draw. My hands do this (gesturing). My spine burns with the slightest task. I am homebound. And if it wasn't for my 31-year-old and 35-year-old, two

adult, grown men children, I would not be standing here today.

I beg you to strengthen the mitochondria warnings. I cannot get in the beach water and get out. I ask for you to please put the tendon ruptures on page 1. I never connected because who in the world would ever think an antibiotic would cause such devastation?

So anyway, I winged it, as my husband said. Like I said, I started on NSAIDs in 2006. After that, my first MRI September 2007; was given Avelox again. And I was given Avelox twice with a methyl pack. I've had Levaquin three times, one refilled with a methyl pack as well, along with five years of prescription NSAIDs.

My central nervous system damage is gone. I have severe autonomic damage. My bowels are gone for six years. I was hospitalized six years ago from the doctor's office, paralyzed, and have given these drugs seven times after a 2007 MRI stating substantial tendinopathy and torn glute.

CAPT PARISE: Excuse me. We just need you to finish up with your last sentence just so I can keep us on time. Thank you.

MS. KING: Thank you, panel. I appreciate it. Please strengthen the warnings for psychiatric.

CAPT PARISE: Thank you.

(Applause.)

CAPT PARISE: Will speaker number 4 step up to the podium and introduce yourself, stating your name and any organization you are representing for the record.

DR. WOLFE: I've been asked to move the microphone up so that I can be heard.

I'm Sidney Wolfe. I'm doing this in conjunction with a second-year internal medicine resident from Johns Hopkins, Victoria Powell, who's doing part of her residency with us.

This slide really talks about what the questions now voiced to the committee are. The only thing I'd like to stress is the last part of it, which is discussion of why including more things

than just tendinopathy and myasthenia gravis in the black box warning, such as abnormal electrocardiograms and arrhythmias, might clarify that the risk/benefit ratio is really higher than people think it is.

The other two diseases have been discussed in depth. Uncomplicated urinary tract infection again is not recommended -- fluoroquinolones are not recommended as the first choice by the IDSA, and yet a huge proportion of the prescriptions for this disease are fluoroquinolones, 32 percent ciprofloxacin and 5 percent levofloxacin.

This is a study which was done on 100 consecutive patients in two academic medical center emergency rooms. The black bars are the inappropriate prescriptions and the light bars are the ones that are appropriate. And the categories are urinary tract infection, respiratory, and so forth and so on.

These were people who were well enough to be discharged from the emergency room, and they were

following the guidelines for those institutions. This paper was published in the then-Archives of Internal Medicine by researchers from the University of Pennsylvania.

Some of the findings were that 25 percent of all the antibiotics in that emergency room were fluoroquinolones; 81 percent of these prescriptions were deemed inappropriate after chart review and using these institutional guidelines; and of those, about half were inappropriate because another agent was first-line.

People that were not allergic to sulfa should have been given sulfamethoxazole-trimethoprim but weren't. Another big chunk were inappropriate because there was no evidence of infection based on the clinical evaluation, and the smaller fraction was never thoroughly evaluated.

This to me was one of the more poignant statements in the whole briefing document. It was by Dr. Andrew Mosholder, who was a physician and epidemiologist who had been with FDA for more than a

couple decades.

He said, "The impact of arrhythmogenic effects on the risk/benefit balance for nonserious infections needs to be considered." He actually recommended, but FDA'S not going with that -- I think I have more than 14 seconds left, but anyway -- but they're not going with it because other people don't think it should be in the boxed warning.

The incidence of tendinopathy was very close to the incidence of these arrhythmias, being caused more often than in people using other antibiotics. So what are the conclusions?

There's clearly significant over-prescribing for fluoroquinolones. The warnings that are buried in the label are not likely to be noticed. We petitioned the FDA in 1996 to put a warning on tendinopathy. People didn't pay attention to it. We re-petitioned for a black box warning, and when FDA didn't respond, we filed a complaint against the agency, and the black box warning went on in 2008.

The FDA prescribing data starts in 2010, but there actually was some decrease -- 10, 15 percent -- before that.

CAPT PARISE: Excuse me. I just need to ask you to wrap up just so I can keep all the speakers --

DR. WOLFE: Two sentences left.

Dr. Mosholder, as I said, recommended just adding QTc prolongation, which is acknowledged to be a problem with all these fluoroquinolones. We would add putting the arrhythmias. And the evidence for this is on a par with the evidence leading to the black box warning for tendinopathy and for myasthenia gravis. Thank you.

CAPT PARISE: Thank you.

(Applause.)

CAPT PARISE: Will speaker number 5 step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record.

MR. MILLER: Good afternoon. My name is

Daniel Miller. I'm an attorney from Baltimore, Maryland. I practice pharmaceutical law. I have no financial interest in the outcome of this meeting, nor do I represent any clients in ongoing litigation.

But for the last six years, I have talked to hundreds of people who have been reporting serious harm after using fluoroquinolones as patients. And these people describe a cluster of debilitating effects, just as Dr. Boxwell has described to the panel today, so I don't need to get into that, except that I've experienced this and actually developed a lot of relationships with people who have formed grassroots organizations trying to get attention to this issue and trying to get some changes because these drugs are overused, over-prescribed, and over-marketed.

My message today is that the fluoroquinolones were inappropriately approved from the beginning for sinusitis and bronchitis. The appropriate terms were turned upside down. These drugs ended up being

compared to other agents that are not efficacious themselves.

So the two points I have as far as benefits go when you do a risk/benefit analysis is there's no substantial evidence of efficacy, as is required, and also there's been a failure to satisfy the comparison requirement of 21 CFR 314.

So when you look at the risk analysis, just going back to the history here where FDA withdrew approval for Ketek; five quinolones were withdrawn from the market by the manufacturer themselves; in December '06, the FDA decided it would deal with these drugs case by case.

So here we are. It's a wonderful opportunity now to look at these drugs and decide whether they should be indicated for minor infections when in fact it's like using an A-bomb to kill a housefly, as many people say.

The substantial evidence of efficacy required was really developed by case law in the Richardson case back in 1970. And in accordance with the law,

if there is no efficacy, the drug is inherently unsafe.

Also, on the comparison requirement, I think Dr. Toerner went through this well himself, too. I don't have time to go through all of this, but they haven't met the comparison requirement as required by 21 CFR 314.126(b)(4), and the noninferiority studies have confirmed this failure since that time.

The fundamental problem is the risks of using these drugs for minor and suspected infections far outweigh the minimal benefits that they offer. I regularly talk to physicians who are unaware of these effects, I think because they've been promoted so successfully, the medical profession in large part is trusting of these drugs. And they aren't even aware, for instance, that they can cause tendon ruptures.

Also, the argument made that side effects are rare really shouldn't apply because if you don't satisfy a risk/benefit analysis, it doesn't matter if a risk is rare or not.

The relief I'm requesting is that the indicated uses for sinusitis and bronchitis be withdrawn. As far as UTIs, they ought to be definitely, as even the manufacturers say, not first-line use, and the warnings should be updated, and the REMS, including medication guide, include these effects that I put here, especially including these neuropsychiatric --

CAPT PARISE: I just need to ask you to wrap up your sentence, please, so I can --

MR. MILLER: Thank you very much.

CAPT PARISE: Thank you.

(Applause.)

CAPT PARISE: Will speaker number 6 please step up to the podium and introduce yourself? Please state your name and any organization you represent for the record.

MS. BLOOMQUIST: My name is Lisa Bloomquist, and I'm speaking on behalf of Linda Livingston. Neither of us have any financial interest. These words were written by Linda Livingston.

"I have three minutes to tell you about the side effects from cipro, given to me for a simple UTI. I could take an hour trying to describe the two nightmarish months where my breathing was so suffocating I gasped for every single breath. Each night I had to take a pill to sleep, and I only got an hour of sleep if I was lucky. And each night before I took the pill, I prayed I wouldn't wake up.

"Words cannot describe the rage I feel for the torture I have endured. I could tell you about the damage to the nerves around my neck that make me feel numb at times and like I'm being choked at other times. I could tell you about the horrific olfactory nerve damage that made everything in the world asphyxiate me, making me a virtual shut-in.

"I could tell you about my pericardial effusion, blurred vision, terrifying light show, excruciating back pain worse than when I had cracked ribs, or being bedridden for a month and having to have food and non-fluoridated water dropped off and laundry picked up.

"I could tell you about my numb fingers and toes, constant bladder pressure, ravaged GI system, and 32-pound weight loss in two months with muscle waste and extreme weakness.

"There is swelling over the ulnar nerve. The spasming, uncontrolled fingers, the light sensitivity, sound sensitivity, newly acquired food sensitivities, electrical zaps, extreme anxiety, depression, crying every day for eight months, and suicidal thoughts.

"I could tell you about my fears, that my breathing will never improve again and be normal, that my eyes will not improve, or that they will even get worse, that my DNA is permanently damaged, or my fears surrounding the diseases linked to these things: ALS, Parkinson's, and Alzheimer's. No one deserves to have their life devastated for a simple UTI.

"My life is so different from how it was nine months ago. I cannot work, and I worry about how I will pay rent, let alone treatments, which are not

covered by my insurance. I can't meet friends for dinner or happy hour. I have not enjoyed a cup of coffee or a glass of wine since January. I can't exercise like I used to. I was in incredible shape before this.

"My diet is so restricted that there are few places I can go. I am tired all the time, and my anxiety prevents me from doing many things I used to do. My passion is theater, and I may never be able to perform again. There is little joy.

"First we are poisoned. Then we are left to fend for ourselves because doctors are mostly oblivious to any of the side effects. They are not reading labels or warnings. We are treated with ridicule and derision by the medical community, and then we are financially devastated as well. If another country did this to us, they would be called war crimes.

"The pharmaceutical companies have known for decades about the hideous side effects. The FDA has allowed them to inappropriately market these drugs

for simple infections. There was recently a GM car recalled because of 78 deaths. These drugs may be responsible for up to 300,000 deaths, not to mention all the life-altering side effects."

CAPT PARISE: I just need to ask you to wrap up your last sentence, please. Thank you.

MS. BLOOMQUIST: "We are not just figures on shareholder settlements. We are people who have been tortured and have had our lives decimated. So why are you even discussing it at this point?"

(Applause.)

CAPT PARISE: Thank you. Will speaker number 7 please step up to the podium and introduce yourself? State your name and your organization, if any, for the record, please.

MS. BRYANT: Hi. My name is Kimberly Bryant. I have no financial interest here. I'm here representing myself and the others that have gotten ill from fluoroquinolones.

I'd like to go back to May 2004, my life before Avelox. I was the mother of three children

holding down a full-time job as a nurse. I was the avid runner you were talking about this morning. I was always exercising.

I was also about to receive my master's degree, which took me years to get. After I received my master's degree, I was given the opportunity to run the health office in my local high school. People thought I was crazy for wanting to work with teenagers. Truth be told, I thought it was an honor to care for them. It's an honor I miss every day today, every day now.

Then in 2008, when I was 49 years old, my life after Avelox began. I visited my primary care physician because I didn't feel well, and I was diagnosed with sinusitis. I was prescribed and took a 10-day dose of Avelox.

Halfway through the dose of Avelox, I started to have pain in my feet, pain in my hips. I started getting a prickling feeling, numbness and tingling, going up my legs. I had sharp, stabbing pains in my legs and what felt like an electrical sensation in

my legs. I also felt like there was something moving underneath my skin.

I started to develop muscle weakness. Shortly thereafter, I was diagnosed with full body neuropathy because it had gone everywhere. They did a small nerve biopsy, which showed I did have full body neuropathy.

My neuropathy causes me to live my days in excruciating pain. It feels like I have little bees stinging me all over my entire body. My hands and feet feel like they are on fire. The pain is with me when I go to bed at night, if I'm able to sleep at all, and it's with me when I wake in the morning.

I have severe muscle weakness. Looking at a flight of stairs is a daunting task to me now. I have constant ringing in my ears. I have never-ending fatigue. I have neurogenic bladder, causing me to lose my urine at any given time. I have severe brain fog and sensitivity to touch. It hurts some days to put a blanket on me or put my clothes on.

What I have lost from this? I have lost my ability to work. I have lost the income that was necessary for my family's survival. I have lost the dreams of my husband and I traveling. I have lost who I was. I have lost everything from this.

I have lost the intelligent woman I was. I have to read off a paper because I don't remember things any more. I now spend my life managing my symptoms. Had I known Avelox was going to do this to me, I never would have taken this drug, especially being a nurse. We were not made aware of this.

I wouldn't be here talking to you today, and I wouldn't have had to go through the countless doctors' appointments and misdiagnoses I had. I am pleading with you today. Please put a stop to this. You have the power to do this. And please make sure that doctors are aware of this because they are not aware. They're not even reading it. Thank you for your time.

CAPT PARISE: Your last sentence. Thank you.

(Applause.)

CAPT PARISE: Will speaker number 8 please step up to the podium and introduce yourself, stating your name and any organization you're representing.

MR. JONES: Hi. My name is Chris Jones. No organization.

I'm a firefighter in Southern California. I started my career 10 years ago fighting brush fires. This job was very physically demanding; in fact, only 12 out of the 30 men that were in the academy graduated.

I then decided I want to help people and became a paramedic. I was working in one of the busiest areas of the nation up until a year ago when that was taken away from me.

I developed minor discomfort and trouble urinating. The doctor diagnosed me with a possible UTI or prostatitis and prescribed me cipro. The only warning I received was to stay out of the sun.

Two days into my treatment I noticed pain in

my hamstrings. I called the doctor and I was told to continue the cipro. After two weeks I was sent to a urologist, and I told him about the pain in my legs and the thousands of stories I've read on the internet of people being harmed by this drug. He scolded me and told me to stay off the internet, that I was young and healthy, and to keep taking the antibiotic. I'll be just fine.

Later I found out the antibiotic was never even needed. I was diagnosed with a urethral stricture I sustained caused by trauma I sustained on a structure fire. Unfortunately, it was too late.

After continuing the cipro, the pain became unbearable. I went from playing soccer in the Firefighter Olympics, working a physically demanding job, just passing a mandatory yearly physical, to not being able to walk to my own mailbox.

I stopped taking cipro on October 31, 2014. I have been tortured ever since. I have pain in every joint, muscle, and tendon in my legs. My

toenails have fallen off. I have muscle twitching, insomnia, extreme fatigue, and many more symptoms.

But worst of all, I cannot be a husband to my wife or a father to my three beautiful children. The ability to teach my son to ride a bike, dance with my daughter, or rock my newborn baby to sleep was taken away from me.

I have seen and talked to countless doctors. Many are unaware of the severity of these side effects and how to disabling they are. Even one stated that I must return to work immediately and the symptoms are all in my head. Almost all of them have the belief that the side effects will resolve after discontinuing the medication. It is a year later, and I'm still suffering every day.

Everyone agrees that there are no tests to determine if a patient developed fluoroquinolone-associated disabilities. You and the drug companies rely on very careful investigations done by doctors to determine how many people are affected, yet doctors don't even know these side effects are

possible. I am the easiest possible diagnosis, and many brushed me off and couldn't figure it out. How on earth can you say that these side effects are rare?

Many patients find out that their health problems are related -- many never find out that they are related to these antibiotics. This was the case with my aunt, who was misdiagnosed with fibromyalgia after taking cipro for an uncomplicated UTI she had. She suffered for three years, and she was brushed of just because she was older. This is happening across the nation.

My hope is that you would put FQAD on the warning label, only use the antibiotic for serious infections, and most importantly, educate doctors on how truly devastating these infections are -- or side effects are to save people from going through this nightmare.

And just one thing that I have that I want to add is, it has been mentioned that only side effects that is put on by patients shouldn't be used, that

only doctors who inform that these side effects are possible should be used.

I just want to say that's very convenient when there's no test to prove that any of these side effects are possible, and so many other medical problems mimic exactly what is happening to all these patients. So it's very convenient. Thank you very much for your time and giving me the opportunity to share my story.

(Applause.)

CAPT PARISE: Thank you.

Will speaker number 9 step up to the podium and introduce yourself, stating your name and any organization you represent for the record.

MS. MCCARTHY: My name is Heather McCarthy. I have no financial interest. I'm here -- I represent my son, O'Shea McCarthy.

This is my son O'Shea. Shortly after this picture was taken, O'Shea had surgery for a deviated septum. He was a college sophomore. He had no history of mental health issues or psychiatric

issues. He was given a 30-day prescription, 500 milligrams a day of Levaquin. He thought it was messing with his mind, and after 20 days he quit taking it.

We could have never imagined the nightmare that came next. Heart palpitations, insomnia, panic, anxiety. Then depression, isolation. O'Shea told his doctors he believed that the Levaquin was responsible. No one listened. Then he entered our mental health system, seeing a psychiatrist, still offering Levaquin as a potential reason for his problems. Rather than listening to O'Shea, his unthinking doctors prescribed him another drug produced by Janssen, risperidone.

Without contemplating his offering of the adverse effects to Levaquin, they did not take his offering into consideration at all. This inappropriate course of treatment intensified his anxiety and caused a host of destructive events.

In an episode of panic and anxiety, he jumped out of the second story window of our home, drove

off, lost control of his vehicle, and, immobilized with agitation and confusion, was unable to avoid a collision with a cement embankment.

For those of you who cannot see, this is the final memory I have of my son. This is his vehicle, crashed against a wall. This was a drug-induced death that was unnecessary.

In 2014, a citizens' petition was presented to you requesting that psychiatric effects be added to the Levaquin label under warnings and precautions, and added to the black box label. Your own adverse effect reporting system provides numerous of these adverse effect accounts.

This proper labeling could validate the symptoms of those suffering, yet this request goes ignored, just as O'Shea was ignored by his treatment providers, although he knew this drug had profoundly changed him.

Psychiatric events are especially serious. Those suffering are extremely vulnerable in a society where mental health issues carry a stigma,

which lends them little credibility. And to think, a proper clear warning label of adverse effects, which are well-documented and impossible to ignore, might have provided weight to O'Shea's rendering to his doctors of what was wrong with him.

It is the purpose of this administration to protect and warn the public. Perhaps my son's providers would have taken heed to the reasons for what he believed caused his illness. But that hope for my family has passed. But for others stuffing now as he did, my hope would be that you take your responsibility to protect seriously and acknowledge what those suffering already know, the potential dangers of this drug and properly warn the public.

CAPT PARISE: I just need you to wrap up with your last sentence, please.

MS. MCCARTHY: And perhaps this image that my family my forever live with will remind you of that.

(Applause.)

CAPT PARISE: Thank you.

Will speaker number 10 please step up to the

podium and introduce yourself? Please state your name and any organization you represent for the record.

MS. SIANI: Thank you for the honor to speak before you today. My name is Andrea Siani, and I am here as a very concerned citizen. I have a B.S. in biochemistry. I am a mother of three medical professionals. And I have worked in community health my entire adult life.

I am also a victim of fluoroquinolones. I was prescribed levofloxacin for a non-life-threatening infection in March 2014. Before taking this antibiotic, I was in perfect health. I had not one preexisting condition. On the weekend prior, I was winter mountaineering on Mount Washington.

After nine pills, my tendons began burning. Within days, all my tendons were damaged, affecting all movement, my vision, my hearing, my heart. I started to lose my ability to walk, and I suffered excruciating pain for over a year and a half. I still suffer crushing fatigue.

When I learned of the mechanism of action of these antibiotics, I was shocked that they were used for first-line defense for me and then so many others. I was not warned about the long-term serious side effects. I took this antibiotic according to product labeling.

My doctors attribute all of my symptoms to levofloxacin, and they have no treatment to offer me. Think of them. I protected my health eating well and exercising for over 50 years, and nine pills took it away.

The medical community does not know or recognize these serious long-term side effects. They are not aware of the boxed and heightened warnings. I live in Boston, a medical hub. Not one doctor treating me knew of these side effects.

Friends of mine -- a heart surgeon at the Brigham, an orthopedist, and ER doc, a urologist, a dentist -- not one knew of these warnings. My children, practicing in New England, confirm the lack of this awareness among their colleagues.

The FDA's job is to protect medical professionals from unknowingly causing harm. And today, you can take that first step by recommending putting fluoroquinolone-associated disability on the labeling in a black box immediately.

These side effects are under-recognized, not rare. I have had over 50 personal contacts trace their disabling tendon and nerve damage to fluoroquinolones, many with their doctors. On my staff of nine, three have long-term damage.

Many others with unexplained plantar fasciitis, rotator cuff tears, knee pain, all trace to fluoroquinolones, returning from overseas in wheelchairs after taking cipro from their travel kits. You now have the knowledge --

CAPT PARISE: I just need to ask you to wrap up with one more sentence, please.

MS. SIANI: Final sentence. You now have the knowledge and privilege to protect yourselves and your families. Please take a step to share this with other medical professionals so they can know

these warnings and protect others. Thank you so much.

(Applause.)

CAPT PARISE: Thank you.

Will speaker number 11 please step up to the podium and introduce yourself, stating your name and any organization for the record.

MS. DELAINE: My name is Nicole Delaine and I am here to tell you how I was poisoned by Levaquin.

In February 2014, I was a healthy 41-year-old who earned this medal for finishing my first half marathon. Two months later, I was poisoned by a combination of Levaquin and Flonase, a black box warning contraindication. They were prescribed for an acute sinus infection that was never cultured.

Despite discussing in great detail my recent and upcoming races with the nurse practitioner, she never warned of the existing black box warnings for tendon rupture, a warning any runner would certainly want to know. Worse, I was never warned of the contraindications of Levaquin and Flonase together.

The prescribing nurse and filling pharmacist said nothing. There was no informed consent.

Isn't a black box warning the highest warning the FDA can put on a drug? Since when did the standard of care for an acute sinus infection include blatantly ignoring a prescription's black boxed warning? If I had been informed, I could have avoided so much physical, emotional, and financial hardship.

Sadly, the truth is that this is how fluoroquinolones are being prescribed. Using Levaquin for a sinus infection is like using an atomic bomb to kill a fly. By sheer luck, I did not exercise while taking these drugs. I only took three of the seven pills I was prescribed, but that was enough to trigger devastating adverse effects.

My symptoms were immediate, and for months this former long-distance runner could barely walk or stand. I started to document my symptoms daily, which have numbered nearly 100 to date. I have suffered from body-wide tendon pain, stabbing pains,

ear and eye pain, thyroid and hormone issues, constant ringing in my ears, vision and heart disturbances, vertigo, brain fog, short-term memory loss, an overwhelming feeling of despair, and so many others, all happening at the same time.

I cried nearly every day for six months. But the worst is that I may now have kidney disease. I cannot even begin to imagine where I would be had I taken all seven pills. Listening to my own words as I try to describe what happened to me sounds so dry and so far-removed from the horrors I actually lived through.

It is impossible to explain this terrible poisoning experience in terms that a non-flox person can understand. Floxing is invisible, and I've never felt so alone. My two young kids watched their stay-at-home mom lay on the couch crying for weeks, unable to properly care for them. My hands were so weak I couldn't even pick up my 2-year-old son when he asked.

