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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE

IN JOINT SESSION WITH THE

DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE

December 14, 2006

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Email: atoigo1@verizon.net
(301) 495-5831

PARTICIPANTS

John Edwards, M.D., Acting Chair, AIDAC
Lt. Sohail Mosaddegh, RPh., Pharm.D.
Executive Secretary, AIDAC

ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE
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Joan Hilton, Sc.D., M.P.H.
Margo Smith, M.D.
Gregory Townsend, M.D.
Bernard Wiedermann, M.D.
Annie Wong-Beringer, Pharm.D.

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Louis A. Morris, Ph.D.
Robyn S. Shapiro, J.D.

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Dean Follmann, Ph.D.
Carol Koski, M.D.
James Leggett, Jr., M.D.
Michael Marco, M.P.H.
Carl Norden, M.D.
Michael Proschan, Ph.D.
Janine Smith, M.D.

CENTER FOR DRUG EVALUATION AND RESEARCH
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William Lee, M.D.
Joanne L. Rhoads, M.D., M.P.H.
Leonard Seeff, M.D.

PARTICIPANTS (Continued)

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
PARTICIPANTS (NON-VOTING)

John Alexander, M.D., M.P.H.
Mark Avigan, M.D., M.H.S.
Edward Cox, M.D., M.P.H.
Gerald Dal Pan, M.D.
John Jenkins, M.D.
Rosemary Johann-Liang, M.D.
Janice Soreth, M.D.

C O N T E N T S

C O N T E N T S (Continued)

Sponsor Presentation

FDA Presentation

Sponsor Presentation

C O N T E N T S (Continued)

FDA Presentation

P R O C E E D I N G S

Call to Order

DR. EDWARDS: I will call the meeting to order.

My name is Jack Edwards. I am from the Harbor-UCLA Medical Center in Los Angeles. I would like to welcome you to this combined meeting of the Anti-Infective Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee.

I would like to ask you to please turn off your pagers and phones for the remainder of the meeting. We are going to try our very best to stay on time. We have a very full schedule this morning and tomorrow. I am anticipating taking our breaks and ending the meeting according to the agenda as it is written.

I wanted to make a couple of introductory comments before we begin. These comments will be amplified on by Dr. Dal Pan in a moment.

Telithromycin, the original approval was controversial, and its continued marketing remains controversial. This is somewhat typical when an

initial approval is controversial. It remains so in a climate of very much increased concern for drug safety, which has been a recent IOM study and report which was actually asked for by the FDA.

It is also in a climate where there has been considerable discussion about drug trial design particularly for infections where the role of antibiotics is not particularly clear, and it is in a climate of great concern for the diminished activity in anti-infective development across the pharmaceutical industry in general.

As outlined by the FDA, the purpose of this meeting is to evaluate the risk-benefit ratio and make advice regarding the continued marketing of telithromycin. In order to do that, we are going to have to focus on the details of the safety and efficacy data that is going to be presented over the next two days.

Now, each of us in the last several days has received a copy of letters to Dr. Eschenbach from Senator Grassley raising questions regarding the original approval of telithromycin.

I wonder if all of the members of the committee have received those two letters. Senator Grassley wanted to make sure everyone was aware of the issues involved in those letters. Many of the points in those letters are referable to the process of the approval.

Certain of the issues are going to be addressed during this meeting, but our primary purpose for this meeting is a review of the risk-benefit issues, and not a focus on the process of the previous decisions.

We are going to focus on the data both in quantitative and qualitative perspectives and our decisions as individuals on this panel are going to be somewhat complex because of two issues relating to the data.

The first is that we do not have a large prospective data safety set for evaluation, and the second is we do not have a consensus on efficacy analysis related to study design for certain of the infections we will be addressing in these discussions specifically.

So we have our work cut out for us. It is going to be a process of our doing our very best to give our very best advice as individuals.

I would like now to continue and Lieutenant Mosaddegh will read the Conflict of Interest Statement.

Conflict of Interest Statement

DR. MOSADDEGH: Thank you, Dr. Edwards. Good morning.

The following announcement addresses the issue of conflict of interest and is made part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda and all financial interests reported by the Committee's participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest at this meeting with the following exceptions.

In accordance with 18 U.S.C. Section 208 (b)(3), full waivers have been granted to the

following participants.

Dr. John Bradley for unrelated research grant for a competitor, for which his employer receives less than $100,000 per year. Also, for his unrelated consulting for a competitor, for which his employer receives less than $10,001 per year.

Dr. John Edwards, Jr., for related consulting for a competitor, for which he receives less than $10,001 per year.

Dr. Lou Morris for current unrelated consulting for two competing firms, for which he receives less than $10,000 per year per firm. Also, for his past unrelated consulting for a competing firm, for which he received greater than $50,000 per year.

Dr. Carl Norden has been granted full waivers under 18 U.S.C. Section 208(b)(3) and 21 U.S.C. 355(n)(4) for stock ownership in a competitor firm valued between $25,000 and $50,000 and for his unrelated consulting for a competitor for which he receives less than $10,000 per year.

Dr. Carol Koski has been granted a waiver under 21 U.S.C. 355(n)(4), an amendment of the Food and Drug Administration Modernization Act, for ownership of stock in a competitor valued between $5,001 and $25,000. Because