How many more people have to be harmed?

These drugs belong in a hospital setting and should only be used for life and death infections.

I leave you with this. It's something my 3-year-old son says to me every night before we go to bed. He says, "Mommy, I wish you hadn't taken that bad drug." I wish I hadn't, either, baby, because it's not okay to poison people.

(Applause.)

CAPT PARISE: Thank you.

Will speaker number 12 please step up to the podium and introduce yourself, stating your name and any organization for the record.

MS. ASTON: Hi. My name is Terry Aston, and I have no financial ties.

I was the organizer of the two FQ DC rallies held in Washington, D.C. in order to get change because my life has been destroyed by fluoroquinolones. I am one of the individuals who meets the definition of FQAD described in the FDA briefing materials for this meeting.

Before I developed FQAD, I was a bartender, a

cosmetologist, a restaurant manager, a phlebotomist, and even a cross-country owner-operator truck driver. I loved being a truck driver most of all. I traveled all over the United States.

Unfortunately, all this ended when I was prescribed Avelox followed by Levaquin and later cipro. My career ended. I was prescribed fluoroquinolones repeatedly after that for routine infections because the doctors did not know about the damage these antibiotics can cause. I am hopeful that today you will recommend the label changes needed to warn doctors that these drugs can cause FQAD.

As the FDA describes in the briefing document, these antibiotics can cause disability and may damage many body systems. As described by the FDA, fluoroquinolones may result in severe damage, including peripheral neuropathy as well as neuropsychiatric, musculoskeletal, senses and skin adverse events. I personally have been damaged in these body systems as a result, and it has been

devastating.

As a result, I have lost my ability to work, my ability to love a normal life, lost important relationships in my life. I lost my life as I knew and the way I loved it. And I'm not the only one. There are thousands of others just like me. Some of them are children.

Several of us have collected hundreds of stories of individuals damaged by the fluoroquinolones. These stories are in the books, which I will give you if you're interested, if you'd like a copy, during the break.

You probably may be wondering what these Mardi Gras beads are for. There are 6,480 purple beads here. I brought them with me in honor of every victim damaged by fluoroquinolone antibiotics in our combined fluoroquinolone support groups on Facebook. They could not be here today because they were either too sick and can no longer travel or can't afford to travel.

I am honored to be here because I look at all

of you and allow myself to hope that things will change. Like so many others, I suffer with FQAD. Please recommend today that the warnings regarding FQAD be added to the fluoroquinolone labels immediately in a black box.

Thank you. And I would like to say rest in peace to Anna Jane Howlett, Dick DeSant, Lisa Wright, Chris Stanley, and Dave Penn, who are no longer with us due to fluoroquinolones. Thank you.

(Applause.)

CAPT PARISE: Thank you.

Will speaker number 13 please step up to the podium and introduce yourself, stating your name and any organization you represent.

MR. FURMAN: My name is Jonathan Furman. I'm representing myself. No financial conflicts of interest.

Beginning in 1999, I began to suffer from mysterious symptoms. I consulted many doctors, including a well-respected neurologist. The symptoms were severe enough that a full MRI scan of

the brain was warranted. I was convinced that death was imminent for months at a time. Above is a partial list of the symptoms I endured. There's more than that.

Here I've plotted the severity of the symptoms over the past 15 years and averaged them together to create a visual representation of my functioning and quality of life during this time. One hundred percent represents fully functioning and zero percent represents the symptoms at their most severe.

This is the same chart with the addition of fluoroquinolone prescriptions. The red bars indicate the time periods where I was consuming fluoroquinolones. I have my entire medical record, and both the symptoms and prescription history is independently documented there.

In spite of the issues that I was experiencing, I was unable to receive any substantive help from doctors or hospitals. This continues to this day. No diagnosis. No treatment.

No recognition.

Here's the MedWatch report I submitted in September of 2012. In spite of the FDA having my contact information, I never heard anything back and no more information was collected.

Since I have become fluoroquinolone aware, I see things differently. Within my own social circles, there have been strange illnesses for which my acquaintances also never received a meaningful explanation as to what was happening.

Often I hear of national health issues where fluoroquinolone toxicity seems to be one of the more rational and likely explanations. Gulf War syndrome is one such subject. I've also read that studies indicate that 70 percent of people discharged from a hospital ICU display Alzheimer's-type mental issues. Both the Gulf War veterans and ICU patients would likely have been exposed to fluoroquinolones, and internal FDA opinion seems to back up a correlation.

During my worst periods, I was relying on benzodiazepines and Benadryl in order to dull the

symptoms just enough so that I could survive. This autopsy report seems to tell a similar story, and sure enough, ciprofloxacin was found.

When I read about things like the Sandy Hook massacre, I can't help but associate the unexplainable mental states with my experiences with fluoroquinolones. We see that Nancy Lanza experienced an impending sense of doom, neurological issues, and no real medical diagnosis. To top it off, she felt her symptoms escalated after surgeries. Fluoroquinolones are often prescribed to prevent infection even after routine surgeries.

We see the same type of thing --

CAPT PARISE: I just need to ask you to wrap up with the last sentence, please.

MR. FURMAN: All right. Well, we see the same thing here with Adam Lanza.

It's of utmost importance that the FDA take action due to the legal environment. The time has come for a comprehensive investigation and exhaustive evaluation into the total impact of these

drugs. Ladies and gentlemen of the FDA, thank you for your time and for your attention.

(Applause.)

CAPT PARISE: Thank you.

Will speaker number 14 please step up to the paradigm and introduce yourself, stating your name and any organization you represent.

MS. LANDMON: Hi. My name is Linda Landmon, and I'm representing myself. I'm here today with my husband David, and we're from Dallas, Texas, and I'm 58 years old.

In 2009, we brought our dream home that we planned to retire in. I'd been self-employed for nine years working from home. I was an avid bicycle rider. I enjoyed swimming, entertaining, traveling, and spoiling our two grandkids. I even had a personal trainer coming to my house twice a week. Life was good.

But then things changed. In December of 2011, I was diagnosed with a kidney stone. My urologist gave me Levaquin samples. He gave me no

information at all on the medication or the possible side effects. I later found out my urine culture came back negative for infection.

In April of 2012, I had a lithotripsy. My urologist prescribed cipro to me as a precautionary measure. In December of 2012, my urologist surgically attempted to remove my kidney stone. Once again I was prescribed cipro as a precautionary measure. I did not have an infection.

One week later, January 2013, I was admitted to the ER for severe pain as fragments of the kidney stone attempted to pass through my ureter. I was immediately given an IV of Levaquin prior to determining if I had an infection. It was found that I did not have one.

Less than two weeks later I was back in the ER with another kidney stone attack, and I was given another four bags of Levaquin by the time I was released three days later. The urine culture had already come back negative. I never had an infection. I was sent home with a prescription for

Levaquin to take for an additional 10 more days.

Since these medications, I've been diagnosed with peripheral neuropathy, ringing in the ears, high anxiety, a torn rotator cuff, a torn meniscus, which has resulted in needing a total knee replacement, spinal stenosis, and tendon damage in my foot. This has all led to depression, and I've basically become a recluse. For me to be here today is huge. I've numerous MRIs, X-rays, steroid shots. I've been prescribed Celebrex, Neurontin, Lyrica, Tramadol, Xanax. I have a walker, crutches, a leg brace, various boots and supports for my foot.

In my opinion, these drugs are prescribed way too often for relatively minor ailments, and at times without any proof of infection. I know because it happened to me five times.

Fluoroquinolones are the only antibiotics I've found that carry a black box warning and it hasn't stopped doctors from passing it out like it's candy.

CAPT PARISE: I just need to ask you to wrap

up with your last sentence, please.

MS. LANDMON: Okay. I didn't have anthrax, the plague, or an infection. I had a kidney stone. Thank you very much.

(Applause.)

CAPT PARISE: Thank you.

Will speaker number 15 step up to the podium and introduce yourself, stating your name and any organization for the record.

MR. KAFERLY: Good afternoon. My name is Michael Christian Kaferly. I have no affiliation.

In September 2008, I was prescribed Levaquin to clear a chest cold before a minor surgery. There was no testing done to determine if I even had a bacterial issue. It was given to me just in case.

Soon a nuclear bomb detonated inside my body, and I quickly went from an intelligent and healthy man who worked out almost daily to being bedridden, unable to understand the world around me, and in horrific pain not of this earth.

For much of the first 18 months, my entire

body had become too weak and too heavy to move, not even to use the washroom. And at its worst, I was so weak I could not hold my head up, chew my food, or produce a voice to tell my little boy that I loved him.

Our search for help took us coast to coast. Among my diagnoses are autonomic neuropathy and mitochondrial damage. Testing shows my body has suppressed cell replication, which is the explicit mechanism of action of the drugs we're here to discuss today. My full list of diagnoses and symptoms spans across multiple systems and is far too long to list here.

I have fought this monster for 2,585 days and nights, but I'm hardly improved. While I have good and bad days, I'm never well and I rarely leave the house. Like a defective battery that discharges far too quickly and doesn't recharge correctly, I have a minimal and unpredictable energy supply to fuel my muscles, systems, and organs. That means as I tire, my entire body gets progressively weaker and

heavier.

My vision worsens. I can become confused, frail, and weak, and many symptoms become unimaginably severe, including layers of unspeakable pain. And even though I've rested for weeks to be here today, this trip is dangerous for me, and I will suffer devastating consequences for the energy spent.

Abandoned by the very medical system that did this to me, I've been forced to give myself over 475 IVs to help manage some of the horrific symptoms Levaquin has caused. I've made videos of my IV process to help other victims, one of which has over 15,000 views. There are many more like me.

Modern medicine offers no cure for my mitochondrial disorder that began as a result of taking Levaquin. It is imperative to manage symptoms to prevent this disorder from progressing, but the only known therapies are not covered by insurance.

I can no longer afford the extensive

supplementation and IVs that had helped me to fight back. I've been forced to go without, and my condition has deteriorated significantly as a result.

Until a few weeks ago my family was homeless again. When I get home with my little boy, I face immediate amputation from the damage Levaquin has caused. In 2008, there was no warning about autonomic neuropathy or mitochondrial damage, just tendon issues. If the FDA would have protected me and allowed me to make an informed decision, I would have absolutely chosen to keep the cough.

The salesmen are here today to tell you that their drugs are safe, but you already know these drugs can cause mitochondrial damage. And I came all this way today to look every one of you in the eyes and tell you in fact that it does.

My little boy was 15 months old when my life was hijacked. Now he has never known his father as a healthy man. He's been forced to see things that no child should ever witness.

My life and his childhood have been stolen in the pursuit of profit, and I'm here today for the hundreds of thousands of people like me labeled as crazy who still don't know what is happening to them. I am here for my son and for his entire generation to implore the FDA to rethink the way that we monitor and label these biological weapons that we call cures.

My life has unquestionably been cut short by decades, and there is no sane measure that makes this level of metabolic damage --

CAPT PARISE: I just need to ask you to wrap up with your last sentence, please.

MR. KAFERLY: There is no sane measure that makes this level of metabolic an acceptable risk except to those whose directive is to sell more pills.

(Applause.)

CAPT PARISE: Thank you.

MR. KAFERLY: Thank you.

CAPT PARISE: Will speaker number 16 please

step up to the podium and introduce yourself, stating your name and any organization you represent.

MS. LALONE: Thank you for allowing me to speak today. My name is Laura Lalone.

Prior to taking cipro nine years ago, I was in excellent health. I was full of energy, had a busy social life. I was 40, and I was building a successful State Farm insurance agency in Indiana. And I was raising my 13-year-old son as a single parent.

Now my body and my quality of life have been devastated by cipro. I have skin biopsy-confirmed poly progressive small fiber neuropathy, tinnitus, debilitating hyperacusis, documented neurocognitive impairments, and a retinal detachment. My condition has gotten progressively worse, and two years ago I had to stop working in my business and avoid noisy environments.

I linked cipro to my health issues in 2013 after FDA announced the warning for permanent nerve

damage. In examining my well-documented health history, I determined it took only seven days for cipro to start its toxic assault on my body.

From the outset I saw the country's finest physicians and had every neurological and blood test one could imagine. They knew I had taken cipro for a UTI, but the possibility of it causing my neuropathy was not even on their radar.

In 2008, one neurologist at the Cleveland Clinic where I'm being treated told me that he sees two patients like me every week who have small fiber neuropathy, but they can find no underlying cause. I am quite certain that if they contacted all of those patients now and looked at their medication history, they will find many more who had taken a fluoroquinolone but have never made the connection and have never notified the FDA.

I wasn't warned by my doctor or my pharmacist about the possibility of any side effects, let along the permanent pain and disability I live with today. I feel like I am Bayer's guinea pig. I wonder what

my health is going to be like 20 years from now.

FDA, I implore you to take action. It may appear at first blush that a small percentage of people have adverse reactions, but you know that the FDA only receives about 10 percent reporting. Even if there were a low percentage, these drugs produce an egregious level of harm.

It is simply unconscionable to allow it to continue. What do you say to those of us suffering from FQAD or to the families of the people who have died from taking a fluoroquinolone or taken their own life because they couldn't take the pain any more? Do you say, it's a shame about your bad luck, but these drugs work real well so we're just going to keep on doing what we're doing? When is enough enough?

Please do not be a group that kills and disables. Our doctors rely on you to help them to uphold their commitment to first do no harm. Please add a black box warning for FQAD. Send all the doctors and nurse practitioners a letter. Let them

know about the harm --

CAPT PARISE: I just need to ask you to wrap up with the last sentence.

MS. LALONE: This is it. Let them know about the harm they cause by misusing these antibiotics in minor infections, and forbid them from using them unless a culture-confirmed, life-threatening infection is present, and that the patient is properly warned. Thank you.

(Applause.)

CAPT PARISE: Thank you.

Will speaker number 17 please step up to the podium and introduce yourself, stating your name and any organization you represent.

DR. RUPP: Thank you for the opportunity to speak today. My name is Tracy Rupp. I was previously a clinical pharmacist at Duke University Medical Center and am now a senior fellow at the National Center for Health Research.

Our research center analyzes scientific and medical data and provides objective health

information to patients, providers, and policy-makers. We do not accept funding from pharmaceutical companies, and I have no conflicts of interest.

We strongly support efforts to improve antibiotic use and drug safety. While quinolones can be life-saving drugs for certain types of infections, we must reexamine their safety and efficacy in light of new information to ensure the benefits outweigh the harms.

The antibiotics we're reviewing today were approved for ABS and ABECB based on noninferiority trials in which effectiveness could not be established because they were compared to drugs that were never compared to placebo, or drugs themselves that were not shown to be better than placebo.

Subsequent postmarket placebo-controlled studies have been conducted in an attempt to answer the effectiveness question, and have found them to be of little or no benefit for ABS and mild ABECB.

Meanwhile, we've learned much more about the

potential harms for patients. We know from experience that quinolones are a high-risk class of antibiotics. In fact, five other quinolones have been withdrawn from the market already because of drug-related adverse effects and unclear benefits.

Those that remain on the market have added warnings on their labeling about the risk of tendinitis and tendon rupture, cardiac arrhythmias, and peripheral neuropathy. And then today we heard about a new condition called fluoroquinolone-associated disability.

Most affected patients were previously healthy and became severely disabled within hours or days or taking a quinolone. Despite 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, quinolone use has not decreased. Therefore, we recommend the following.

First, since there is no evidence of benefit

in pre- or post-approval studies for ABS and mild ABECB and clear evidence of harm, we strongly urge that quinolone manufacturers voluntarily withdraw the indications for ABS and mild ABECB. If these indications are not voluntarily removed, we recommend FDA use its authority to remove them.

Second, since quinolones present a risk of harm that is disproportionate to the benefit for uncomplicated UTI, we recommend revising the label to state the quinolones should be reserved as second-line therapy for symptomatic uncomplicated urinary tract infection.

Third, since current warnings have been ineffective, we recommend FDA implement a Risk Evaluation and Mitigation Strategy for the quinolone class of antibiotics. REMS information should include all of the warnings and boxed warnings already on the label as well as those we discuss today, including the possibility of fluoroquinolone-associated disability.

Thank you for the opportunity to comment

today and for consideration of our views.

(Applause.)

CAPT PARISE: Thank you.

Will speaker number 18 please step up to the podium and introduce yourself, stating your name and any organization.

MR. NEWELL: Well, my name is Nicholas Newell. I'm a bioinformatics analyst from Boston. And I'm here on behalf of my brother, Oliver Newell. This is Oliver.

Oliver was a member of the senior staff at the Lincoln Laboratory at MIT, working with FAA, sometimes right here in Silver Spring. He developed IT systems to support the U.S. air traffic network. He was an extremely competent, no-nonsense, athletic and tough guy. He was a rock. We expected him to be around forever.

But in February of 2012, this all changed when he was prescribed the fluoroquinolone antibiotic cipro to treat a possible UTI. He began to experience severe muscle weakness, tendon pain

and stiffness, joint problems, neuropathy, sensitivity to heat and sunlight, skin rashes, insomnia, cardiac effects, what he described as brain fog, intestinal problems, and other issues.

His muscles were so affected that he could only use them three or four times before they became fatigued. He was only able to walk slowly for short distances. He immediately stopped going to work and was never able to resume.

Doctors he went to did not understand his condition and were completely unable to help. One even suggested that he take prednisone, despite the known negative synergy between steroid use and cipro side effects.

Suicidal thoughts and actions are a known side effect of FQ drugs, and on September 21, 2012, Oliver took his own life. He left this note, in which he describes his symptoms in the understated way that's typical of him.

"Dear family and friends: If you're reading this, then I guess this affliction beat me one way

or another. I did try pretty hard to get past it, for what it's worth. Sort of tough to do with all systems affected: muscles, joints, skin, nerves, heart, intestinal, memory, hearing, et cetera.

"And really no end in sight to the ongoing symptoms, ongoing knee pain and weakness, hands and feet weakening and losing strength over time, jaw joint problems, shoulders creaking and popping, toes bending at different angles than they used to, skin burning sensation and stickiness, bruises appearing on skin in various spots, arm numbness, et cetera.

"Thanks to all for all the help and well-wishes during the past several months, and apologies that I didn't make it."

In his car we found his original prescription for cipro. On it he had written a warning about fluoroquinolone drugs. This is prescribed on February 16, 2012, his cipro prescription. He wrote a warning at the end of it. He says, "For those who are sensitive to this drug, the side effects can be debilitating. I am just one example. Oliver

Newell."

The most important scientific point, I think, from this hearing is in FDA figure 6. The two most commonly prescribed fluoroquinolone drugs, cipro and Levaquin, have a much higher fraction of disabling effects amongst all serious effects by a fraction of 4.3 than non-FQ antibiotics.

Because of this, we agree with Golomb et al. and BMJ Case Reports in October of this year that these drugs should be reserved for only the most serious cases of all conditions, not just sinusitis, bronchitis, and UTIs until we can identify susceptible people or mitigate side effects with co-therapies like antioxidants. Thank you.

CAPT PARISE: Thank you.

(Applause.)

CAPT PARISE: Will speaker number 19 please step up to the podium and introduce yourself and any organization you represent.

MR. BRODINE: My name is Joe Brodine, and I'm a medical student representing the National

Physicians Alliance, an organization of medical doctors who advocate on behalf of clinicians, patients, and public health that does not accept any funding from medical device or pharmaceutical companies. I'm also speaking on behalf of my current and future patients. I have no conflicts of interest to disclose.

The CDC estimates half of outpatient antibiotic prescriptions are unnecessary, with about 20 percent for bronchitis and sinusitis. Quinolones are one of the most widely prescribed antibiotics.

Cochrane reviews show a lack of evidence that antibiotics have clinically meaningful effectiveness that is greater than 10 percent, considered clinically inconsequential, in the noninferiority trials that formed the basis of approval, nor do they prevent serious complications in these two self-resolving diseases. These same placebo-controlled trials collectively showed increased symptomatic adverse effects with antibiotics compared to placebo.

Two more recent placebo-controlled trials, including one funded by NIH, again did not show benefit. FDA did not grant an indication for sinusitis for gemifloxacin in 2006, and withdrew these indications for telithromycin. An FDA Guidance published back in 2007 stated that noninferiority trials are no longer acceptable in these diseases.

Drug sponsors have already withdrawn five other quinolones due to adverse effects, a large number for a single class of drugs. These antibiotics should be reserved only for life-threatening infections, where the benefits are clear and their use outweighs disabling adverse effects.

We call on the sponsors of quinolone antibiotics and manufacturers of other antibiotics for sinusitis and bronchitis to make a clear statement in favor of public health and take a serious stand against antibiotic resistance by voluntarily withdrawing drugs for these two indications.

Bayer Pharmaceuticals refused to voluntarily withdraw enrofloxacin in poultry until forced to do so by an administrative law judge. Today Bayer has another chance to do the right thing. If the manufacturers decline to spontaneously withdraw the drugs for two indications, it is incumbent upon the FDA to do so.

While the symptomatic benefits of antibiotics compared to placebo are clear in uncomplicated UTI, quinolones have not shown superior benefit to other drugs on patient-centered outcomes and should not be used as first-line agents. Quinolones should be relabeled to be used only when all other drugs have failed and based on the results of clear diagnosis from cultures.

We need to do more. Limiting approvals of antibiotics for self-resolving diseases where there is an absence of evidence of benefit and the presence of a clear harm is a step in the right direction for patients.

(Applause.)

CAPT PARISE: Thank you.

Will speaker number 20 please step up to the podium and introduce yourself, stating your name and any organization you represent for the record.

Speaker number 20, can you please step up to the podium?

(No response.)

CAPT PARISE: Will speaker number 21 please step up to the podium and introduce yourself, stating your name and any organization you represent for the record.

MS. BRUMMERT: Good afternoon. My name is Rachel Brummert, and I am the executive director of the Quinolone Vigilance Foundation. Neither the foundation nor I have any financial ties to this hearing.

Fluoroquinolone antibiotics are incredibly powerful, with the capacity to save lives when they're used as a treatment of last resort for life-threatening bacterial infections like anthrax. These antibiotics have the equal power to destroy

lives when they are prescribed for routine infections like sinus infections and UTIs that don't need their strength.

Just as it is irresponsible to squelch a kitchen fire with the defenses that we would mount against a wildfire, likewise it is reckless to use a fluoroquinolone antibiotic to squelch a routine infection. There are safer, effective alternatives for treatments of routine infections in the event that an antibiotic is even necessary.

I am living proof that the risks in using a fluoroquinolone to treat a routine infection far outweighs the benefits. In 2006, I was prescribed Levaquin for a sinus infection. Within weeks my Achilles tendon ruptured in a parking lot, the first of ten tendon ruptures that I've suffered over nine years.

A first line of defense antibiotic like amoxicillin would have resolved my sinus infection, and I would not have been exposed to the relatively disproportionate risks of known fluoroquinolone-

associated injury, which includes a progressive neurodegenerative disorder from which I will never recover.

With just one prescription, a once-healthy wage earner, parent, or grandparent, just like you and just like me, can no longer enjoy a reasonable quality of life and now lives with the risks of the development of an illness that is life-threatening.

What can the FDA do to help patients from profound, preventable harm? A preventable problem is a fixable problem. The FDA is responsible for protecting and promoting public health through the regulation and supervision of a wide variety of consumer products, including prescription medications.

Fluoroquinolone antibiotics are causing widespread disability, and their overuse is a contributing factor in the antibiotic resistance epidemic. Antibiotic resistance is such an important issue that there is a White House initiative to do something about it.

If fluoroquinolones are being prescribed for routine infections which don't need the strength, and they are disabling otherwise healthy patients, and their overuse is leading to an international epidemic, the answer is clear. The FDA must apply its highest level of scrutiny, regulation, and surveillance of fluoroquinolones to achieve this shared goal.

Thank you for your time and consideration.

(Applause.)

CAPT PARISE: Thank you.

Will speaker number 22 please step up to the podium and introduce yourself, stating your name and any organization you represent.

MS. HARLEY: Hello. My name is Shan Harley. I'm a registered nurse, 17 years experience in ICU, the last five and a half years as the director of the medical ICU there.

At the time that I was treated with Levaquin for acute sinusitis and bronchitis, I was riding a bicycle 20 miles a day four and five days a week.

But since then, the person that I was in 2012 I don't recognize today.

Within months, I had this constellation of symptoms which the FDA presented today on the slides, and every body system is affected: central nervous system, neurological, vision, sense of smell, which I lost, which is somewhat regained but not completely, joint pain, joint stiffness, GI problems, and this year, after two years of being off the drug, I've developed peripheral neuropathy, which has progressed even to my shoulders and my back in the last month.

The doctor who talked about other syndromes, I was ruled out for rheumatoid arthritis, lupus, thyroid problems. I'm not diabetic. My hemoglobin A1C is 5.1, so the possible clusters and potential overlap with other syndromes.

Had I not been subjected to levofloxacin for the second round a few months later, I would have bought the diagnosis that I had been given of fibromyalgia and chronic fatigue syndrome, which I

clearly don't have. What I do have is a tremendously changed life from being poisoned by levofloxacin.

I challenge the people who studied the syndromes of fibromyalgia and chronic fatigue syndrome to just check and see how many of those people were actually people like myself who were damaged by a fluoroquinolone drug.

I have word-finding problems, and a three-minute speech would have been no problem three years ago. I have twice ruled out by the rheumatologist, the second time this year for lupus, rheumatoid arthritis, any autoimmune disease, and he documented that, "However, it's certainly seen that Levaquin induced her issues."

I'm not asking for another black box warning simply because this is a black box and doctors and nurses don't even request what's on this as a black box warning. They aren't even aware of what's on here. Adding another won't help, sadly. They don't even know often what a fluoroquinolone is. They

certainly don't know the problems that they're causing by prescribing them, so I certainly don't blame them.

These drugs are so serious and toxic, they should only be given in the case of life-threatening illness, and only with legitimate informed consent. Thank you.

(Applause.)

CAPT PARISE: Thank you.

Will speaker number 23 please step up to the podium, stating your name and any other organization you represent for the record?

AUDIENCE MEMBER: I believe that was Dr. Linda Martin. Is number 23 Linda Martin? She's not here.

CAPT PARISE: Thank you.

Will speaker number 24 please step up to the podium, stating your name and any organization you represent.

MS. REIVER: Good afternoon, Chair and committee people. I'm quite nervous right now. I

represent myself, and I'm an advocate for everyone who has been damaged. I am so angry after hearing the drug companies today. But I had my speech written already.

My name is Sherry Reiver and I am 64 years old. I have been sick from FQ since I was 43. I moved from New York to Charlotte 10 years ago, and for 21 years, it is difficult to find a doctor that will validate that FQs has destroyed my life and health.

Each year that goes by, it's harder for doctors to believe that these effects last so long. Over two years ago, during a surgery at Duke University, against my consent, Floxin-soaked Gelfoam pledgets and steroids were placed in my head, and I am 200 times worse.

Let's not kid ourselves. Topicals are just as dangerous as any FQs, and the topicals need to be included, not excluded, from that PN warning the FDA came out with in August of 2013. The perils of topicals used on children for ear and eye infections

should cause great concern and should be researched as well. What are these drugs doing to their little brains and bodies?

This is a bittersweet day for me. Four years ago today, my 93-year-old dad died. He fell at home and was taken to the hospital by a neighbor. By the time my husband and I arrived in Florida, my dad had no idea who we were. They thought he had pneumonia, so they IV'd him with Levaquin. It turned out that he did not have pneumonia, but he continued to hallucinate for six weeks and then died.

He was sharp as a tack before Levaquin dripped into his body. He did have an aortic aneurysm for many years, which was being watched, but it ruptured on November 4th. I would have never connected the AA with FQs until I read the research paper dated October 5, 2015. Here is the link.

So here is another rare side effect that can occur, which it did in my dad's case. How many others have died from AAs and had taken an FQ drug? It took 10 years for this report to come to light.

Was the FDA aware of this research from Taiwan?

Do you know that after each cystoscopy, urologists hand out the gift of one cipro -- thank you, Bayer -- for the just-in-case scenario? I know this is a fact. Cipro is also free at most pharmacies. So therefore, it is prescribed more.

Three minutes does not allow me time to talk about my own health issues, but understand there are many; the slides shown today from Dr. Boxwell. We have flares which come and go at the whim of these drugs. It's a drug that keeps on giving even years later. It has no time constraints. It holds no barriers. Doctors are clueless. We get no warnings. Doctors do not --

CAPT PARISE: I just need to ask you to wrap up with your last sentence, please.

MS. REIVER: Doctors do not report our concerns, and they don't read the labels themselves. I thank you.

(Applause.)

CAPT PARISE: Thank you.

Will speaker number 25 please step up to the podium and introduce yourself, stating your name and any organization you represent for the record.

MS. KAPLAN: I'm Virginia Kaplan. I'm a victim. Here's a magazine spread that was done on me at age 61. It's about my 50-year career as a fashion model and actress. It's about my then-current job as a manager of a very large health and fitness club.

Two years later, I came down with what I thought was a sinus infection, went to my nearest ER, and I was prescribed two weeks IV Levaquin. I had the first dosage the first night. The plan was for the nurses to come the next 13 days to my house. They came the next four nights, hooked me up. On the fifth night or so, both my hands had blown up like boxing gloves. The IVs had infiltrated my tissues.

They sent me back to the ER. They did another EKG. My EKG on the first trip to the ER was 100 percent perfect. My second trip, all of a

sudden I had PVCs and SVTs. And pardon the expression, I [sic] thought maybe it was a sexually contracted disease. I was a widow of four years, so that wasn't the case. I said to the doctor in the ER, I said, "Well, what are those?" And he says, "You need to see a cardiologist." Did not have them five nights prior.

So I continued on the Levaquin, 10 days by mouth. Couldn't do the hands any more. And about the eighth day into the whole deal, I went back to the medical association that had prescribed me the two weeks of IV Levaquin.

My first appointment, the doctor said, and I have it all in my doctor's notes, "Oh, my God. I need to do some blood work to make sure you're kidneys are not digesting your muscles." I had an ANA test come out positive. Now I have a connective tissue disorder.

From that point on, Amy will tell you because I've lost my -- I can't spell and I can't speak too well any more.

AMY: Virginia has been diagnosed with PVTs, SVTs, myositis, seven problems with her feet and ankles, Achilles tendon issues, macular degeneration, myofascial pain syndrome, peripheral neuropathy, occipital neuropathy, trigeminal neuralgia, toxicity due to drug, medicine, or biological substances.

MS. KAPLAN: And all through the last seven years, the treatment that I have received for all this, I was issued a wheelchair, an orthopedic boot, physical therapy, which nearly killed me --

CAPT PARISE: I just need you to wrap up the last sentence, please.

MS. KAPLAN: And a handicap license plate and tag. Well, this past weekend I drew out all my doctors' notes from then. I did not have -- I had two cultures taken those first two nights. I did not have any bacteria in my blood. And I have the results right with me.

So I was given two weeks of IV Levaquin and oral Levaquin for no infection. My life is ruined.

Those first four years, my 10-year-old grandson slept on the floor next to me because he was afraid I was going to die during the night. I was paralyzed. He's now 17.

CAPT PARISE: Thank you. Thank you very much.

(Applause.)

CAPT PARISE: Will speaker number 26 please step up to the podium and introduce yourself, stating your name and any organization you represent.

DR. AVERCH: Madam Chairperson and committee members, my name is Dr. Tim Averch, and I'm a practicing urologist from Pittsburgh, Pennsylvania. I'm here today representing the American Urologic Association, or AUA, which is an organization that represents 15,000 members who provide urologic patient care in the United States.

Our organization has maintained that fluoroquinolones, such as cipro and Levaquin, should be available for the uncomplicated UTI in very

select patients, specifically not as a first-line drug. It is well noted that UTIs are a common patient infection. Not only are UTIs among the most common type of nosocomial infection, but they frequently lead to morbidity.

Treatment of an uncomplicated UTI should be efficacious, simple, and low risk. Additionally, we recognize that warnings regarding these medications also need to be strengthened.

There is currently a public health risk of bacterial resistance in the patient and in the community microbial reservoir. Antimicrobial usage has a clear impact on the emergence of resistant bacterial strains. A substantial cause of the emergence of these resistant strains is the overuse, treatment when none is needed, and prolonged therapy exposures of antimicrobial agents for all indications.

Data is suggesting that fluoroquinolone resistance is rising in areas of high use, supporting the contention that microbial resistance

is directly related to repeated exposure of microbes to microbes of these unique antimicrobial agents. It is likely that the appropriate use of antimicrobial prophylaxis, indication-specific, and of limited duration, would limit these resistance trends.

The AUA supports the use of fluoroquinolones for the treatment of uncomplicated UTIs only as noted previously. We agree that it should not be considered first-line unless there is a contraindication or allergy to the recommended first-line therapy, such as macrolides or sulfa-trimethoprim.

In summary, the AUA believes that the continued use of fluoroquinolones for urinary tract treatment is warranted, but only in very particular instances. We would not want to take it out of the hands of the providers to utilize and to use warnings appropriately.

Providers must be aware of best practices in terms of antimicrobial selection and in an effort to

decrease bacterial resistance and reduce side effects. Guidance authored by the AUA through published guidelines and best practice statements available in our urologic literature and on the AUA website provide this information, and therefore encourages appropriate antibiotic use, hopefully remaining beneficial to both patient and public health.

We make ourselves available to provide additional support or answer questions as necessary. Thank you for your attention.

CAPT PARISE: Thank you.

(Applause.)

CAPT PARISE: Will speaker number 27 please step up to the podium and introduce yourself, stating your name and any organization you represent.

MS. CHAJON: Good afternoon. My name is Christabelle Chajon, and I'm here to represent myself and others affected by fluoroquinolones. Thank you, Chair and committee members, for the

opportunity to speak here today. I am 35 years old and live in Washington, D.C. with my husband and 5-year-old daughter. Prior to February 2014, I was loving life. I was healthy and active and on no medications. I was a full-time mom with the able to also work part-time from home, and enjoyed exercising, hiking, reading, and playing music.

In February 2014, I went to the doctor for a lingering cough. I was diagnosed with bronchitis and given a five-day course of levofloxacin. I asked at the pharmacy if there were side effects and was told that they were rare and that tendon damage was only a concern in elderly patients.

After the last pill, I woke in the middle of the night shaking, unable to speak, and numb from head to toe, with my heart racing, and my husband rushed me to the ER. This happened three more times within six months after taking levofloxacin, and each time I was discharged with nothing more than heart palpitations.

I also developed many other symptoms,

including insomnia, intense muscle and joint pain and weakness, digestive issues, vertigo, fatigue, painful neuropathy, cognitive impairment, and extreme chemical sensitivities.

This translated into changing my life completely, having to cancel planned family trips, being unable to carry my daughter when she needed me, falling asleep unexpectedly while caring for my daughter, being unable to exercise and enjoy hobbies, let alone walk and get out of bed some days.

Food that I ate with no problems before made me sick, and I also lost over 10 percent of my weight, which is attributed to my body no longer digesting fats and proteins.

Many of these symptoms I still struggle with today, and my quality of life has declined tremendously. I do not work, and the proper care and treatments I need are a financial burden on my family. It has been a frightening struggle, to say the least.

But what is most frightening is that most doctors fail to realize that fluoroquinolones can cause this type of systemic damage. In my search for help, I even encountered one doctor who was insulted that I considered that my symptoms were caused by levofloxacin. How can that be, when the connection was obvious as I went from perfectly healthy to unable to get out of bed and function normally most days?

I joined the Fluoroquinolone Toxicity Group online in the spring of 2014, which at the time had around 2,000 members, all who have suffered from a constellation of symptoms. That number has more than doubled since then.

It is evident that fluoroquinolone-associated disability is not rare. And per today's meeting briefs, it has been concluded that antibiotics don't make much of a difference on uncomplicated conditions. Yet potent fluoroquinolones are being prescribed for them. Limiting --

CAPT PARISE: I just need to ask you to wrap

up the last sentence, please.

MS. CHAJON: My last sentence. Limiting the indications to only include serious and life-threatening infections, full disclosure to patients about these drugs, and adding FQAD to the warning labels are fluoroquinolones are absolutely necessary to stop the countless number of lives damaged and even lost to these drugs. Thank you.

(Applause.)

CAPT PARISE: Thank you.

Will speaker numbering 28 please step up to the podium and introduce yourself and any organization you represent for the record.

MR. FRATTI: Good afternoon. My name is John Fratti. I have no financial conflicts of interest.

I have been disabled for over nine years from Levaquin. My life has been ruined. My diagnostic tests document nerve, tendon, and central nervous system damage.

Prior to Levaquin, I was healthy, active, earned my MBA degree, and was employed as a

pharmaceutical sales rep and district trainer. I sold the antibiotics Ceftin and Quixin, and even I wasn't aware of these devastating effects.

Many of the Levaquin clinical trials submitted to the FDA for approval were considered significantly flawed in protocol design and protocol implementation. This is listed on the FDA website. According to FDA MedWatch data, fluoroquinolones have been linked to over 4,000 deaths.

It is generally agreed that only 1 to 10 percent of all adverse drug reactions are reported to the FDA. Therefore, death outcomes associated with fluoroquinolones could range anywhere between 40,000 to 400,000 people. At the conclusion of this presentation, please observe a brief moment of silence for those people that have since passed away.

On a personal note, I traveled to the FDA on July 13 and November 17, 2010. I presented extensive documentation on fluoroquinolone toxicity to the director of the FDA's Safe Use Initiative.

Adverse drug reaction information which is listed in the clinical trials is not on the label. Not one of my safety recommendations were adopted. The medical director I met with has since left the FDA to work for Johnson and Johnson, which markets Levaquin.

In addition, both of my senators, my congressman, and five of my state representatives sent letters to the FDA requesting label changes for fluoroquinolones. Again, the FDA took no action. The response letter from the FDA cited highly inaccurate FDA MedWatch data. These are just two examples of some of the many challenges we face here today.

Fluoroquinolone-associated disability needs to be placed in a boxed warning to reflect a severe and permanent nature of tendon injuries, peripheral neuropathy, mitochondrial damage, and prolonged neurological disorders.

Conditions being reviewed today, such as acute bacterial sinusitis, often resolve on its own. The over-prescribing of fluoroquinolones leads to

significant harm and contributes to the growing problem of bacterial resistance. Thank you.

(Applause.)

CAPT PARISE: Thank you.

Will speaker number 29 please step up to the podium and introduce yourself and state any organization you're representing for the record.

(No response.)

CAPT PARISE: We're going to move on to speaker number 30. Will speaker number 30 please step up to the podium and introduce yourself and any organization you're representing.

MS. BLOOMQUIST: My name is Lisa Bloomquist, and this is the presentation of Suzanne Higley in Suzanne's words.

"In the slide show playing above me, you will see pictures of me trying to learn how to walk and function several months after being poisoned. I was prescribed cipro in 2010 for an uncomplicated UTI. I had no reaction during this first round. In 2012, I was prescribed cipro again, but this time for an

unconfirmed infection. It took 12 pills to forever change my life.

"About a month after finishing cipro, my body became very stiff, to the point that my husband had to blend all of my food for me because I couldn't chew. It took me two hands to hold a plastic Solo cup with my blended meals just to get it into my mouth.

"No one could hug me or touch me. I hurt too bad. I was experiencing eye issues. I would try and speak to people, and my mind would go blank. I started having high fevers. My heart would race and I would have problems breathing.

"My colon would spasm to the point that I would pass out. I couldn't reach out my arm to pet my dog. My feet turned blue. My knees were the size of softballs. I suffered from full body paralysis shortly thereafter.

"I required 24-hour care. I couldn't sit up out of bed. I couldn't wiggle my toes. I just had to lay there. People would come and pick me up like

a princess. They would put me in a wheelchair and take me to the bathroom. There they would have to pick me up and put me on the toilet.

"People had to bathe me, brush my teeth, do my hair, and dress me. I turned a pasty white, so sick and in so much pain that I wanted to die. Seconds felt like minutes, minutes like hours, hours like days, days like years.

"The amount of pain and suffering that I have been through is incomprehensible to the human brain. I myself cannot even wrap my head around what I have experienced. I went downhill for five months. Somehow, I made it.

"I'm in pain every single second of every day. My entire body hurts, and my hands and arms barely work. It took me two and a half years to learn how to stand and walk well enough for short periods of time without my wheelchair. It has been almost three years since I was floxed, and I will never again run, golf, hike, play tennis, swim, or hold a career.

"I cannot clean my house, and rely on others to help me with this along with cooking, washing my hair, et cetera. I did everything right in my life except for take cipro. I thought that there were systems in place protecting me from things like this, but I was wrong.

"I had a relapse a year ago and survived that as well. How does a person relapse from a drug they stopped taking two years earlier? That is my question as will.

"Fluoroquinolone toxicity creates survivors, people that have consciously made a decision to live even when they didn't want to. There have been others who have chosen suicide, and I would be lying if I said that I hadn't thought about it before on several occasions.

"I am telling you today that we are not just statistics. We are real people, with families and friends and lives that have been altered or destroyed by fluoroquinolones. I ask you to please do the right thing and save people's lives.

"No one should have to become a guinea pig, tortured day in and day out for the rest of their lives. There are other, safer alternatives. I often think about how my life would have been like if I had taken one of those alternatives."

And she would like to thank her daughter, Addy, for the slide show.

(Applause.)

CAPT PARISE: Thank you.

And speaker 31.

MS. BLOOMQUIST: I am speaker 31 as well.

My name is Lisa Bloomquist. I flew in from Denver in order to testify about the damage that ciprofloxacin did to me, and to encourage you to cut the approved uses for fluoroquinolones so that they are only used in life or death situations.

In 2011, I took ciprofloxacin to treat an uncomplicated urinary tract infection. I experienced the following symptoms after taking it: hives all over my body, weakness in my legs to the point that I could barely walk, tightness and pain

in my tendons, brain fog, memory loss, autonomic nervous system dysfunction, fatigue, anxiety, fear, and other central nervous system symptoms.

I was sick for 18 months of my life in my early 30s because of a drug I took to treat a simple urinary tract infection. I have gotten rid of subsequent uncomplicated UTIs with D-Mannose and my immune system.

It is not appropriate for drugs that are as dangerous and consequential as ciprofloxacin and other fluoroquinolones to be prescribed to treat simple infections that can be cured with more benign methods.

You will hear the testimony of people who have had much worse reactions than I did. You will hear from people whose lives have been destroyed by fluoroquinolones. The adverse effects of these drugs are severe.

The Janssen and Bayer lawyers claim that there is no mechanism of action for the constellation of symptoms described today. They are

wrong. Fluoroquinolones cause mitochondrial damage, which starts the cycle of oxidative stress and further mitochondrial damage in a vicious cycle. This has been documented.

Fluoroquinolones also cause acute fluoride toxicity, as well as they chelate vital minerals from cells, including magnesium and iron. These minerals are necessary for hundreds of vital enzymatic reactions.

Fluoroquinolones also cause the downgrading of GABA receptors, and essentially throw people into protracted benzodiazepine withdrawal. Fluoroquinolones cause a massive histamine release and mast cell activation. They've also been shown to cause a collagen synthesis disorder and microbiome destruction.

All topoisomerase-interrupting drugs cause epigenetic damage. They are chemo drugs. Fluoroquinolones should be treated as chemo drugs. They should only be used in life or death situations. I know these effects, and I can refer

you to the studies that show them. Why don't you?

(Applause.)

CAPT PARISE: Thank you.

Will speaker number 32 please step up to the podium and introduce yourself? State your name and any organization for the record.

(No response.)

CAPT PARISE: Will speaker number 33 please step up to the podium, stating your name and any organization you represent.

MS. HELLER: Hi. I'm Stephanie Heller. I'm not representing any organizations.

I'm 34 years old from Washington, D.C., and before I took Avelox -- I took Avelox for a period of four days. Before taking Avelox, I was a very happy, healthy, 31-year-old who loved swimming, biking, rollerblading, camping, going out with friends, doing anything any regular 31-year-old would do.

My life was forever changed after getting a mild sinus infection. I went to the doctor and was

prescribed Avelox, and after four days I knew that something serious was wrong. All of a sudden I felt horrible pain in my legs, tingling throughout my arms and legs, brain fog, severe digestive problems, and many other symptoms.

As a hospital administrator, I was able to go to a multitude of specialists right away. I've seen so many specialists through this experience. I went to Cleveland Clinic, have spent thousands of dollars on alternative therapies, and now I'm here with you today, two and a half years later, and I wish I could say that my symptoms have greatly improved.

But I still, even standing here, have difficulty standing, have tingling down my knee that won't go away, have been to multiple specialists about it, and it's something that I'm still dealing with.

Why I'm here with you today is to say that I know that there was an alternative to Avelox. And I wish other people knew that, and knew of the safer alternatives. And I always think I could have had

something else, or I could have had the watchful waiting.

So I'm requesting for you today a label change for nonthreatening sinus infections. Thank you.

(Applause.)

CAPT PARISE: Thank you.

Will speaker number 34 please step up to the podium, and state your name and any organization you represent.

MS. CHAPMAN: Hi. My name is Zoe Chapman, and I am not representing any organization. I am a 17-year-old high school senior from Olympia, Washington. I traveled 2,811 miles yesterday to tell my story.

February 16th, about nine months ago, my life was wonderful. I had just earned 100 percent on my AP calculus midterm, performed cello in my high school's production of The Sound of Music, qualified for state with my percussion ensemble, and began my third job as an after-school caregiver and tutor. I

was happy, healthy, and making the most of my time in high school.

February 17th, I was prescribed ciprofloxacin for an uncomplicated UTI. Five days later, I was in the hospital. CAT scans, ultrasounds, MRIs, EMGs, spinal taps, urine samples, blood draws, and no answers, just the repetitive mantra, "Finish the cipro."

No one ever checked the side effects to see if they matched up with my problems, numbness in my arms, legs, and face, then extreme pain, first in my abdomen, then everywhere. I couldn't sit up or feed myself, let alone walk.

I began showing behavioral changes and then full-on hallucinations. Even when, two weeks later, I broke free from that mental regression, I could no longer attend school, play my cello, hang out with my friends, or do anything because of the debilitating pain and exhaustion.

The physical pain was ghastly, but the emotional pain was murderous. Depression and

anxiety cruelly convinced me that I had lost everything that made my life wonderful.

Now my life is a nasty mess of appointments and pain and absences and exhaustion, and I am a long way from where I was physically and emotionally before I took cipro. However, I have come miraculously far compared to most people. I sent back my wheelchair a month ago, and I've returned to school almost full-time.

My heart goes out to everyone who has had a much longer and harder timeline, and that is an unacceptable amount of people. Within my sphere of life alone, my acupuncturist, my physical therapist's wife, my 15-year-old friend Caroline, my mom's coworker, and the thousands of people that I have met online through support groups all have FQAD.

I understand fluoroquinolones' usefulness. They can save people's lives. But they can also destroy them. I plead with you, please find a way to limit them to the last resort.

I tell my story today because I cannot bear the thought of other kids going through what I am. I tell my story today to turn this horrible part of my life into protection for others. I am a reminder that fluoroquinolones don't discriminate by age. I am a reminder that your children's lives could be destroyed by these drugs.

A three-minute speech requires everything to be concise. However, my past nine months have not been concise. They have stretched out for what seems to be an eternity. The many facets of suffering that fluoroquinolones cause are long and drawn-out tortures that myself and so many others have had to, and continue to, endure.

Please fight for stories like mine to stop becoming people's realities. Thank you.

(Applause.)

CAPT PARISE: Thank you.

Will speaker number 35 please step up to the microphone and introduce yourself, and state any organization you represent for the record.

MR. GIRARD: First, I thank you for allowing me to come here and speak. If it does come out intelligible, it's about the only thing I can speak about intelligently because I've been living it for eight years.

My name is Mark Girard. I represent no one. I have no financial interests. I am the leader of the largest support group on Facebook, Fluoroquinolone Toxicity Group, as well as many other groups, Flox Canada, and Christian Floxies, and some others that we've developed to support the community.

On August 27, 2007, I was given Levaquin in the hospital for a flesh-eating hospital-acquired infection on my ankle. So in my case, I believe the drug saved my life. However, my doctor prescribed massive doses of Naproxen and numerous other drugs that are contraindicated simultaneously, and neither he nor any doctor I have spoken to since, dozens or dozens, have acknowledged the possibility that Levaquin did this to me.

I immediately had blood clots, cartilage lesions, tendon ruptures, brain damage, stomach problems. Veins had to be cut from my leg. I have just head to toe devastation. The worst is the mental. The mental damage is beyond description.

The doctors are in denial. In the groups, it's common. Everybody comes in and they have the same story, that their doctors don't believe them, that no matter -- even when it's just so blatantly obviously and they have all the symptoms on the list, that the worse shape we are, the more the doctors are inclined to believe it has to be something else.

The numbers that we saw here today, with 85 percent of the people self-reporting instead of the 2 to 6 percent normal. The FDA claims you get between 1 percent and 10 percent of the actual ADRs out there, and in this case, it's not even 1 percent. It's probably a 20th of 1 percent.

This is common, very, very common, and we need action. We need many, many more meetings like

this. We need hundreds of millions of dollars in research to be funded by the corporations that did this to us, but not run by them because we can't trust them. And we need a media blitz. We need to fix MedWatch; you can't even report on Firefox or whatever. It's a joke.

We need a congressional investigation into crimes against humanity. It's hard to imagine failure on a grander scale than what is happening here now. You are at fault for what has happened to us here, and I hold you responsible. And it's just wrong.

Thank you for your time.

(Applause.)

CAPT PARISE: Thank you.

The open public hearing portion of this meeting has now concluded, and we will no longer take comments from the audience.

We will now take 15-minute break. Panel members, please remember there should be no discussion of the meeting topic during the break

among yourselves or with any member of the audience. We will resume at 3:10 p.m.

(Whereupon, at 2:54 p.m., a brief recess was taken.)

Clarifying Questions to the Presenters (continued)

CAPT PARISE: Okay, everyone. We are going to get back to business. Because we didn't get to finish the clarifying questions this morning, we're going to revisit that now. And the way we're going to do it is in order. We'll do the FDA, clarifying questions for the FDA, first. Then we'll take clarifying questions from the committee for industry before we move into the charge to the committee.

Dr. Honegger, you had -- I apologize. People had them this morning and hopefully can remember what they were. Go ahead.

DR. HONEGGER: Yes. Looking back, I did have a question for Dr. Boxwell. In the review of FQAD, it was noted that onset was often quite early in the course of the treatment.

Were you able to delineate in those reports

whether this was often the first course of fluoroquinolones or if this was after patients had received several prior courses, and then they finally had onset with a subsequent course?

DR. BOXWELL: I don't know the answer to that specifically. But it was documented in the reports that 22 percent of the patients had previously received fluoroquinolones. And some of them described as they had taken them once and had some tingling, and then the next time they took it, I think it's like they just went over the edge type of thing. But I do think there were some that took it for the first time and had symptoms.

CAPT PARISE: Dr. Arrieta? Oh, I'm sorry. Dr. Floyd? Sorry.

DR. FLOYD: My first question is for Dr. Toerner. This is a follow-up on a question about trials of fluoroquinolone use in your review of treatment effects for acute bacterial sinusitis and for COPD.

For acute bacterial sinusitis, were there any

fluoroquinolone trials in that review? And if so, could you ascertain the treatment effect for quinolones by themselves?

DR. TOERNER: For the review of the treatment effects for ABS, there was only one trial of the 20 that evaluated a fluoroquinolone. But keep in mind the first slide that I went through represented the landscape of antibacterial drug development at that time that included an active control trial design.

So part of our review was to describe the effect of the active control that was used in the trial design. So that was part of our rationale for including all antibacterial drugs in our description of treatment effect.

DR. FLOYD: No. I understand that. But I wanted to clarify, could you establish a treatment effect for fluoroquinolones against placebo in your analysis? And same for exacerbation of COPD as well?

DR. TOERNER: For those two indications, that wasn't our approach. It was to look at the

antibacterial drugs in general. We did not single out any one particular class versus another class to ascertain treatment effect.

DR. FLOYD: Thank you. My comment to follow up on that is that we do have some evidence of a small treatment effect for ABS and even for mild COPD. But we're actually extrapolating from that setting to fluoroquinolones if we're saying that there's a treatment benefit that we're weighing against the risk. I think that's an important distinction.

My second question is actually about the AERS analysis. My question is actually, do you intend to publish this work?

DR. BOXWELL: I don't know. I think it's important information, so possibly.

DR. FLOYD: I would encourage you to. I think that more information is needed, perhaps before we even establish a causal association. But I think you've done important work as a first step.

I'm actually thinking of a paper by

Dr. Staffa about rhabdomyolysis related to statins that came from errors over a decade ago. And in that paper, he looked at reporting rates using national prescribing data and reporting rates, and that helped establish an adverse effect off cerivastatin.

So even though it's not as good as a population-based epidemiologic study, because you actually have the case reports and more granular data than people might have downloading from the AERS database, if you can do some of those analyses and publish them, I think that would be useful.

I think you've had a number of useful suggestions today about looking at subgroups, looking at effect modifiers, looking at time trends. And having that report go through the scrutiny of peer review and be commented on by others I think would improve the work as well.

DR. BOXWELL: Thank you.

CAPT PARISE: Just a reminder to the FDA to state your name for the record, please.

Now, Dr. Arrieta?

DR. ARRIETA: Thank you. I have a question I believe is a question or a request for commentary. I believe it would be for Dr. Mandell. The issues that have been --

CAPT PARISE: Excuse me. We're going to take the FDA questions first. But we'll do the industry next, so just hold that question.

Dr. Russell?

DR. RUSSELL: Thank you. Russell, San Antonio. I wanted to call Dr. Boxwell back. And while she's coming to the microphone, I'd like to introduce into the record a publication by Caro, Winter, Dumas entitled, "A subset of fibromyalgia patients have findings suggestive of chronic inflammatory demyelinating polyneuropathy and appear to respond to IVIG."

The reason that I bring this attention to this is Dr. Boxwell's case, which was toward the last of her presentation. And in this case, we heard a history but no examination or evidence from

biopsy or other, let's say, EMG that would support a neuropathy. Was that information available that just wasn't included?

DR. BOXWELL: For the case report?

DR. RUSSELL: Yes.

DR. BOXWELL: Debbie Boxwell. No. There were no lab data.

DR. RUSSELL: Thank you. And then I just would like to make another comment. I'm aghast at the small number of cultures that are taken with urinary tract infections, even chronic urinary tract infections, and bronchitis. There are ways to get culture material, biologic fluids, in those situations, and much easier than, I think, with sinusitis.

So I think we should be very strongly encouraging cultures. And physicians have been asked for some time to put an indication on their prescriptions. I think that could be heralded much more strongly so that physicians actually do it, so that it would be possible to know what they're

treating, and it would prompt physicians also to think about that indication that somebody's going to look at and to rethink the idea of not bothering to get culture information.

The use of IVIG in this combination syndrome, overlap syndrome of fibromyalgia and chronic inflammatory demyelinating polyneuropathy, which sounds very much like the syndrome that we heard case reports about today, it is a complicated syndrome, and the use of IVIG is not free of side effects, either.

There is a list of side effects that I could go through, but it may not be relevant at this point, except that it may be possible that treatment with something like that might have prevented some of the complications that occurred in a small number of patients who received these medications.

CAPT PARISE: Just one reminder to the committee, actually, before we go to the next questioner. This part is for clarifying questions. So I'll just ask you to -- this is clarifying

questions to FDA now and then to industry.

For recommendations, we're going to hold that until after the vote. Then we're going to be going around to each one and asking for specific recommendations. So just a reminder.

Next, Dr. Staud?

DR. STAUD: Yes. My question's also for you, and it relates to our understanding of the mechanisms how these syndromes and side effects occur. And it in particular is related to where we heard only evidence today about these side effects and the occurrence of syndromes that are associated with the intake of these antibiotics in individuals who took oral medications. And I think it would be very important to know how they shape up in terms of comparison with IV application of the same drugs.

So I was wondering if you have evidence or data that could elucidate this.

DR. BOXWELL: Debbie Boxwell. We only looked at the oral. Of course, bioavailability is very close. And I think it would be interesting to also

look into eyedrops and eardrops and at other dosage forms.

(Applause.)

DR. BOXWELL: But for this, I really was trying to narrow it down to looking at healthy patients or described previously healthy patients, and look at that small group. But certainly IV and other dosage forms is something that we can look at.

CAPT PARISE: So I actually had a question for the agency. On the FQAD, we obviously had a largely descriptive analysis. Does the agency have other -- aware of other databases or resources that might be available to look at these rather rare events in a more comprehensive say?

DR. STAFFA: Judy Staffa from epidemiology. We looked into this when this syndrome was described from the FAERS data. And in looking in the epidemiologic literature, what you saw presented was a summary of what we found, which were the individual components where some epi investigations had been done.

We have not seen any epi investigations of this syndrome. And as we discussed it internally, it would be very challenging because the kinds of data that used, the electronic healthcare data, the strength of those is in determining outcomes that are admitted to hospital.

As you saw from the case reports and heard from the testimony, many of these events are not hospitalized, and if they were, it's not clear what kind of coding would be used.

So we have been thinking about this and struggling with this, but we're not really able to come up with epi techniques from the data that the agency has access to, to be able to study this effectively.

CAPT PARISE: Thank you.

Next, Dr. Hogans?

DR. HOGANS: I have a first question for Dr. Boxwell, and that was, we heard from one of the industry representatives that for the FAERS reporting of the complex syndrome that you're

talking about, that 12 percent of the events were reported by providers.

Is that correct? And could you give us any more sense of whether or not the syndrome, as described by providers, was different or looked the same as the syndrome as described by patients? Were there distinguishing characteristics between those populations?

DR. BOXWELL: I would have to check on my numbers. Twelve percent doesn't sound unreasonable. Some of the professional ones, I felt, didn't have a lot of extra information. Some could provide additional information.

I didn't find that the healthcare professional expedited reports were significantly better or provided more information or -- really, it was a compilation of everything.

DR. HOGANS: Great. Thank you.

My next question is for Dr. Trinidad, and that regards I think you presented information about the case control study of peripheral neuropathy. We

have just one study that you looked at in detail there. Correct?

LCDR TRINIDAD: That's correct.

DR. HOGANS: But that study was based on essentially a million claims. So the million was the denominator, and then they found 6,200-some-odd cases. Right? Which by my calculation means that the incidence is 6,000 per 100,000.

LCDR TRINIDAD: That's actually incorrect. The population was initially selected from a random sample of a million men, or a million persons, and then there was exclusion and inclusion criteria then. So the denominator is actually much smaller.

If you have any additional questions, the epidemiologist on this is from Dr. Sansing.

DR. HOGANS: Wonderful. Thank you so much.

So Dr. Sansing, the denominator, then, was significantly less than a million.

DR. SANSING-FOSTER: Correct.

DR. HOGANS: Which means that the incidence -- I mean, the rough numbers would be

significantly greater than 600 per 100,000.

DR. SANSING-FOSTER: Correct.

DR. HOGANS: Which then puts it no longer in the rare disease category.

DR. SANSING-FOSTER: You actually have to understand that we are actually dealing with a greater exclusion criteria. The rare definitely will vary by disease. But we are dealing with an extremely specific criteria for people who were also used for a previous research study.

So it's not exactly that we have rare. It's just that our denominator for this study is coming from a different cohort study. These people were specifically selected for another research study.

DR. HOGANS: Great. So being peripheral neurologist, which is what I am, I looked up the study and I looked at the details. And I understand that the criteria, the inclusion criteria, for the study were that you had to go to your doctor with a symptom that was then diagnosed as peripheral neuropathy.

So that means it's a symptomatic neuropathy. It's not the best ascertainment method for all comers, really. So there's bias there, which means presumably the neuropathy is more severe, on the severe end, because someone's going with the complaint.

DR. SANSING-FOSTER: Yes. It is idiopathic neuropathy.

DR. HOGANS: Right. And it turned out that they were called idiopathic or possibly drug-induced. But the incidence at the end of the day is no longer going to be rare, and that's the point that I'm trying to get to, which is that when you actually boil down the numbers, I don't believe it still meets the criteria for being called rare. And I just want to hear your thoughts on that.

(Applause.)

DR. SANSING-FOSTER: You make a very good point. And do understand, too, that one of the criticisms within my literature review, which you can find in the appendix, states about the

validation of the algorithm that they used to even define the outcome of peripheral neuropathy.

So therefore, you can err on the side that this is either overestimated, which it possibly is, or underestimated. It has a probability of being both. So you made excellent observations in terms of the reading of this document.

DR. HOGANS: Thank you. Thank you very much.

CAPT PARISE: Dr. Lo Re?

DR. LO RE: My question's for Dr. Boxwell. Dr. Boxwell, when you presented your slide on the fluoroquinolone-associated disability definition, I was just wondering if you could take us through how you formulated that definition since this was the new one, specifically how you came up with things like that it had to last for 30 days or longer, why you selected multiple criteria.

Then just to follow up on Dr. Parise's question, I was wondering if the agency was thinking, since they had the data potentially from the Sentinel Initiative at its disposal, and that

outpatient diagnoses are available in some of the data sources, if there was a potential thought about using the Sentinel Initiative to estimate incidence rates of some of these outcomes, if protocol-driven analyses could be conducted.

DR. STAFFA: This is Judy Staffa. I can tackle the second part about Sentinel. We did think about using Sentinel. Sentinel is a distributed network of electronic healthcare data, most of which at this point are administrative claims.

Again, the strength of that system is in looking at outcomes where they might present to a hospital because the inpatient diagnoses tend to be more valid than those in an outpatient system.

Since this would be an algorithm that we would be looking at symptoms and ICD-9 codes that would cross multiple organ systems and result in outpatient visits, it would require getting medical charts to try to validate.

So we considered it. It's just not using the strength of that system to be able to do that. So

there would be a lot of challenges there. But, on the other hand, there certainly would be a lot of prescriptions of fluoroquinolone users in that system to be able to look. It's something we've been thinking about but haven't found a clear way to actually implement.

DR. LO RE: Early on the Sentinel did conduct validations of a number of different health outcomes of interest by getting various medical records. So it may be something just to consider, just in terms of once the definition of the outcome could be nailed down, that this may be something to evaluate, including for the other individual concerns regarding the tendinopathies, the peripheral neuropathy, where you all presented a number of different limitations to the existing data, that potentially these could be addressed in that --

DR. STAFFA: You're correct. And then where validation efforts were done and a number of literature reviews were done to identify, typically they were mostly limited, again, to the inpatient

diagnoses.

When it's something that's severe enough that a patient is hospitalized, it's much more challenging to validate and get charts for outpatient. It's very expensive. It requires going to a lot of physician offices. So there's some logistic challenges we have to bear in mind with that kind of approach.

DR. BOXWELL: Dr. Debbie Boxwell. So for your question about the definition, really what I was trying to do is just characterize or describe this. This is not carved in stone in anything official. It's the first time we've attempted to try to describe it.

So we were looking for patients who reported that they had received a disability because of taking the fluoroquinolone, and just used the regulatory definition of disruption of a person's life.

Then what I had observed in the previous review I had done was that I wanted to have two or

more of the following body systems because the single body system adverse events are already in the label, and they're all in the boxed warning or they're in the warnings and precautions and are not necessarily noticed.

In addition, I was seeing 38 percent of the patients had all three of the big -- neuromuscular, peripheral neuropathy, and neuropsychiatric -- events. A lot of these events were occurring in two or more. So I was trying to describe that.

Then in terms of long-term, I picked 30 days after stopping the AE because at that point, it's beyond a negativity challenge. If you stop the drug, you would expect an AE to resolve over a period of time. And so it was an arbitrary choice of 30 days, but we figured that was a reasonable enough time for an AE to disappear or resolve.

CAPT PARISE: Dr. Vitiello?

DR. VITIELLO: This is to make sure I got it right. It's a question, probably, for Dr. Toerner.

So for demonstrating efficacy in uncomplicated urinary tract infection, the recommended design now is noninferiority, or superiority but noninferiority is also accepted? Is there a position at this point?

DR. TOERNER: We did issue final guidance for complicated UTI, and we include pyelonephritis in our definition of complicated UTI. And there we found a treatment effect over placebo that was actually quite large. And so we do think the noninferiority trial design with an active control is an appropriate trial design to demonstrate efficacy for treatment of complicated UTI.

Of course, a finding a superiority is always a finding of efficacy that's clear and well-established. But we do think the noninferiority trial design is also a clear and well-established finding of efficacy for complicated UTI.

DR. VITIELLO: Right. But my question was about the uncomplicated. What is the standard for uncomplicated in our recommendation? The

complicated, I understand, noninferiority acceptable, obviously. But for uncomplicated, do you need a placebo-controlled study or a superiority? Or noninferiority is good enough?

DR. TOERNER: Joe Toerner from FDA. For uncomplicated UTI, we would entertain all of the above. As I had went through, we did find evidence to support a treatment effect on a microbiologic eradication.

That endpoint itself could be called into question because it may not represent how a patient feels, functions, or survives. And so it may be construed as a biomarker. So we would want evidence that a drug is having an effect on how a patient feels or functions, and so we would want to see symptom improvement in that situation.

So looking only at the trials that used a placebo control, there was also evidence to support a treatment effect of an antibacterial drug on symptom improvement. Using an ibuprofen control, if we throw that fifth trial into an evaluation of

treatment effects, it's unclear whether symptom improvement with an antibacterial drug -- it's unclear whether there's a treatment benefit over ibuprofen. But the findings from the microbiologic eradication endpoint are also important to consider for this.

Going back to the complicated UTI, we recommend a responder endpoint where patients have microbiologic eradication and resolution of symptoms. So that's our recommended efficacy endpoint for complicated UTI.

So looking ahead, I would imagine that that same endpoint should be used for a trial design for uncomplicated UTI. And I think we'll just have to have more discussion internally and with a sponsor on the endpoint that would be used for a trial design for an uncomplicated UTI.

CAPT PARISE: Dr. Nambiar, did you want to add something?

DR. NAMBIAR: Yes. Sumathi Nambiar from the FDA. Just to summarize, I think we at this point

do not have a guidance on developing drugs or uncomplicated urinary tract infections. The evidence we've provided today suggests that there is a treatment benefit.

The details of what the noninferiority margin would be, what percent of the treatment effect we need to preserve, et cetera, would be something we'd have to discuss should somebody be interested in developing a trial. I hope that answers your question.

CAPT PARISE: Dr. Phillips?

MS. PHILLIPS: I think this is for Dr. Staffa. I heard one of the speakers from FDA comment about a collaboration with the Department of Defense. And to follow up on our chair's question, I'm just trying to wrap my brains around how this could be dealt with from a database standpoint, VA, Department of Defense, TRICARE.

Are there some databases where you could look at symptoms identified or reasons for office visits through either government databases or collaboration

with a big group like Kaiser, such as you've done before, that might help tie frequency of prior drug use being temporally associated with some of these symptoms that we heard about today?

DR. STAFFA: This is Judy Staffa. The study that was referred to was FDA and DOD trying to explore specifically tendinopathy, tendon rupture, which is an event that would take you oftentimes to a procedure or to a hospitalization to explore.

The challenge here for any of the individual outcomes, again, if something presents to hospital, the more severe it is, the better these kinds of electronic healthcare systems can detect it because you can go to those hospitals. You can look at the charts. There's typically ICD-9 coding, and now ICD-10 coding, for these outcomes.

But when you have something, which you hear people having diffuse symptoms from multiple body systems, going to many different physicians, the physicians are running tests and they're not finding anything, it's not clear to know how this would be

coded and then how we would then be able to capture that, and then in a practical way, be able to get enough charts from all these different physicians and piece this together at a population level.

So I think that's the challenge of using these kinds of systems for this particular kind of disability outcome, where we're still piecing together what this actually is medically. Does that make sense?

CAPT PARISE: Ms. Schwartzott?

MS. SCHWARTZOTT: I have mitochondrial disease. It's a genetic form. I have a question for the FDA. Has the FDA done any specific investigation on the risk of mitochondrial toxicity? And might this be something that can be further studied and perhaps added to the risks and maybe the boxed warnings?

There were definitely people in the public that made that association, and I know that there have been studies.

(Applause.)

DR. PROESTEL: This is Scott Proestel from FDA. So we've worked with the critical pharmacology group within FDA, and basically I can read to you the summary of their consult. There is some evidence for mitochondrial toxicity. I think their final conclusion was that it's uncertain. So this is straight from their consult.

"There is no SAR," meaning structural activity relationship, "or published evidence showing that levofloxacin itself can cause mitochondrial injury. Direct damage to mitochondria with other fluoroquinolones has only been observed with in vitro systems at concentrations 2 times higher than the clinical Cmax.

"There is limited evidence that some but not all fluoroquinolones can cause production of reactive oxygen species in mammalian cells, which may result in downstream," meaning secondary, "injury to multiple cellular systems, including mitochondria."

So I would describe it as there's some

evidence for mitochondrial toxicity, but the description that they provided us was that it was not completely certain.

CAPT PARISE: Dr. Russell?

DR. RUSSELL: For the agency, I'm not sure who specifically. We don't have a national health service database, and so that's one of the problems that we're discussing here and reasons we don't have data.

There was a bridge study several years ago looking at the diagnosis of fibromyalgia, and following the diagnosis of fibromyalgia, there was a dramatic decrease in the number of visits and costs for healthcare for individuals who had the diagnosis.

Were there studies that you reviewed that would be relevant to that in this regard? That is, a person got a fluoroquinolone, and medical visits increased, or something like that? That might be a resource to try to get a handle at this question.

(Applause.)

DR. STAFFA: This is Judy Staffa. I don't believe we saw anything like that in the literature per se, and that is something that could be looked into. But we have to be careful because that will also be associated with the severity of the infection in terms of actual medical visits.

CAPT PARISE: Dr. Besco?

DR. BESCO: Yes. Kelly Besco. I have a clarifying question, and it's just for my own knowledge. None of the fluoroquinolones currently fall under the jurisdiction of a REMS program. Correct?

DR. TOERNER: That's correct.

DR. BESCO: Thank you.

CAPT PARISE: Unless any of the panel -- okay, Dr. Phillips has a question for the FDA. Go ahead.

MS. PHILLIPS: I've got a follow-up question that's somewhat rhetorical. So there is a medication guide, and I know there's some submission commenting that it's not necessarily the clearest

document in the world. Does the FDA have any evidence on how often those medication guides are actually distributed with the product or the uptake of those medication guides?

(Applause.)

DR. STAFFA: This is Judy Staffa. The data you saw presented on drug use is dispensed prescriptions. But whether the med guide is distributed with that is not collected in those data.

CAPT PARISE: Dr. Besco?

DR. BESCO: Kelly Besco again. So if we were to recommend that fluoroquinolones as a class would fall under a REMS program, we could require the provision that the medication guide would be required to be dispensed with every prescription. Correct?

DR. NAMBIAR: Sumathi Nambiar from the FDA. It would depend on what elements of the REMS you are recommending. So a medication guide could be part of the REMS. Medication guide alone do not

constitute a REMS, but they can still be part of REMS.

So whether you have a communication plan or whether you have elements to assure safe use, it would be in the context of the REMS. Certainly a medication guide is an transaction.

CAPT PARISE: Chair's prerogative. Just one second. Can you just clarify for us what is REMS? Because we're not all familiar.

DR. NAMBIAR: Sure. Sorry. Risk Evaluation and Mitigation Strategy. It's an authority that we have, and it was made available, if I remember correctly, in 2007 when FDAAA was passed, Food and Drug Administration Amendments Act of 2007.

So if there are known or serious safety risks with certain products and we want certain mitigation strategies in place to ensure that the benefits still outweigh the risks, we have certain options available. So there are certain elements.

You could have elements to assure safe use. And again, I'm not an expert in it, but these are

very broad elements. And then you can have a communication plan, which requires the sponsor to communicate on periodic basis, and how often and to whom. It can all be dictated. A medication guide can be part of that.

Many years ago medication guide-only REMS were in place, and at that time fluoroquinolones did have a REMS. But they were medication guide-only. Subsequently, when there's a change and if medication guide is the only element of REMS, they no longer required to have REMS.

CAPT PARISE: Thank you.

DR. BADEN: What's the medication guide?

DR. NAMBIAR: Sorry?

DR. BADEN: Medication guide? Is that something that the pharmacist gives to the patient, or what is it?

DR. NAMBIAR: Correct. So a medication guide is part of labeling. So at the end of the package insert, we have this document called Medication Guide in which we describe the risks, and they are

described in lay language. And under our regulations, every time a prescription is given for that particular product that has a medication guide, a patient is supposed to get a copy of the medication guide.

CAPT PARISE: Okay. Let's go to Dr. Besco.

DR. BESCO: Has there been any precedent to include an informed consent process as part of a REMS program, where a patient and their provider would sign some sort of paper or document saying that they have reviewed the side effects of a medication?

(Applause.)

DR. COX: So far, no. Yes, there are medication guides that are part of the labeling, but an attestation or something along those lines has not been done with fluoroquinolones.

DR. BESCO: I'm not just referring to fluoroquinolones, but other medications. I believe some of the erythropoietin-stimulating agents, the patient has to sign a piece of paper, along with

their physician, discussing the side effects of those drugs, that they've been counseled on them.

DR. COX: Yes. There are other drugs that have such forms.

DR. BESCO: All right. I just wanted to clarify that that was the case, that there is precedent for that. Thank you.

CAPT PARISE: So that concludes the clarifying questions for the FDA, unless any of the panel members -- go ahead, Dr. Choudhry.

DR. CHOUDHRY: Just a quick one. So is there any precedent for imposing postmarketing requirements on drug makers many years down the road? So this question we've been talking a lot about, about the ability to detect this unusual syndrome in claims or other routinely collected data, certainly as a pharmacoepidemiologist myself, I could appreciate the complexity of doing that.

But there are other ways to go about this, and some of that could be imposed upon the makers. Is there precedent for doing this many years down

the road?

DR. NAMBIAR: Yes. This is Sumathi Nambiar, FDA. So yes, we do have the authorities, again, under FDAAA to require postmarket studies. And it's a postmarketing requirement. There is no timeline that you can only impose that within X number of years of approval. It's as and when a safety signal arises, or there is suspicion that there is a safety concern. We do have the authority to require postmarket studies.

CAPT PARISE: Dr. Winterstein?

DR. WINTERSTEIN: In follow-up to these REMS discussion, also for the FDA, the questions that are posed to the committee basically talk about one action, which would be removal of the indication.

I see two other actions. One would be changing the label such that this would be a second-line therapy and approved as a second-line therapy. And the other one would be a REMS of some kind that would be more than just a med guide, which I understand is currently dispensed. Right? So there

is a med guide. Yes.

Was there a reason why the questions were phrased in that way only? Or would there be an option to have several options here? And I know that I'm messing around with questions now. It just --

CAPT PARISE: We're going to hold the questions, any clarification on the questions. We will get to that. Yes, we'll get to it.

DR. WINTERSTEIN: All right. Hold the question about the questions.

CAPT PARISE: I just need to keep the order of the day here, but we'll get to you.

Yes, Dr. Hogans?

DR. HOGANS: I will just speak with my experience from the world of pain medicine, and that is that some REMS do involve education. The REMS that I'm most familiar with, which are for the long-acting opioids, involve a mandatory education component.

I just wonder if conveying essential

information such as the recommendations of the infectious disease organization might be the point here. So how brief can an educational REMS be, I guess is my clarifying question.

Just being a neurologist, it seems to me it's the sort of thing -- 15 minutes and you can say, these are the recommendations, and test for that knowledge, and you're out the door.

DR. COX: That's almost part of the questions, I think, ideas with regards to managing risk. So we appreciate your comment, and I think, as we progress here and we get to the questions, there'll be opportunity to talk more about ways to manage risk.

CAPT PARISE: Dr. Phillips?

MS. PHILLIPS: Marjorie Shaw Phillips. I think this is a clarifying question. I believe we heard this morning that 98 percent of the use of these fluoroquinolones is from generic manufacturers, not the innovator companies.

How does that impact the FDA's ability to

require postmarketing surveillance? How does that happen in practice with so much generic drug use?

DR. NAMBIAR: This is Sumathi Nambiar. As long as an NDA is active, the NDA has not been withdrawn, the sponsor of the NDA is still responsible.

CAPT PARISE: Dr. Daskalakis?

DR. DASKALAKIS: Two clarifying questions, the first again regarding the REMS and education. My understanding is that REMS can be used to do broader provider education and not just focus on an ID society because it seems as if, based on the list of providers that are using the drug, it may need to be a broader conversation that just a society. So can REMS target a class of providers, or broadly providers?

DR. NAMBIAR: Yes. I think we can target it to whom we think it is appropriate. There is no restriction on limiting it to any particular provider.

DR. COX: And similarly, the key messages to

communicate can range across a variety of things, whether it be recommendations on appropriate treatment, or adverse effects to be aware of, or other ways to manage risk.

DR. DASKALAKIS: My second question is if one were to change the indication, so today that recommendation is made or the questions are made, our answer to that in that way, what is the actual impact? So what happens on the provider level if today we say, acute bacterial sinusitis probably shouldn't be treated with a fluoroquinolone? What happens, from the FDA perspective?

DR. COX: The labeling is the basis and essence for promotional materials. So it would obviously impact upon promotional materials. When there are changes like alteration of an indication or a significant new safety finding, there's also efforts to communicate to healthcare providers these new changes. Oftentimes a "Dear Healthcare Provider" letter is sent.

There can also be other activities to try and

communicate the change so that folks are aware of the change to the prescribing information, and also as part of that, the basis for the change in the prescribing information.

CAPT PARISE: Dr. Hogans?

DR. HOGANS: Sorry. Just to go back to the REMS, it's my understanding that REMS are medication-specific. So I think it means that even from the primary care practitioner to the ID specialist who knows all about cipro, they would still have to do the REMS in order to be able to use the cipro. But that would be my understanding, that the REMS is linked to the drug and is not linked to the provider type.

DR. NAMBIAR: Yes. This is Sumathi Nambiar. Just to clarify, I think the question earlier was, whom do you decide to communicate? So in that, you don't really have to restrict it. It would be anybody who is using it. It's applicable to the drug, so irrespective of who is using the product. So is that your point?

DR. HOGANS: My point was that what I heard being said was that who is the target of the education, and it's not that you're targeting a population of learners, say, primary care providers. But the actual driver is whoever prescribes cipro or -- sorry, the fluoroquinolone. If I don't prescribe it, I can opt not to take the REMS and thereby not provide that within my armamentarium of treatment options as a prescriber.

DR. NAMBIAR: It really depends on what elements of REMS you're talking about. If there is just a communication plan that's part of the REMS, then it goes out to providers. And that's where we can decide, these are the main categories of providers who use this product, and the communication plan should include them. But if you're talking about special elements to address safe use, then that is really focused on the particular provider who is giving it. So there's a difference depending on which element of REMS you're talking about.

DR. COX: Yes. So it would generally be connected to the person who's prescribing the drug and wouldn't necessarily change too much, depending upon which particular specialty or subspecialty they were involved in.

CAPT PARISE: We're going to have two more. We have two on the list for questions. And then we're going to move to the industry just because we have to make sure we get to the later parts.

Dr. Scheetz?

DR. SCHEETZ: I just wanted to ask one more clarifying question on REMS, mostly because of my lack of knowledge. I thought it was interesting that there's only 2 percent industry stake still left in the game. But if we do recommend a REMS, most of that would fall on the holders of the NDA.

I'm just wondering in general what the thoughts are about downstream effects. We already know that we're having trouble getting antibiotics to the market. There's been a 2020 initiative. I don't think we're going to make it to 20 new

antibiotics by 2020. We don't have enough drugs to treat antimicrobial-resistant infections.

Just when we think about the big picture as well, if we recommend REMS, does that mean that we're now going to ask people to get out of the game? I don't know.

DR. COX: I take your question more as a comment, unless there's a particular question that you can crystallize from that.

DR. SCHEETZ: I guess the clarifying question, if we recommend a REMS, that would then be tied to the holder of the NDA. And it could be their priority to then drop the NDA. Is that correct?

DR. COX: I think you're getting into a fairly complicated issue because you're looking not only at safety and efficacy, but you're also looking at economic implications and many other questions that are much bigger and probably beyond the focus of what we're looking at here today.

I think we really are trying to look at the

safety and efficacy here and trying to understand how best to define the safety and efficacy of these products and use these products in a way to mitigate risk.

CAPT PARISE: Last question, Dr. Besco?

DR. BESCO: Yes. I think it might be helpful to clarify the different options of REMS programs. So I'll try to state what I know. There are three varieties that you can build up. Correct?

The first initially is the requirement of a medication guide that gets dispensed for every prescription. Then you can elect to do an education program -- oh, I'm sorry -- elect to do an education program, which could be a mandatory education program that all providers would go through. Or it could be something that's as simple as a "Dear Provider" letter.

So the first two I find very passive. The third is where you build upon patient registries, those informed consent processes. So maybe it might be good for the group to have a better understanding

of the menu of options, for lack of a better description, of what could be required as part of a REMS program.

DR. COX: You're correct. Medication guides is the first layer. Second layer gets to communication plans, and they can include various different educational efforts and such. And then moving to a third layer is something along the lines of elements to assure safe use. So there may be certain tests or forms or attestations that would be part of that third layer.

DR. LaCIVITA: Hi. This is Cynthia LaCivita. I'm the division director for the Division of Risk Management in CDER and OSE.

The elements to assure safe use for a REMS include prescriber certification. It could be certification of those who dispense. It could be restricted to specific healthcare settings.

It could be elements to assure safe use, where we would ask for specific information to be conveyed to a patient or specific information

regarding -- let me think -- a test or something like that to be done beforehand. It could be monitoring after the drug is given. And it could be enrollment in a registry.

CAPT PARISE: Thank you.

Now we're going to move on to clarifying questions for industry. We do have a queue here, but if you want to be added to the queue, just signal to Jennifer. And just a reminder -- if possible, direct your question to a specific person, if possible.

So first we have Dr. Arrieta.

DR. ARRIETA: All right. I think it is a question for Dr. Mandell or whoever you choose to answer this.

So the quinolones, I think, as it has been presented here are basically two, at least from the ID point of view, are grouped oral bioavailable agents that can be switched from IV to oral on the treatment of serious infections so patients can transition from hospital to home. The second one,

which has been highlighted, is for resistant organisms.

The studies that were conducted to evaluate the quinolones for respiratory infections were conducted or fostered, spearheaded -- I'm sorry, my English is limited, so I cannot come up with the right word -- but it was a time when the pneumococcus resistance was substantially increasing year by year, and the need for a replacement agent to the beta-lactams appeared to be urgent.

So the quinolones were studied. We can debate the studies forever, but the agents or the doses that were used as comparators were probably not the best. Regardless, the quinolones performed well, as good as the comparators and got approved for respiratory infections.

Uncomplicated urinary tract infections, although are a problem, a well-recognized problem. They have the benefit of a very simple urinalysis and urine culture to establish the presence of an infection and the presence of a resistant organism.

So as significant as I think it is, it would be not terrible, I think, to expect a patient to wait 24 hours for an uncomplicated urinary tract infection until we have susceptibilities available and certainty of infection.

So since the advent of new vaccines, pneumococcus resistance has pretty much disappeared, and hopefully will continue to do so. As we have a urinalysis and a urine culture, do you think that perhaps in the future, the IDSA, the Canadian Infectious Diseases Society, may consider that the quinolones are no longer necessary for community-acquired respiratory infections or for uncomplicated, known culture-proven urinary tract infections?

DR. ALDER: I take that to be a two-part question, one on respiratory infections.

DR. ARRIETA: Sure.

DR. ALDER: And could we visualize a day when quinolones are not necessary because of decreasing pneumococcal resistance rates. And the other is

similar, but for UTI. Is that correct?

DR. ARRIETA: Well, yes. The UTIs, we ought to be able to know when resistance is present. Is not a matter of severity.

DR. ARRIETA: It's a culture. Yes.

DR. ARRIETA: It's an uncomplicated urinary tract infection, so the presence of pyuria should indicate infection, and the presence of the culture should dictate whether it is resistant to all other alternative antibiotics or not, so that that rationale for using quinolones empirically should really disappear.

DR. ALDER: Got it. For the first part, Dr. Mandell will respond, and then we'll have a second responder for the second part of your question.

DR. ARRIETA: Sure. Thank you very much. Appreciate that.

DR. MANDELL: Thank you for the question. Again, just before I answer you, and I promise I'll answer, I just want to reiterate, and I can't

emphasize this enough, no one is saying whether it's industry or the ID groups, these societies, the guidelines, et cetera, that we need quinolones for first-line mild infections. Absolutely not, full stop.

With that as a given, if you look at things like the AECB -- because that's probably the one that ultimately can have the worst consequences, AECB in the context of COPD -- and again, respectfully to the FDA and Dr. Toerner, I would submit and so would any respirologist or ID person who deals with it, that severe and moderate is not limited to the hospital. We see them in the community all the time.

So the quinolones very definitely have a place. And to your point or to your question about the pneumococcus going down because of the conjugate vaccine, it is. Pneumococcus is going down, and there's always a tradeoff.

So H. flu and M. cat are going up, and there is quite a bit of beta-lactamase as well. So the

other drugs that were being used a lot in the past, drugs like trimethoprim-sulfa, drugs like amoxicillin, no longer that good any more.

So in fact, that's one of the reasons why we're now faced with these patients on the outside -- there's no question about the hospital, but on the outside, where they're sicker. They have real problems. And we want a drug that will cover these resistant pathogens.

But not only that, there's the issue of, can I get this person better for this episode, but can I also get the freebie of extending the interval to the next infection? And I would submit that with the quinolones, you get both. You're getting coverage of resistant pathogens, and you're also getting this extension.

This extension has been shown -- or having more frequent exacerbations, that's the one thing that is going to guarantee that your lung function is going to decline and your potential mortality rate will go up. So I would argue that the

quinolones there absolutely have an important role.

For the things like acute bacterial sinusitis, again, if it's viral, nobody in this room will disagree. You do not need an antibiotic. If they do fit the criteria, though -- and those criteria are laid out quite clearly for acute bacterial rhinosinusitis. If you decide, yes, it's bacterial but it's not the end of the world for this patient, then again, recommended is something like amox-clav. But certainly if there was a question of resistance, a contraindication to a beta-lactam, a recent beta-lactam he might have taken for something else and a risk of resistance, I would go to a quinolone.

DR. ARRIETA: Thank you.

DR. ALDER: For the second part of your question regarding recommending culture positivity before initiating treatment of UTI, I would call Dr. Abrahamian to respond, please.

DR. ABRAHAMIAN: Thank you. Fred Abrahamian. I just wanted to also say that -- to reiterate

regarding conflicts of interest, I have received consulting honoraria for my time, and I do not have any financial interest in the companies or the outcome of this meeting.

The question with respect to cultures, we do not get cultures for patients with acute uncomplicated cystitis. This practice has been banned forever, for a number of years, for at least 10 years. There are many reasons we don't do that.

Why? One is that most of our antimicrobial therapy that we give is very short-term. It's for three days. And cultures oftentimes don't come back by then. Most patients do well on the antibiotics that we give, and by the time cultures come back, regardless of what it is, patients already feel better.

I'm not aware, I do not believe -- you mentioned cultures coming back in one day. I have not heard of anything like that, for any cultures to come back in 24 hours. Most often, when we assess urinary tract infections, we either get urinalysis

or we get dipstick urine. So we confirm evidence of pyuria on our urine samples.

If cultures are sent, it takes at least 48 hours just to figure out what organisms we're dealing with. It takes another 24 hours to know what the susceptibility patterns are. By then, most patients feel better and have completed a course of therapy, if it was given.

On the other aspect, so what would happen if we sent a culture and we have a resistant organism? Well, studies have shown that resistance doesn't always mean that you're going to have clinical failure. About 50 percent of patients that have resistant organisms will have likelihood of clinical cure.

One last note. I'm a practicing physician, and I'm not sure I can tell my patients who come in with symptoms of urinary tract infection, which is severe enough for them to seek medical care, for me to tell them, go ahead and wait another three days and let's just see what happens.

Studies have shown urinary tract infections have effect on quality of life: 2.4 days of restricted activity, 1.2 days of absence from work and school, and half a day stay in bed. These infections have considerable morbidity. It is hard for me to tell my patient, go home and wait three days until your cultures come back and we'll see what happens.

DR. ARRIETA: I think I should comment.

CAPT PARISE: Good clarifying question.

DR. ARRIETA: So the cultures don't take 72 hours. Urine cultures take 13 hours. Now, if you have to send it to an outside lab, the courier, et cetera, it might take 24 hours. But you immediately will know if there is a gram-negative. You will know if it is an Enterobacteriaceae. You will have a lot of information out of the urine culture. That's number one. It doesn't take 72 hours.

You would never send your patient home without any treatment. But there are mitigating

therapies that can improve their lifestyle. There are analgesics. There are analgesics for a urinary tract. There is a multitude of things that could be done to help a patient until you get the appropriate microbiological information. So it's not 72 hours.

(Applause.)

CAPT PARISE: Dr. Staud?

DR. STAUD: The question is for Dr. Alder. We have heard multiple times today about the indication for quinolones for a particular -- for urinary tract infections. And it is not clear at least to me if the large number of physician who prescribes quinolones, since as first-line treatment for UTIs, they're aware of the indication for this.

So I was wondering if the industry has actually queried physicians and asked them about their base of knowledge, if they're aware of what the appropriate order of treatment is for something like an uncomplicated UTI.

DR. ALDER: Well, what you're really asking, I think, is a question on appropriate use of

antibacterials in UTIs. And there's been some scant data done, some literature on this. Now, it's not fluoroquinolone-specific, that is, first-line, second-line, last-line therapy for treatment of uncomplicated UTI. But there was one publication that I know of that looked at appropriateness of antibacterial, and also gets a bit to the earlier question -- are we over-prescribing or not? Slide up.

This was a somewhat smaller study by Sigler, 128 patients, looking at guideline adherence right now. To be clear, this isn't whether the patient should or should not get an antibacterial, but rather, were guidelines followed or not? And the overall guideline compliance rate, I think, was about 64 percent overall, looking at a pretty small sampling of patients.

I know some other studies in other therapeutic infectious disease areas that give roughly similar numbers when it comes to guideline adherence.

CAPT PARISE: Thank you.

Dr. Scheetz?

DR. SCHEETZ: My question was also for Dr. Alder. I won't belabor it too much, but on slide CD-9, you showed some data on the use of systemic antibiotics for sinusitis.

The second most commonly used antibiotic is amoxicillin, which is not guideline-recommended. Thinking about that, thinking about the fact that there is a very large proportion of therapy that is not guideline-concordant, do you have any recommendations for the package labeling, anything that you suggest that could increase guideline concordance?

DR. ALDER: Regarding fluoroquinolones, or are we talking antibacterials?

DR. SCHEETZ: Yes. In regard to fluoroquinolones. You mentioned that the levofloxacin use was 6 percent, moxifloxacin use was 3 percent, and if I understood right, you suggested that that meant that they were being used as second-

line. I'm not sure that those data absolutely show that, but it may imply that.

But the amoxicillin shows that there's probably not guideline concordance, so people are not following guidelines. How would we help to make sure that physicians would use these as second-line agents if that's the way they're being recommended and being suggested by the groups?

DR. ALDER: So a couple things. With the data up here, the fluoroquinolones, as was presented this morning, have a little less than 9 percent of the overall uses of 8.8 million. Let's call it 9 percent that's clearly not being used first-line therapy.

I think your other point though, is that appropriate, i.e., are they being used in patients that might have viral infections? Well, we can't tell. We can't tell if the overall usage here of 8.8 million, is it all appropriate? Is it all inappropriate? Is it some sort of mix of appropriate and inappropriate? Which obviously it

is.

Now, as far as specific labeling recommendations, part of the reason we're all here today, part of the reason, is to listen to the advice from this council. The FDA holds these panel discussions, and they hold them pretty regularly, to get advice from people like you.

One of the possible outcomes of today is your advice on potential label language. We hold interactions with the FDA all the time on language updates. This isn't unusual, to have a discussion on what to do to improve the use, the safety, and the efficacy of our drugs. Basically, we're here to listen. We will provide all of our data, and we are committed to working and following through with advice and with the FDA following today's discussion.

CAPT PARISE: Thank you.

Dr. Winterstein?

DR. WINTERSTEIN: I think also for Dr. Alder, a clarifying question. During the discussion before

the break, there was this inference that in UTI, quinolones might actually have some superiority over other agents. And there were some treatment rates or cure rates presented.

I went back to your slide 6 that showed we have to have comparisons. And that suggested there was noninferiority, but not more than that. What were the comparators here, and how would you interpret those data compared to what you showed in that other slide?

DR. ALDER: Sure. So for these, the comparator for ciprofloxacin -- so that's the penultimate line -- was trimethoprim-sulfa. And you see the overall response rates, 95 and 92 percent for cipro and for TMP/SMX, respectively. For levo, the comparator was ofloxacin, and you see the response rates there, 98 to 97 percent. These were the pivotal trials in support of the NDA, and they solidly demonstrated noninferiority.

Now, the other piece of data we showed was one that utilized cipro as a positive control.

Cipro was approved in 1987. It's been generic for many, many years. And it is frequently employed as a positive control in trials. So that's the fosfomycin label, a slide that we showed earlier. Slide up.

This comes from actually the label, the package insert for fosfomycin. So this was a pivotal study done in support of fosfomycin. Cipro just happened to be the positive control here because it was approved for UTI.

You see the clinical response rates in the far right column, 70 percent, 96 percent. Trimethoprim-sulfa had 94 percent, nitrofurantoin 77 percent. And the footnote -- I know it's a little small -- footnote 1 indicates fosfomycin inferior to comparator. That was from the authors. That's not a sponsored study in support of cipro. This actually was the study that gained support for fosfomycin.

DR. WINTERSTEIN: So these drugs actually had to have comparison? I thought they came from

different placebo-controlled studies, but cipro is the comparator for all of those? Yes.

DR. ALDER: Yes. All the data I just showed, both tables, are not placebo-controlled. They're all active versus active. There's no placebo in either case, either in the cipro or the levo phase 3 studies, or here with fosfomycin. Everything's an active.

CAPT PARISE: Dr. Daskalakis?

DR. DASKALAKIS: Demetre Daskalakis. Could I ask the industry folks to comment on what their marketing strategy has been for the fluoroquinolones for the indication of the acute bacterial sinusitis indication, the indication for an exacerbation of bronchitis in COPD, and also for the urinary tract infection?

DR. ALDER: I can tell you that the quinolones under discussion today are generic. They've all been generic for quite -- well, cipro since 2004 and levo and moxi for one and two years, respectively. To our knowledge, as the innovators,

they're not actively marketed or promoted anywhere in the USA.

DR. DASKALAKIS: Short- and long-acting?

DR. ALDER: I'm sorry?

DR. DASKALAKIS: The long-acting as well?

DR. ALDER: Yes. I don't have any information on a marketing strategy. The people here are the innovators. The clinicians and medical people are not the marketeers, so I don't have any information.

CAPT PARISE: Dr. Russell?

DR. RUSSELL: I think it's Dr. Nicholson that I would like to help me get my head around the numerator and denominator of one of the complications that we're talking about today. Let's just, say, pick neuropathy or symptoms that suggest neuropathy.

I see one place in your presentation, I think quoting the FDA report, that 178 patients exhibited something, and the most common thing among those was neuropathy. So can we say that 178 people of some

database had neuropathy? And what would be the denominator of that database in terms of how many doses or prescriptions were written that resulted in that 178?

CAPT PARISE: Dr. Nicholson?

DR. NICHOLSON: Susan Nicholson, Johnson and Johnson. Slide up, please. First I'm going to show you a few of the pieces of data on peripheral neuropathy, and then I'm going to ask one of my colleagues to comment on this epidemiologic study that we've discussed a little bit previously.

First, there is very little information about what mechanism might explain the association of peripheral neuropathy with fluoroquinolones. As you'll see in the bullet here in the slide, there's no direct clinical or experimental evidence linking specific cellular abnormalities to pathology of peripheral nerves in fluoroquinolone-treated patients.

I think this is a great example of a situation where we've observed a phenomenon. It

happened more times in fluoroquinolone-treated individuals than not, which gave us reason, even though we didn't have a causal relationship per se or a mechanism of action but rather an association with use, it was added to the fluoroquinolone labels.

The way you're asking about for the 178 patients, two things. Let me ask my colleague Dr. Lautenbach to speak about the epidemiologic data, and then we have a neurologist who can speak about that 178 cases.

DR. LAUTENBACH: Thank you. I'm Ebbing Lautenbach, chief of infectious diseases from University of Pennsylvania. I've received a consulting honoraria for my time, but have no financial interest in the companies represented or in the outcome of the meeting.

I think with regard to the 178, that refers to the patients that were identified by the FDA as representing those who manifested the constellation of symptoms as FQAD. And I think the questions,

which have been highlighted already by Dr. Staffa and by Dr. Lo Re and others, is severalfold.

One, how do you take the information from what looks like a relatively broad distribution of symptoms represented by those patients, albeit, as we've heard today from the speakers very compellingly, obviously symptoms that have resulted in considerable pain and suffering.

How do you take that information and better define exactly what that constellation of symptoms is and what it may be related to? And I think that very much speaks to the need for a larger epidemiologic study, or a large epidemiologic study, in which, first, one identifies what the case definition is.

So taking the information that Dr. Boxwell has presented, how do you put that together into a coherent case definition? And then how can you take that forward into either a claims database, into a database that relies on electronic medical records?

There are obviously challenges whichever

approach you might take. But it's certainly worth doing to better define what this constellation of symptoms represents and exactly what it's related to.

(Applause.)

DR. LAUTENBACH: I've been asked also to comment on the Etminan study, which I think was on the slide that was previously up, which I'll be happy to do. So this was the study, I think related again to the question -- oh, I'm sorry, slide up, please -- which was related to the question of what do we know about the epidemiologic association between fluoroquinolones and neuropathy. And this is a study that was presented before.

I think the challenges in this sort of study, which again is limited to males only and those aged 40 to 85, excludes those with diabetes, I think is severalfold. One, these are diagnoses that rely on claims data, so validation of these diagnoses wasn't achieved. There are a limited number of comorbidities that were assessed as part of this

study, and obviously generalizability is a concern.

So I think while this represents an early piece of information, I think there are a lot of limitations in this sort of study, again, I think, demonstrating the need for a broader epidemiologic study, not just for neuropathy but for the FQAD constellation of symptoms as well.

DR. RUSSELL: Is there any way that we can tie that number to a number of doses or prescriptions or anything like that?

DR. LAUTENBACH: Within this study?

DR. RUSSELL: To get a denominator?

DR. LAUTENBACH: I'm sorry?

DR. RUSSELL: To get a denominator?

DR. LAUTENBACH: I think the denominator -- A, I don't believe there was any demonstration in this study of the dose or duration of therapy although, obviously, as it relates to the FQAD constellation of symptoms, those, as opposed to many of the other adverse events that have been epidemiologically linked to fluoroquinolones, tend

to occur very early in therapy.

In terms of the denominator here in this study, there's a report of a million males that were followed as part of this. But there were exclusion criteria, and so it's unclear exactly what this denominator represents.

DR. NICHOLSON: Thank you. So I think the point on this epidemiologic study is that we don't have a numerator and a denominator. This study was about relative risk of fluoroquinolone-treated versus not-treated individuals and peripheral neuropathy.

For the 178, that was 178 cases reported over 17 and a half years. So that's about 10 cases per year and 10 million exposures per year. But that's a reporting rate, not an incidence rate, and I think that's why Dr. Lautenbach was referring to an epidemiologic study where we can get a true n over n, provided we can get a clear definition of a case constellation.

Dr. Houlihan can comment on the peripheral

neuropathy as part of that 78-case [sic] cluster.

DR. HOULIHAN: Thank you. My name's Joe Houlihan. I'm a neurologist and acting as a consultant for Janssen, for which I'm being compensated.

I'd just like to step back a little bit and, first of all, for the public and the patients who are here, I don't want this to be misconstrued as anything denying symptoms or the severity or your symptoms or the disability, simply making some comments about where they're coming from.

Are they coming from the peripheral nerves? Are they coming from neurologic symptoms? Sensorimotor symptoms can come anywhere from the brain down through the spinal cord out to the peripheral nerves, the skin, the muscles. And I think we're lumping a lot of things together as neuropathy. And I think there are three different things going on besides what's in the label.

So we've got the Etminan study looking at an increased use of or prescribing of quinolones in

patients with neuropathy compared to patients without. Dr. Trinidad mentioned in passing Guillain-Barre syndrome. Guillain-Barre syndrome is a demyelinating neuropathy provoked most often by infectious illness.

We talked about confound by indication. I think there's a potentially big confound that could be related to that or other causes of neuropathy. If you have 6,000-and-some incident cases of neuropathy, a fair number of those are going to be Guillain-Barre. A lot of those are going to be proceeded by bacterial infections treated by antibiotics, and there could be an imbalance. So I just wanted to make that comment about that study.

Very briefly, there's a small series from the Swedish health authority that was reported 1996 or so, isolated peripheral neuropathy without the other constellation of symptoms we're talking about today. And those were very different. They resolved over time. Seventy-one percent resolved within two weeks, the remainder within weeks to months. The

longest was a year. So we've got other cases that look quite different.

Now, we've got the 178 cases we're talking about and some of the other published cases that look quite similar that have a constellation of symptoms and prolonged severe symptoms. And I reviewed all of the cases.

I think there are great limitations in the data on those cases. I didn't see a single localizing neurologic exam, and a lot of these are not from physicians. But even in the published cases, the exams were noncontributory or some contradictory limited EMG nerve conduction studies. There were some punch biopsies that were suggestive.

I only saw one history that had a history of progressive stocking-glove distribution sensory symptoms.

CAPT PARISE: We're going to have to shorten this since this study wasn't brought up in the question just because I'm trying to -- we have only a few more in our ability to do before we have to

vote --

DR. HOULIHAN: Yes, yes. And I'm finished. I just think it's important to stress that we're looking at a lot of different symptoms and calling them all neuropathy.

CAPT PARISE: Thank you.

We're going to take two more, and we're going to just ask people to be as brief as possible because we need to get to the vote by 4:40 at the latest. Ms. Schwartzott?

MS. SCHWARTZOTT: Yes. I have a real concern about the mitochondrial toxicity with this medication because if you are giving a medication that has potential toxicity to mitochondrial disease to somebody who already has a mitochondrial disorder, I can just imagine that the damage would be way worse. And I'm wondering if that might be what's going on. Have you guys studied that?

DR. ALDER: For that, I would ask Dr. Zhanel to please comment.

DR. ZHANEL: It's my real honor to be here.

My name is George Zhanel. I'm a medical microbiologist and a clinical pharmacologist by training. I've been asked to be here specifically today because I've been teaching, researching, writing, and recommending antimicrobials to be used for select prevention and treatment of infectious disease for 25 years.

On the quinolone side, my group that I chair has published over 250 papers, abstracts, and book chapters dealing with fluoroquinolone properties, including their mechanisms of action, mechanisms of safety.

To answer your question, antimicrobial assessment of whether antibiotics cause mitochondrial toxicity is at its infancy, and I apologize for that. When I reviewed the literature for whether quinolones cause mitochondrial toxicity -- and I did; I reviewed clinical cases, healthy volunteers, animal data, and in vitro data -- the answer is the same as what the FDA concluded. We cannot conclude that quinolones cause

mitochondrial toxicity.

However, other drugs have been studied much more. The cardiac drugs. Some of the antivirals for HIV have been studied. The cardiology drugs, many have been studied. Some nonsteroidals. Antipsychotic antidepressants. We need to study antibiotics to find out what they do.

But as of today, having reviewed the literature, I'm confident to tell you that the data tells us that the fluoroquinolones -- we cannot conclude that they are mitochondrial toxins.

MS. SCHWARTZOTT: Would there be future evaluations and testing, studies done?

DR. ZHANEL: My sincere hope is absolutely. When I reviewed the quinolone literature for mitochondrial toxicity, I compared it to other antibiotics that were studied, I compared it to antivirals, and I compared it to other drug-induced toxicity of mitochondria.

It is as its infancy, but it is now growingly routine in industry, in the drug discovery process,

to test these compounds at a very early stage. But I have to emphasize this is extremely difficult. And the reason is, there is no predictive tool that we can use with patients to assess mitochondrial toxicity in terms of, if we should give them an antibiotic for their infectious disease, how they will do.

We can't draw blood and look at white blood cells and assess whether they have mitochondrial toxicity that would be exacerbated by an antibiotic such as quinolone. We don't have that test. But researchers are working on this test. It'll be a very complex text, but we need to have this done.

(Applause.)

CAPT PARISE: Thank you.

Dr. Floyd?

DR. FLOYD: Briefly, this is a follow-up to Dr. Winterstein's question about noninferiority and treatment effect for fluoroquinolones. So I think this question is for Dr. Alder. If you wouldn't mind putting the slide up that you showed

previously.

DR. ALDER: You mean the forest plot? Yes. Slide up, please.

DR. FLOYD: I believe these trials were conducted long before thinking on noninferiority trials has evolved, as reflected in current guidance for a number of conditions. And they're actually quite rigorous now to claim noninferiority, which implies effectiveness, efficacy.

I'll boil it down to three items. One is to establish a treatment effect for the comparator drug in a clinically meaningful outcome, and actually to have a precise estimate. The second is to actually measure that same outcome at a similar time in your noninferiority trial.

Third, to actually conduct the trial in a way to minimize bias, meaning studying similar patients with the right disease severity, with the right disease, the right distribution of comorbidities, not giving rescue therapies, prior antibacterial therapies, concomitant therapies. All these things

need to be done before a claim to noninferiority, and therefore efficacy, can be made.

So this is kind of a yes or no. Were these trials conducted in such a manner? Because if not, I think it's difficult to establish a treatment effect for these specific fluoroquinolones for these conditions.

DR. ALDER: There are a couple of things in your question. But they were conducted over roughly 20 years, if you look at the lifespan from cipro to Avelox was the recent.

Now, the thinking about how to conduct a trial evolved over the late '90s. In fact, we used to call them equivalence trials. But they really weren't equivalence trials, they were almost noninferiority but not quite, but they certainly weren't equivalence trials.

The later studies were done to noninferiority standards, and most of these studies, with the exception of the very early cipro ones like the cipro AECB trials, were conducted basically to a

noninferiority standard even though in the literature you will often see the word "equivalence" relative to compare used erroneously.

Now, the bigger question, though, really, is not is this equivalence or noninferior to something else, but what's the treatment effect? That's the big question. And to get to a treatment effect in at least two of these now, the FDA has changed their draft guidance recently to requiring placebo-controlled studies.

So for ABS, placebo or superiority to establish therapy; either one would work. And same for milder infections and acute exacerbations for the milder COPD patients. So overall --

DR. FLOYD: Just to respond to that, we have evidence of a treatment effect for COPD that seems very dependent on the severity of the disease. And the clinical response of 100 percent or close to it suggests that these are not in the distribution of where we expect a large treatment effect. In fact, these are quite healthy patients where there

probably is very little treatment effect as far as that trial.

DR. ALDER: Yes. Well, and there are multiple problems, then. One is even conducting a large placebo-controlled trial.

To take a group of patients, and you know or you strongly suspect that a group of them have an active bacterial pathogen causing disease, and then knowingly subject them to a placebo is something that many feel is inappropriate, even if it's acute bacterial sinusitis, certainly for uncomplicated UTI. And you've heard from the COPD patients.

Many centers won't do them. Many of the pharmaceutical companies and their representatives also consider that inappropriate. I don't think you've seen any very large placebo-controlled studies.

So whenever we're looking at treatment effect, it's always scattered studies, usually done at small academic centers, 40 patients here, 60 there, 70 there, not these large 5-, 600-patient

studies.

We could poll our clinicians here, but I saw heads shaking up and that they would not consider this appropriate, to take their patients and subject them to placebo if they knew or strongly suspected a bacterial pathogen.

So we're in a dilemma. How do we ever get to a treatment effect if you need a placebo? But we're not going to do a placebo because we consider that inappropriate. That's something we need to work on further.

CAPT PARISE: Thank you.

I'm now going to ask Dr. Nambiar to come up and give a charge to the committee.

Charge to the Committee - Nambiar

DR. NAMBIAR: Thank you, Dr. Parise. I'll do it from here, if it's okay with you.

At the meeting today, we've discussed the benefits and risks of the systemic fluoroquinolones, focusing on three indications: acute bacterial sinusitis, acute bacterial exacerbation of chronic

bronchitis, and uncomplicated urinary tract infections.

You have heard presentations from the FDA and the industry, and comments from speakers at the open public hearing. Based on the information provided to you in the briefing documents, the presentations, and discussions today, we seek your input on three voting questions, one for each of the three indications being considered.

In addition to your yes/no vote, your rationale and any recommendations you have are extremely valuable to us, and we look forward to hearing your perspectives on this important and challenging issue. Thank you.

Questions to Committee and Discussion

CAPT PARISE: Thank you.

We'll now proceed with the questions to the committee and panel discussion. I'd like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the

panel.

We'll be using an electronic voting system for this meeting. Once we begin the vote, the buttons will start flashing and will continue to flash even after you have entered your vote. Please press the button firmly that corresponds to your vote. If you're unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. The DFO will read the vote from the screen into the record.

Next, we will go around the room and each individual who voted will state their name and vote into the record. You can also state the reason why you voted as you did if you want to. We'll continue in the same manner until all questions have been answered or discussed.

When we go around the room, you can also address recommendations. We'll do that at one time.

You'll do the vote and then recommendations, and Jennifer will read the question in just a minute.

So are there any questions or comments concerning the wording of the question before we proceed?

(No response.)

CAPT PARISE: Question number 1, vote. Do the benefits and risks kind of the systemic fluoroquinolone antibacterial drugs support the current labeled indication for the treatment of acute bacterial sinusitis, ABS?

Following your vote, provide specific recommendations, if any, concerning the indications for treatment of ABS and safety information, including the constellation of adverse reactions that were characterized as a fluoroquinolone-associated disability or FQAD.

DR. SCHEETZ: Before we vote, are we going to get the question from Dr. Winterstein?

CAPT PARISE: Oh, yes. Good thinking. Go ahead.

DR. WINTERSTEIN: Usually there is a question session for the question. No? Or a discussion session for the questions? No? So we just vote?

CAPT PARISE: We can ask questions here about the question. So I'm sorry, you did have a question about the question.

DR. WINTERSTEIN: Well, actually it's general. Usually before a vote is up, there's usually a brief discussion before the vote happens. No?

DR. COX: It's really the chair's prerogative. You can do it either way. If there's specific clarifying issues that you need before you vote, it's probably the time to ask them now. So please.

DR. WINTERSTEIN: Well, here's my question. From what I understand, a REMS is introduced if the agency wants to assure that a drug's benefit outweighs its risk. So essentially, if there is an unfavorable risk/benefit consideration overall, then a REMS could be used to shift that into something

where risk/benefit might be again favorable.

So thinking about that in the context of this question, would it make sense to consider such a scenario, or would you like us to vote on this question under the current scenario as the drugs are being used right now?

I think that's the clarification. So basically, the question is, do we use the scenario the way the quinolones are currently approved, or should we consider a scenario where the approval would look differently and there might be a REMS in there?

DR. COX: Sure. Let me try and clarify. So the question asked with regards to the current labeled indication. So we're asking you about the current label as it stands now. It sounds like what you're proposing --

DR. WINTERSTEIN: Yes. I'm not asking about the indication. I'm asking about a REMS.

DR. COX: Just let me finish. So the question is about the current situation. Okay?

You're bringing up the idea that there may be other things that could be done to help mitigate risk. I think that comes in the second part of the question, when we get to A, because if in fact there are other things, other suggestions or ideas that you have to mitigate risk, when we get to the point of going around and asking folks for their comments, their rationale and comments following your vote, please provide specific recommendations, that's where we would welcome additional thoughts on other things that should be considered. Does that help?

DR. WINTERSTEIN: Kind of, yes.

DR. BADEN: Dr. Cox, including adjustments to the label?

DR. COX: Yes. So the questions are essentially voting on the current state of affairs, and then A is, in essence, the opportunity to describe how you would see things needing to change, what the suggestions would be there.

It can be with regards to label language, other procedures, or other things that might need to

be put in place that would be important for balancing the benefit/risk. So I understand the reason for the question. It's a good question, and I'm hoping that provides clarity.

CAPT PARISE: Dr. Gerhard?

DR. GERHARD: Just a very quick follow-up to maybe clarify the actual yes/no voting. So the way I read this, and just state whether you would see it the same way, if we see any significant change to the label, then we would vote no. And then in the justification, we provide where that change would take place and how we would see it?

DR. COX: I think that's correct. The question is, do the benefits and risks of the systemic fluoroquinolone antibacterial drug support the current labeled indication for the treatment of acute bacterial sinusitis? So you may have other ideas and suggestions with regards to what else should be done.

CAPT PARISE: Dr. Cox, did you have something else to --

DR. COX: Just one more thing, too. Very important to us are the rationales behind your votes. I realize that sometimes it may be difficult to get to the binary result, so that's why it's very important for us to understand your rationale as we go around the table. So please help us understand exactly what you're thinking because that's very valuable to us.

CAPT PARISE: Another clarifying --

DR. SCHMID: One more clarifying question. If what's in the label is not being followed, that could be a reason for saying the label was not sufficient?

DR. COX: The label gets to where the drug has been shown to be safe and effective. I think you're raising an additional issue, which is in clinical practice of medicine there may be additional things that are going on out there. And that's, I think again, an opportunity for -- are there ways, in essence, to be able to improve the practice by providing additional information, other

things that you may think of that could help the situation.

So I think it gets to, in essence, almost the question that started this out, other things that might be included. So we'd welcome those comments and suggestions when we get to the A part and as we go around the table.

CAPT PARISE: Dr. Baden, another clarifying question?

DR. BADEN: Yes. If, for example, one of us were to think that there could be adjustments to the label, that suggests that one should have a no vote, as opposed to a yes vote with suggestions to change the label?

DR. COX: Right. And you can see that there's many different ways that you can write the question and a lot of different permutations. So we had to pick one. So the one we picked was the current label. So we're asking the question around the current label as it stands now.

We're recognizing that a no vote may mean

that there's the idea of additional changes or additional things that would need to be in place. And if we can get those suggestions and comments as we work through the A part, I think that will be very helpful to us.

CAPT PARISE: Are there any more clarifying questions?

(No response.)

CAPT PARISE: I guess I actually have a question. I'm sorry. This just came up as you gave your answer. So if we feel the current label needs change, then that would mean we think that it does not support the current label indication. Is that what you just said?

DR. COX: I think that's correct because imagine the alternative where we say, do you think some semblance of the label that's currently out there with some changes and undefined, is that okay. You can see that's an unanswerable question because we haven't even agreed what those changes would be.

So I think we really do have to focus on the

current label in its current state and vote on that accordingly. And then, when we get to the A part, we can hear what the suggestions are as to how things change. Because if we don't anchor the question in the current state of affairs, then everybody's voting on a different question, and it becomes essentially even more difficult than I think the difficult situation that we're already trying to work through here.

CAPT PARISE: If there's no further discussion, we'll now begin the voting process. Please press the button on your microphone that corresponds to your vote. You will have approximately 20 seconds to vote. Please press the button firmly. After you've made your selection, the light may continue to flash. If you're unsure of your vote or you wish to change your vote, please press the corresponding button again before the vote is closed.

(Vote taken.)

CAPT PARISE: Everyone has voted. The vote

is now complete.

(Applause.)

LCDR SHEPHERD: For the record, the vote is zero yes, 21 no, zero abstain.

CAPT PARISE: Now that the vote's complete, we'll go around the table and have everyone who voted state their name, their vote, and if you want to, the reason why you voted as you did into the record. This is also the time to provide any specific recommendations, as stated in 1A.

We'll start down at this end. Dr. Staud?

DR. STAUD: Roland Staud. I voted no. I think the lack of significant efficacy of this medication for the indication is a great concern to me. And I think that some form of REMS would be an important addition to this medication. And I would suggest really at least a medication guide.

CAPT PARISE: Thank you.

DR. RUSSELL: Russell, San Antonio. I voted no because I think we're not getting sufficient information about the infections we're treating.

And I think it's not appropriate to be treating acute uncomplicated cystitis with these medications.

There are no medications that are free, entirely free, of adverse risk. But I think -- oh, we're talking about just sinusitis for this one? Sorry. I think education is going to be important for physicians, and we need more information to determine the risk versus benefit for these medications.

(Applause.)

DR. VITIELLO: Ben Vitiello. I voted no. The reason is there is an uncertainty of efficacy, and there are safety concerns.

(Applause.)

DR. HOGANS: Beth Hogans. I noted that the package insert says acute sinusitis. And I think that in light of the fact that some of the other conditions specify bacterial -- I mean, for the infectious disease expert it's obvious. But I think because so many general practitioners and mid-level providers are providing this, I think that the

current package insert doesn't provide sufficient guidance.

I think that the evidence that we were presented with today indicates that people are not sufficiently aware of the guidelines, that this is a second tier agent. Consideration should be given to REMS, but the package insert should be revised, certainly, to reflect that it must be a bacterial sinusitis. And it would be more helpful if it provided the information about it being a second-tier agent.

(Applause.)

DR. FLOYD: I voted no because of a lack of evidence of a treatment effect for this indication and what I think are pretty convincing evidence of safety risks. I don't think that the risk/benefit profile can be improved through REMS or labeling. So my recommendation is to remove this indication entirely. I do, however, think that changes in labeling and potentially REMS are needed for some of the other indications.

(Applause.)

DR. CHOUDHRY: Niteesh Choudhry. I voted no as well, for most of the reasons that have been stated. I have three specific recommendations to be considered.

First, that the label should specifically indicate that this is second-line therapy.

Second, that in the label for this indication, we clarify the idea of what "severe treatment" really means -- or "severe disease" really means. And what I mean by that is duration or failure of other treatment. Part of that is implicit in the idea of second-line. But clearly, there's a wide overuse of antibiotics in general in this class.

The third, following up on a comment I made before is I think given the consolations of these nonspecific but clearly debilitating and disabling symptoms that we don't quite understand, that we need to do something. And I would offer a requirement for a postmarketing study to better

evaluate these.

(Applause.)

CAPT PARISE: Excuse me one second.

Dr. Floyd, you, I think, didn't state your name into the record and we really need that. Could you do that?

DR. FLOYD: Oh, my apologies. James Floyd, the previous response.

CAPT PARISE: Thank you.

MS. PHILLIPS: I'm Marjorie Shaw Phillips. I voted no, and had some of the same concerns as Dr. Floyd did. Business as usual is not acceptable, and I have some particular concerns in the case of this indication because the risk/benefit ratio is much different in otherwise healthy adults than in somebody that's more seriously ill, such as the other indication, the COPD indication.

Some of my comments will also go across all three indications and beyond because the speakers sharing their stories today made clear that there is a lot of use outside of all the labeled indications.

So I think misuse of these products needs to be addressed through a med guide, through a REMS, through education of all types.

So the med guide needs to be reformatted in the FDA's new format that is much more user- and consumer-friendly than some of the older versions to really highlight recognition of these fluoroquinolone-associated toxicities on the first page in language that the lay person can understand.

Education needs to be for both providers to identify the patients who would most benefit, who should be getting these medications, from those where the risks exceed the benefit; but also to make it easier for them to identify these toxic reactions when a patient presents with symptoms.

(Applause.)

MS. PHILLIPS: Furthermore, I think we need patient education both to recognize when they should contact a provider, stop the drug immediately if that occurs, but also to address patient and family expectations when they go to a provider because

we still have so many that go expecting that prescription, and are very reluctant to take their practitioner's advice when it's a watch and wait approach or a nonpharmacological approach. So that's an important part of the education and management plan as well.

(Applause.)

CAPT PARISE: Excuse me. We're just going to ask the audience, if you could just hold your applause till the end just for the sake of time. But we will give you an opportunity.

DR. BESCO: Kelly Besco, for the record. I also voted for the same reasons as the other panel members. And many of my comments can also be lateralized to the additional questions.

I do want to say that I do think that FQAD appears to be a legitimate, unrecognized condition that requires case definition and study. Depending on the outcome of this evaluation, there should be a warning added to the labeling to warn providers of FQAD symptoms and potential side effects.

I believe that the labeling could be enhanced to include additional mitigation strategies, especially in the outpatient setting, to ensure providers are using these medications appropriately and that patients are well-informed about the risks associated with fluoroquinolones because relying on labeling alone is too passive.

DR. CORBETT: Amanda Corbett, and I also voted no, for also many of the same reasons that have already been stated. But mostly I feel like we have to do something more than just let this continue. I think this is absolutely a real phenomenon. We cannot discount these patients that are here and the hundreds and thousands of other patients that we know this is happening.

I don't know that we exactly know what this all means, but I think that's going to take some time to really figure that out. And in the meantime, I think we have to let prescribers understand the severity, other than the people that are in this room and those that actually pay

attention.

So that was my main reasons for voting here, and then also carrying forward to the next two indications as well.

DR. SCHEETZ: Hi. Marc Scheetz. I voted no as well. First I want to say, as practitioners, we always have the utmost sympathy for anybody that has an adverse drug event, and the reason that we got into healthcare is to try to improve public health. That said, there's always a balance here.

I think the fluoroquinolones are an important drug in our armamentarium, so I don't want to throw the baby out with the bath water. But I think we definitely do need a much better understanding of the risk/benefit with these drugs.

We were asked to look at three primary adverse drug reactions, those being tendinopathies or things related to tendinopathies, cardiac arrhythmias, and peripheral neuropathies. Statistically, it seemed most probable that tendinopathies were the most well-justified, but

there were definitely pretty reasonable cases for the other syndromes as well.

We were also presented with FQAD, a syndrome that -- at least this is the first time I have heard of this syndrome. I think I definitely think we need more research on FQAD. I think that the current clinical predictors that we have suggested, such as patients being older, patients potentially taking things like steroids, and patients being transplant patients, are not sufficient to describe those who might get FQAD.

Now, FQAD could encompass many different syndromes. But the largest single syndrome in FQAD was musculoskeletal concerns. And so I think that our predictors for musculoskeletal concerns for some reason do not seem to hold for FQAD. So I think we need more research there.

Finally, the other side of that coin, I think we still do need antibiotics, and I think we still need to provide clinicians with the options to use second-line treatments when they are appropriate.

We've seen plenty of data today to suggest that they are not being used appropriately, and I think that the labeling could help with this.

I'm not an expert in things such as REMS or other strategies to help clinicians make the right decisions, but I think we definitely need more research in that realm.

DR. GERHARD: Tobias Gerhard. I also voted no. I think the adverse effects that were discussed today are reasonably rare, although there are a lot of questions about the exact incidence, but is underscored by the remarkable testimony that we heard today as well as the unusually high direct adverse event reporting rates, highly disabling and persistent.

So I think there are two implications for me, at least, to avoid quinolones in situations where the benefit is either not established or minimal in size, and reduce inappropriate first-line use, and, probably most importantly, clearly communicate these risks to patients and providers, so including the

events or the concerns discussed today in the black box, consider additional forms of information and education to both patients and providers.

I think it was very apparent in the testimonials today that the current labeling does not communicate these risks clearly and that most, if not all, of the patients that made statements today did not knowingly take on these risks.

As to the question of FQAD as a syndrome, I think the evidence at this point is, from FAERS, not supported yet by epidemiological data, and therefore quite weak. I think, however, that the distinction of whether there is this syndrome or not is somewhat secondary at this point to communicating that there are risks for several severe, disabling, and permanent adverse effects that may appear individually or in combination. And then in future work, we can address to what extent there really is a syndrome that can be clearly described.

One last comment. The potential psychiatric side effects were not discussed at today's meeting,

but it seems clearly that they deserve some attention in the future. And for this specific indication of ABS, I don't see evidence for meaningful benefit, and thus would recommend removing the indication completely.

DR. WINTERSTEIN: Almut Winterstein. I voted no. Risk/benefit here is mediated by the fact that current guidelines are not necessarily followed. The guidelines seem to acknowledge an unfavorable risk/benefit ratio already, but we have seen evidence that quinolones are still heavily prescribed.

There is sufficient evidence to support treatment of ABS as well as the other two indications, but treatment should only use quinolones if first-line agents have failed or are contraindicated. However, quinolones should be available as second choice.

Given the evidence of risk, both providers and patients need to have sufficient information to weigh risk/benefit. We have seen that the

medication guide does not assure this because one is in place. So based on this, I would suggest that a communication plan would be implemented. So that would be the level 2 REMS, as we had the description earlier, that would require documentation that both patients and providers have received information of risk.

I suggest further that the labeled indication spells out that quinolones are indicated if first-line agents have failed or are contraindicated.

CAPT PARISE: Monica Parise. I also voted no. As far as the indication, I actually do think there is a role for these antibiotics in severe cases of sinusitis. I think part of the problem is that the recommendations that are out there, as others have said, are not being followed, and it's not all going to that more severe spectrum. I think others have had good ideas about REMS and education, and I don't need to repeat that.

Two of the things that bothered me that I

feel should somehow be addressed in letting people know are, one, that the label doesn't -- even though we don't know about the frequency of this or still have questions about the FQADs, I really think something should be said about this constellation in the label.

Then my last part of comments really goes to what needs better studied. I think clearly the FQAD does need better studied. I was involved in a multi-system syndrome, study of a multi-system syndrome that had never been described before. And I think some of what was stated earlier about you have a case definition and you look for databases, I think some encouragement about continuing -- I know it's difficult being creative about it. We, for example, went to a large HMO that had electronic medical records that made it possible. I just encourage the agency to continue to try to look into that.

I think my last comment was on peripheral neuropathy. And these comments on the safety side

really apply for me on really all these indications as far as safety. I was really struck by the poor information that was available on neuropathy; it was only one trial. And to me, persistent neuropathy that may be irreversible is really a big deal, and I think some way to be able to better study that we should all think about.

DR. LO RE: My name is Vincent Lo Re. I voted no, for many of the reasons that have already been stated. I had concerns about the way that the medication was being used, and particularly thought that the label should specify more clearly that this should be a second-line drug, and particularly for the indication noted here, that it would be for severe acute bacterial sinusitis.

From the standpoint of safety, I was struck by the dearth of data on peripheral neuropathy and the psychiatric adverse events, which were discussed certainly by the public comments. And I think that we need better validation of these outcomes in pharmacoepidemiologic data sources to allow good

epidemiology to be conducted.

I recognize the challenges that are inherent, but I think that certainly if we can validate these individual diagnoses within data sources, they could potentially be studied more for the purposes of understanding FQAD and its syndrome.

MS. SCHWARTZOTT: My name is Jennifer Schwartzott. I also voted no. In the case of the acute bacterial sinusitis, the risks outweigh the small benefits.

I also feel that the black box warnings should be expanded to include other severe effects of the medications. And they also need to be more obvious, with large print and colored highlighting or something that indicates this is very important. You need to pay attention.

When I was prescribed cipro a little over a month ago, I was handed something from Walgreens that looked the same as every other printout I've ever gotten, nothing indicating that it should be that severe. The labeling should raise an alarm

with the patients and also for the medical professionals and the pharmacists.

I also think further studies should be continued to establish safety for all, including those at risk, and to include literature reviews, patient reports with no exclusions -- I would be one of the people excluded -- and reports from specialists of specific disorders.

They should be talking to doctors that treat mitochondrial disease, that treat myasthenia gravis, and get their input along with from the patients, with natural history studies, not just like a clinical trial.

DR. ANDREWS: I'm Ellen Andrews, and I voted no because of the same reasons that everyone's talked about, the questions about effectiveness and the serious safety concerns.

I'm reluctant to go as far as saying that we remove it as a tool because it is an antibiotic, however flawed it is. And also, this has come before in this committee, But when we remove it as

an indication, we also remove the opportunity to educate people. And if it does continue to be used off-label, we lose the ability to have those red flags.

Having said that, we need some big red flags. We need to strengthen the language about disability. This should be used as a last resort, with confirmed bacterial infections, I would suggest only in hospitalized patients that have a really severe infection. That's where the best, most likely to be effective research was.

You definitely need to get to informed consent. That includes at least a level 2 REMS, and really get to a point where people understand the seriousness of the disability because the black box that I read didn't look all that serious to me.

I would just say that I do understand the concerns around patient reports that drive a lot of the discussion about the disability, and that's why it seems diffuse, maybe.

However, this is all full of weak data and

weak information, and I think that that is one of the best things that the FDA does, is to get information directly from patients about their conditions. And I think that's really important, really vital information, and it shouldn't be minimized.

I actually am grateful to the patient groups and the press for bringing this to awareness. They seem to be the only ones working on that. And far from improving and expanding the maybe biasing reporting, I think they're really providing a public service in letting people know about this.

DR. BADEN: Lindsey Baden. I voted no. However, I think the vote has a lot to do with how the question was asked and worded. I think that we have to remember that untreated serious infection has serious morbidity.

We're all struck by how these agents appear to be used, and the current way healthcare is delivered, and the burden on the patient and the frontline provider in delivering care. And that's

not an excuse for delivering substandard care, but the risk/benefit, on the benefit side, one needs to remember that untreated infection has substantial morbidity.

If I'm reading the various guidelines that were provided from the major societies, all of them -- ATS, IDSA, Urology, ACOG -- favored the accessing of fluoroquinolones as part of treatment for the respective conditions in their space. And I think that given the available options, we need to be very careful in minimizing what is available to treat active infection where we have limited options.

Having said that, there are aspects of how these agents are used that could enrich the benefit. And that gets to the question I asked before about thinking about strengthening the label. And I am not a label expert and do not know what can or cannot go into a label.

But one could imagine, and this was alluded to in some of the talks about where benefit may have

been better in prior studies for ABS, where one actually uses the criteria that societies have put forward and have that as part of the threshold in the label, saying, this is the clinical phenotype that has a higher benefit, trying to minimize the unwanted use in every runny nose.

If there's some way that the label can help the practitioner enrich and educate to where benefit is more likely to be, i.e., a bacterial infection that is progressing as opposed to a viral infection that's running its course.

I think that's one side of the equation that can potentially be addressed. And I think the role of fluoroquinolones in that setting, not as first line but being available to practitioners as second or third line, is quite important, and we need to think carefully if we want to remove that access because there are consequences to untreated infection.

On the other side, the issue of risk. I think one needs to be careful about creating new

acronyms. FQAD, I still am not sure I fully understand it. I think that inserting it into a label quickly or into common parlance quickly comes with a risk of lots of confusion. The concept that there are constellations of side effects that may be delayed and prolonged and uncommon or rare but severe, is quite important.

But to some degree that is in the label, on the black box warning for tendinopathy. Part of the front page also has the warning of many things -- bacterial resistance, C. dif -- as well as neuropathy and QTc. So there are data on the front of the label that alert practitioners to these issues.

I think we have to be careful about over-concluding the cause and effect with peripheral neuropathy, given the state of the data. And I think there is a clear unmet need of understanding the real risks here.

Is it better to create an integrated FQAD concept, or is it better to look at each of the side

effects, which may have different mechanisms, and therefore may not be combined easily, each of them individually or those that are related mechanistically, and there distill out a better side effect profile versus creating a catchall that has some convenience and tries to address an issue of overlap, but may confound the indication and therefore the mechanism, and therefore confuse an ability to mitigate.

So I am not yet persuaded that integrating the side effects is wiser than looking at the side effects, each for what they are, and then calling for and pushing for further confirmatory work to better delineate, define, and understand.

What that could mean in the label is the front page has these highlighted, but deeper in the label can actually be the data available that's being discussed so that people can understand the strength of where these observations are coming from.

All of the data we've discussed have

strengths and weaknesses, and enabling the community to understand them I think is very important. And whether REMS or other communicating vehicles is the right way to educate, I think there are different ways. But largely what we're all talk about is how to improve communication to provide our end patient so they understand this risk/benefit balance.

DR. DASKALAKIS: This is Demetre Daskalakis. I also voted no. And many comments have been made that I agree with, primarily around the concept that from the perspective of the label, an overlap that includes some commentary on severity for bacterial sinusitis is likely really important. I think that it will create some guidance for providers and will reinforce what the guidelines do say.

I also want to talk a little bit about the concept of the REMS. I feel like this is a very important opportunity because just looking at the REMS that was recently designed for long-acting opioids, a very similar REMS could be designed around the conversation of judicious use of

antibiotics.

So rather than just necessarily focusing specifically on just this issue with a fluoroquinolone, I think it's a global issue because the commentary of using an atom bomb to kill a fly is a very good one.

When you do use these drugs, they're very significant and very important in severe infection. And it is shocking that a sniffle potentially could be treated with the same thing that you would treat nosocomial pneumonia with in the hospital, with great effect.

So I think it's a chance for an educational process that we have not had. And this drug is not being used judiciously, not just levo and cipro, et cetera, but antibiotics in general. So this is an opportunity for these indications to make it clear that there should be judicious use of antibiotics.

I also think that from the perspective of fluoroquinolone-associated disability, this

phenomenon that's coalesced a bit, this sounds like a great opportunity for a case control type study that could actually include some fabulous basic science looking at some of the origins of why people may be having the neuropathy, deeper studies into mitochondrial dysfunction.

So I feel that it seemed as if the community has come forward with a very good group of individuals who've identified themselves as potentially people who are experiencing this phenomenon. So it's a good way to differentiate whether this is phenomenon in itself or if it is just a conglomeration of multiple phenomena, and if there is a biological answer that either lets one, two, or three of these things hang together.

So I think ultimately my vote for a no is not to limit the use of valuable drugs, but to use them more judiciously.

DR. ARRIETA: My name is Antonio Arrieta. I voted no. The rationale behind that vote was stated on the fact that I believe emphatically that there

aren't any antibiotics that are safe. They all have risks. The more we use them, the more we'll have to face those risks.

Some have more serious risks than others, but for example, penicillin, there is an expected number of people who are going to die in this country from anaphylaxis or not sitting here and talking about it. The issue is how much benefit am I going to get from this agent. When there is an entity with such a large placebo phenomenon, almost every agent will look very good.

Furthermore, if we look strictly at the microbiology of these infections when they are bacterial, they are going to be pneumococcus, Haemophilus influenza, or Moraxella catarrhalis, occasionally others.

There are very little, if any, advantages of the quinolones over the beta-lactam antibiotics or the beta-lactam and beta-lactam combinations, which have a much greater safety profile.

I think all of us have stated that these are

important drugs. I would hate to see these drugs go away and I couldn't treat my CF patients with sinusitis, or patients who are highly likely to have highly beta-lactam-resistant pneumococcus, or those who have anaphylaxis to penicillin.

So I think it is important for these agents to be around. But the use of it not only has to be left as a second-line agent, it has to be actively discouraged due to its safety/benefit ratio as well as other issues of resistance that are beyond the scope of this meeting. Thank you.

DR. HONEGGER: Jonathan Honegger. I also voted no, for many of the same reasons that were discussed. I have some reluctance to delve into too much detail in the labeling on how to use an antibiotic compared to other antibiotics for a particular indication, thinking that it might be best left to societies that are making practice guidelines.

For instance, bacterial sinusitis where there are multiple other options and there does seem to be

a safety issue with fluoroquinolones in excess of the other choices even though all of them do have their own risks, I think in this case it's reasonably to go ahead and get more specific and suggest its use as a second-line therapy in the labeling.

Also, I learned a lot today, and I feel that the REMS effort definitely needs to be focused on patients and providers. I agree with everyone that there's need for more study of FQAD and the individual entities themselves and particular risk factors.

I don't know if this is true. It looks like the FQAD has an over-representation of respiratory infections compared to the utilization of fluoroquinolones in respiratory infections compared to UTIs. So it may be important to control for the indications as well. Thank you.

DR. SCHMID: I guess I'm last. Chris Schmid. I also voted no. The basic reason I voted no was clearly the labeling must be inadequate if it's not

being used correctly. There must be better ways of doing the labeling.

I was struck by a couple things. One is that there are a lot of guidelines out there from specialty societies, and yet 70 percent of the prescriptions are being made by non-specialists.

So I'm wondering how much the non-specialists are actually reading these guidelines, and I'm wondering whether, in the recertification that physicians have to go through every so often, that somehow, into that process, we could build some kind of education for things like this.

I'm also struck by the lack of data. As a statistician, we can't come up with a model unless there's some data out there. And various members of the committee have suggested ways of getting data, and I think that's really important.

Another point that struck me during the day is I actually was the statistician on a couple of the Lyme disease trials, in particular the one that looked at chronic Lyme disease. And there's been a

lot of push-back on that that the infectious disease society has dealt with for years.

One of the things that is very clear there is that there are a lot of people who suffer from a constellation of symptoms, which they call chronic Lyme, and that they claim has affected them after they were infected by the Lyme spirochete. But the other interesting thing is that all of these people want to use more antibiotics. And I'm wondering whether some of these other syndromes that we have could be caused by other collections of drugs that people are taking.

So it suggests to me that maybe we want to do something a little bit more widespread in terms of looking at the effects of medications like this, which clearly are very beneficial in some cases but also can be toxic in others.

CAPT PARISE: Thank you. We're now going to go to question number 2.

(Applause.)

CAPT PARISE: Do the benefits and risks of

the systemic fluoroquinolone antibacterial drugs support the current labeled indication for the treatment of acute bacterial exacerbation of chronic bronchitis in patients who have chronic obstructive pulmonary disease, ABECB COPD?

Following your vote, provide specific recommendations, if any, concerning the indications for treatment of ABECB and safety information, including the constellation of adverse reactions that were characterized as a fluoroquinolone-associated disability or FQAD.

Just one other note. After the vote, whenever we go around, if your recommendations are the same on any certain topics, it's okay. You can just state that for the record but don't need to repeat them, just in the sake of time.

(Vote taken.)

CAPT PARISE: Everyone has voted. The vote is now complete.

LCDR SHEPHERD: For the record, the vote is 2 yes, 18 no, 1 abstain.

CAPT PARISE: We will start down here again. If you could state your name and your vote and reasons, and anything else you wanted to say regarding the A part of the question.

DR. STAUD: My name is Roland Staud. I voted yes due to the fact that the indication that is on the label seemed to be appropriate as a second-line agent for severe infections.

There was some evidence of effectiveness that was presented. And I think the recommendation that I made in terms of risk mitigation before would be helpful under these circumstances, too.

DR. RUSSELL: Russell, San Antonio. I voted no. And the reason I voted no is that I think the label doesn't put the onus enough on physicians to document that there is a bacterial infection. And I think the same is true for the acute bacterial sinusitis.

The problem is that chronic bronchitis can occur with recurrent aspiration of gastric acid with reflux, for example, or with inhalant allergy. And

I think it takes some effort to distinguish that from bacterial bronchitis. Those things, I think, really need to be identified, and not using an antibiotic when it's not needed for a bacterial infection.

I think one way of reducing the apparent efficacy of a medication that really does do its job is that the diagnosis is wrong. And if we're not treating bacterial infection when we use an antibiotic, then the patient is not going to have the efficacy that would be true if the diagnosis were correct.

DR. VITIELLO: Ben Vitiello. I voted yes because I thought there was evidence of efficacy for this population that suffer from chronic obstructive pulmonary disease. And therefore, I thought that the fluoroquinolone antibiotic would be appropriate as second line of treatment in case of acute bacterial bronchitis.

DR. HOGANS: I voted no.

CAPT PARISE: Please state your name for the

record.

DR. HOGANS: Oh. My name is Beth Hogans. I wanted to sound a note of caution about the newly defined syndrome that we were presented with here today.

I think that the stories and the testimony of the patients and patient advocates that presented here today were very helpful, and I think deepened the appreciation of myself and other committee members. It's clear that something is going on. The syndrome, when it occurs, has a clearly profound and often devastating effect on the person's life.

Being trained in biostatistics when I did my masters degree, I'm very concerned here about ascertainment bias. And I think it's very clear from the evidence that was presented that there has been an active social media campaign.

Frankly, reading through the 679 pages for background material that were provided to us, many of the case reports sounded like almost carbon copies. And whether they're carbon copies because

there is a true syndrome, or whether they're carbon copies because people are sharing information and somehow that shapes, then, the presentation, I think really cannot be established by an open internet kind of research methodology.

It doesn't take away from the suffering that has occurred, but I think that it could be a rare but serious complication, and that remains to be defined. So I would say that the labeling could appropriately be revised to reflect that there is a rare but potentially serious and disabling syndrome, but at this point, it is poorly defined.

DR. FLOYD: I voted no. I think the label should reflect the indication for moderate and severe COPD only -- oh, sorry, it's James Floyd -- and not mild. I think we saw clear evidence of modification of the effect by severity.

I would actually define this operationally by the criteria for enrollment in the trials where we saw the largest treatment effect, which was hospitalization, even though there's been

disagreement about that.

I also want to make the other comment that removing an indication for a disease or a subset doesn't mean that the drug is off the market or no longer available. It means that it's not possible to market for that indication. And I think that's an important distinction.

I've reserved my comments about safety for this second round, so I'll make them now. I think the evidence for cardiovascular risks were actually substantial. My interpretation of the limitations mirrored the FDA's, but I think the conclusion I drew is a little bit different.

I think the evidence of causality was actually more convincing than for tendinopathy. We had several well-designed epidemiologic studies with findings that replicated across different settings. And one thing that wasn't mentioned was there was actually a dose-response in terms of the QT-prolonging effect of the antibiotics.

For example, the increase in risk was

largest for moxifloxacin, then levofloxacin, then ciprofloxacin, which mimics the QT-prolonging effects of these drugs, which I found QT convincing biologically. So I think this belongs in a boxed warning along with tendinopathy.

I agree with comments made about FQAD. I don't understand it well. I think that the suggestion to do a case control study and actually obtain deep phenotyping and information on genomics and other assays is a great idea to understand this further. And although I don't have a clear sense of whether it's a causal association yet, I think there's enough concern that some information belongs in the label so physicians can begin to recognize it, that patients have this constellation of symptoms, and possibly discontinue therapy.

I also agree for calls for a REMS, including a medication guide, a "Dear Doctor" letter, with or without some elements to assure safe use.

DR. CHOUDHRY: Niteesh Choudhry. I voted no. I'm going to agree once again with the idea that the

label should be modified to indicate this is second line and reserved for patients with moderate to severe exacerbation, again, to be defined. But certainly based on the constellation of symptoms, the Anthonisen criteria are good, for example, independent of hospitalization just based on symptoms themselves.

The one thing that's confusing in the current label is that, for example, reading the levofloxacin label, it says, "Levaquin is indicated for the treatment of acute bacterial exacerbation of chronic bronchitis due to Methicillin-resistant Staph. aureus, Strep. pneumo," so on and so forth. So it specifies specific microbiology, but in fact, the data for the trials comes in the absence of confirmation, which is almost always the case. So we use these drugs empirically; certainly I do as a hospitalist.

So the label, in fact, might add -- the specificity of the microbiology in the label might add confusion. So I would argue that that should

probably be removed as well.

MS. PHILLIPS: Marjorie Shaw Phillips. I voted no, and I think there have already been enough comments about the difference between how it should be used in a more narrowly defined group of patients versus the expanded labeling.

One additional comment and thoughts related to prospective surveillance, would it be possible to tie the med guide to alerting patients and providers to a prospective registry that would enroll individuals who had a constellation of symptoms or these unexpected symptoms, similar to what the study in California is trying to do now with the internet recruiting.

I think it's important that whatever is done is more global, and that the innovator firms don't have to bear the burden of a product that's on the market and used 98 percent of the time as a generic. But I think we as a public and as a country need to have an answer to this question.

DR. BESCO: For the record, Kelly Besco, and

I concur with all the remarks thus far for this particular question, and again, would lean on my previous comments; and also heavily recommend that we do define better what the difference is between the moderate and severe infection for this category.

DR. CORBETT: Amanda Corbett, and I did vote no. Just a couple of things I wanted to mention that I didn't mention before that I just thought about.

Yes, I don't think the indication is worded appropriately, but I think we need to think really, really, really hard -- the FDA needs to think really hard -- about how this can be worded so patients do get this medication. And if it is not in the package insert labeled indication, there is a huge risk that patients may not get this drug paid for.

I spend, as a pharmacist, numerous hours trying to get patients medications that I know need them. And when I say hours, I mean hours of time trying to get medications paid for by multiple third party payers, whether they're federal funded or

private funded.

So I think it's very, very critical that this information is very clear so that the patients that do need them are actually getting them. So that's also kind of the flip side, but I think that's a critical piece.

DR. SCHEETZ: Mark Scheetz. I voted no. We've already talked about the safety so I won't recount that. In terms of efficacy, I do think that efficacy does depend on severity of disease, and I think the package label could better reflect that, specifically something more than categorical, moderate, severe; perhaps more quantitative values, something like what is a patient's FEV1, something like that, would be very helpful.

I also think that defining it by whether or not a patient is hospitalized is probably not the way to go.

DR. GERHARD: Tobias Gerhard. I also voted no. All my previous comments regarding the safety apply. I think for this indication, the label

should reflect the limitation to moderate and severe cases. Again, that needs to be operationally defined, not necessarily by hospitalization. The label also should emphasize the second-line status of the treatment.

DR. WINTERSTEIN: Almut Winterstein. I voted no, for the exact same reason that Dr. Gerhard just stated.

CAPT PARISE: Monica Parise. I voted no. I don't think I have anything to add to what was just recently said about the indication in what subgroup of patients with the exacerbation to use it. And my comments on safety I really stated before, and they're really the same for this indication, too.

DR. LO RE: My name is Vincent Lo Re. I voted no. Regarding the efficacy, I thought there was good data on efficacy regarding moderate and severe. I particularly was intrigued by the data about prolonging time to recurrence, and I already made comments about the risk.

MS. SCHWARTZOTT: My name is Jennifer

Schwartzott, and I also voted no. The treatment should only be used to treat moderate to severe cases, and only when other less risky options have been considered.

The medications need to stay on the market. People like me that have serious allergic reactions to other non-FQ antibiotics need to have this option. But we have to label these medications so that the people clearly understand, that the doctors clearly understand, what the risks are. And then we as patients can make the determination if it's worth the risk.

DR. ANDREWS: Ellen Andrews. I voted no again, for mostly the same reasons. I do want to respond to the concern -- I get it -- about identifying a new disability very specifically and putting it in a warning. But I do think it's really important to say that the side effects could be so severe that they could cause disability. I think that's important for people to understand that.

DR. BADEN: Lindsey Baden. I voted no. I

want to be clear that for 1 and 2, I think there is efficacy even though I voted no. My no has more to do with improving the label to enhance clinical phenotype characterization and therefore enrich the population who will benefit.

This actually impacts not just fluoroquinolones for treating ABE COPD but any antibiotic used in this space. This is really a comment. My comment has to do with when we treat bacterial infection with any agent, we need to deal with the issue of do they actually have the condition that we're treating.

I think it's a more generic issue that is highlighted because we are having this conversation now. And it speaks to antibiotic stewardship, and in the outpatient arena, that is quite anemic. And this might be a way to help shine a light on it.

DR. DASKALAKIS: This is Demetre Daskalakis. I also voted no, and just for brevity, based on the same concept, that there needs to be a comment on severity of disease for appropriateness of use for

fluoroquinolones for the indication of an acute exacerbation in COPD.

I also really wanted to say I like the idea that Ellen brought up, Ellen Andrews, the idea that rather than creating a new syndrome, say that there is a risk of a constellation of symptoms that can lead to disability, which then allows some time to learn more about these disabilities to see if they hang together as a syndrome. I think that that's a really smart idea.

DR. ARRIETA: I abstained. And the main reason for which I abstained is because I'm a pediatrician, and I don't see COPD. I don't think I could have such an authoritative opinion in that regard.

Having said that, from the microbiological point of view and from the studies, at any stage of the disease, from mild, moderate, or severe, the quinolones have not shown superiority to a comparator, usually a beta-lactam, beta-lactam as combination agent. But I was very struck by the

comment about increased recurrences and risk of mortality.

So since I am a humble, small-town pediatrician, I didn't think I could make a statement against that. So I had to abstain. Oh. Antonio Arrieta.

DR. HONEGGER: Jonathan Honegger. I too am a pediatrician, but I did vote no, with some trepidation. But I did have the concern that the same risk is there, potentially, and that there could be alterations to the label to focus on the subgroup of patients that we think it's most appropriate for.

DR. SCHMID: Chris Schmid. I'm a statistician, but I did actually vote, even though I've never seen a patient in my life.

(Laughter.)

DR. SCHMID: I voted no. I think it's pretty clear that what's needed here is education. And I'm wondering, since we're talking about quantifying what's on the label, one thing that you could put on

is to give these drugs, you need to have a positive culture, and if you don't have a positive culture, don't give the drug. That may not be practical, but it's something that could be considered.

The other thing is, there are a lot of medications. I think people think of antibiotics as magic drugs, and they just go and ask for them. And I think that's why they're over-prescribed. But there's a lot of other drugs which people have thought were magic drugs which eventually, either on the positive or a negative side, were not used as frequently.

Things like tobacco, estrogen receptors, vaccines, have all seen less use than they used to when people learned more about them. And sometimes that change in habit is good, and sometimes it's bad. But I think it does show that education can work.

CAPT PARISE: Okay. We're going to move on to the third and final question. Do the benefits and risks of the systemic fluoroquinolone

antibacterial drugs support the current label indication for the treatment of uncomplicated urinary tract infection, uUTI?

Following your vote, provide specific recommendations, if any, concerning the indications for treatment of uncomplicated UTI and safety information, including the constellation of adverse reactions that were characterized as FQAD.

The vote's open.

(Vote taken.)

CAPT PARISE: Everyone has voted. The vote is now complete.

LCDR SHEPHERD: For the record, the vote is 1 yes, 20 no, zero abstain.

CAPT PARISE: Thank you.

So we're going to start at this side, with Dr. Schmid. We'll go around, following the same format. State your name, what you voted, if you want to say why, and any additional recommendations. We're going to try to just be as brief as we can. Planes are leaving, so my goal is to get all the

information to the FDA, but yet we try to finish on time. Thank you.

DR. SCHMID: This is Chris Schmid. I voted no. I think everything's been said, so I won't say anything more.

DR. HONEGGER: Jonathan Honegger. I voted no. Again, I think there needs to be some indication that this is second-line. And in pediatrics, urine culture is still important for a diagnosis and treatment of UTI. Societies, given these concerns, may need to look at the use of culture more in adult patients.

DR. ARRIETA: I voted no. I think I know a little bit about infections, even though I'm a pediatrician. I think there are means to ascertain the etiology of the infection. I think there are means to postpone treatment or at least perhaps shorten the empiric treatment.

I expect beta-lactams and Bactrim, or trimethoprim-sulfamethoxazole, to be effective in urine in the bladder as it concentrates so highly.

Just a brief comment from safety point of view, since I did not do that earlier to be short. There are side effects that are infrequent. If we use a drug 20 million times, the infrequent side effects add up.

So if there are 1,000 very rare phenomena or in a rate of 4 per million, which I did on my simple little math here, if we use 20 million and there is only 10 percent of the total, we're going to be seeing 160 or more very rare cases per year. So very rare side effects will be magnified when we abuse an antibiotic millions of times.

CAPT PARISE: Please state your name for the record.

DR. ARRIETA: Antonio Arrieta.

DR. DASKALAKIS: This is Demetre Daskalakis. I voted no, for many of the same reasons as I did for the other two questions. I also do think that from the perspective of guidelines, this is the indication for which fluoroquinolones seem to be the most misused.

I just want to say that that is probably the strongest indication for me that we need to look at the label to make a change because it's not just about the side effects, but also about the fact that we're exposing people to these drugs that we really need to save for other indications as well.

DR. BADEN: Lindsey Baden. I voted no. My previous comments apply. One needs to think carefully about the burden on the patients who need care as we sort out ways to strengthen the label to make sure we get it right and minimize overuse.

DR. ANDREWS: Ellen Andrews. I voted no because we need to really dial back the times that this medication is used; 33 million scrips is far too many in America.

I understand the concern about not letting somebody in pain leave your office with no treatment. But I was really intrigued by the one study that found that ibuprofen is more effective at that. So I think that deserves more thought.

MS. SCHWARTZOTT: My name is Jennifer

Schwartzott, and I voted no, for many of the reasons for the other applications. I also want to stress I feel it's very important to expand the boxed warning to include the increased risk to those with tendon disorders, especially of myasthenia gravis, which they've discussed, and also RA, and also for those that exercise strenuously. That should be higher up on the level of where it is now. Thank you.

DR. LO RE: My name is Vincent Lo Re. I voted no. I mentioned all the issues of risk previously. And I thought there was efficacy shown here, but I felt like there needs to be changes to the label to reflect the inappropriate antimicrobial prescribing.

CAPT PARISE: Monica Parise. I voted no. I think on the efficacy side, I don't really have anything to add to what's already been stated to better adherence to what the guidelines are. And I've stated my safety concerns already.

DR. WINTERSTEIN: Almut Winterstein. I voted no. The recommendations I made in the first round

apply here as well. I think that really needs a strong risk communication, REMS.

DR. GERHARD: Tobias Gerhard. I voted no. I think this is really the most critical indication and reflects over 90 percent of quinolone use in the indications that we were asked to consider today. So the second-line status of the quinolones has to be significantly emphasized to really reduce the risk on the population level.

DR. SCHEETZ: Marc Scheetz. I voted no. I think there is efficacy here, and that's been shown with microbiologic benefit and then combined with clinical benefit as well. However, I think the comment specifically from the FDA presentation of the clinical course of untreated uncomplicated urinary tract infection has not been well-characterized. It's very important.

I think that we should commission studies to find out what happens to this 30 percent of people that would have a bacteria that would not be treated. What happens? Are they better off

receiving treatment or better off not receiving treatment?

DR. CORBETT: Amanda Corbett. I also voted no. Not really anything additional than what has already been mentioned.

DR. BESCO: Kelly Besco. I voted no, for reasons that I previously stated. Thank you.

MS. PHILLIPS: Marjorie Shaw Phillips. I agree with the previous respondents, and my earlier comments about safety and monitoring still apply.

CAPT PARISE: And your vote? Your vote?

MS. PHILLIPS: I voted no.

DR. CHOUDHRY: Niteesh Choudhry. I voted no, for the same reasons that have been stated.

DR. FLOYD: James Floyd. I voted no. I think the indication should stand, but I think the label should reflect that fluoroquinolones should be used when other available effective treatments cannot be used. And reasons could be resistance, treatment failure, or drug allergies.

DR. HOGANS: Beth Hogans. I voted no. I

concurred that these agents should be reserved for -- I neglected to mention the moderate to severe COPD. But in the case of UTI, it would be a second-line agent.

I wanted to add a couple very brief comments. One is regarding the black box warning for tendinitis. I think, given the evidence that we heard today, that strenuous activity could reasonably be ordered added to the advanced age, steroids, et cetera.

Then I wanted to comment about peripheral neuropathy because as I noted earlier, I think we had just one high-quality study that was looked at in detail. But it was a very powerful study. It looked at a large number of people. It found a substantive number of patients exposed to fluoroquinolones did present with peripheral neuropathy.

I think the current warning language, which says, "Rare cases" -- I looked a lot for the latest package insert, which would be nice if the materials

could include the latest package insert just so we can turn to it rapidly in the future -- but the one I found says, "Rare cases of sensory," et cetera, et cetera. And in fact, it's not isolated to rare cases at this point. I think we could say that it's a recognizable phenomenon. I don't think that the data supports it being called rare.

Then I wanted to comment that the language says, "resulting in paresthesias, hypoesthesias, dysesthesias." I suspect I might be one of two people in the room that could offer correct formal definitions for those terms. They are terms recognized by the International Association for the Study of Pain, but I think the language could be clearer for the general practitioner. Thank you.

DR. VITIELLO: Ben Vitiello. I voted yes because I voted on the indication, and I think there are data that support that fluoroquinolones are effective in the treatment of uncomplicated urinary tract infection.

I agree that the label should be amended,

indicating that it should be a second-line treatment, and also there should be additional warning about peripheral neuropathy and also QT prolongation. Thank you.

DR. RUSSELL: Russell, San Antonio. I voted no, for the reasons that pertain to the other two questions, in specific regarding uncomplicated urinary tract infection. I think in many cases that can be handled by other medications as first line.

I think this class of antibiotics is very important because it gives physicians an option. And we have pitifully few antibiotics, and we need them. So I think particularly in patients with known allergies and serious allergies to sulfa and beta-lactam, this class of medication is important.

Finally, in regard to the FQAD, I've spent a lifetime working on a disorder that was poorly understood and not recognized by physicians and not popular to study. I think this is an opportunity for study and needs to be studied, and we clearly need a case definition and epidemiology so that we

know both the numerator and denominator for this disorder. And that will help us work toward solving the problem.

(Applause.)

CAPT PARISE: Excuse me. We have one more person that's going to give their vote.

DR. STAUD: Roland Staud. I voted no because of significant concerns about risk/benefit ratio. And like in the other indication, I would recommend a risk mitigation strategy.

CAPT PARISE: Thank you.

(Applause.)

CAPT PARISE: Before we adjourn, are there any last comments from the FDA?

DR. NAMBIAR: Yes. Thank you, Dr. Parise. Some closing remarks from us.

We convened this advisory committee meeting today to receive expert scientific advice regarding the benefits and risks of systemic fluoroquinolone antibacterial drugs for the treatment of acute bacterial sinusitis, acute bacterial exacerbation of

chronic bronchitis, and uncomplicated urinary tract infections. This included a discussion of the detail regarding the benefit of these products to treat these conditions as well as the adverse effects of the drugs.

This meeting has provided valuable information and perspectives to help inform the FDA's decision-making processes. The FDA plans to consider the input from committee members and the public from this advisory committee meeting and determine what future actions may be appropriate.

I want to reiterate that this is an important issue for the agency. The FDA will keep healthcare providers and the public informed of new information regarding the use of systemic fluoroquinolones to treat these three indications.

I would also like to extend my sincere thanks to members of the Antimicrobial Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee for their valuable input at today's meeting.

A special thanks to you, Dr. Parise, as you rotate off as the chair of the Antimicrobial Drugs Advisory Committee. Thank you very much for chairing today's meeting and for your contribution as the chair over the years.

We would also like to thank the various industry participants for their today and for their collaborative efforts in today's meeting. A sincere thanks also to the various speakers at the open public hearing for sharing their stories and perspectives on the issue at hand.

Today's discussions have been very useful, and we will take them under consideration as we determine future actions. Safe travels. Thank you.

CAPT PARISE: Thank you. We'll now adjourn the meeting.

(Applause.)

Adjournment

CAPT PARISE: Panel members, please take all personal belongings with you as the room is cleared at the end of the day. All materials left on the

table will be disposed of. Please also remember to drop off your name badge at the registration table on your way out so they may be recycled. Thank you.

(Whereupon, at 6:05 p.m., the meeting was adjourned.)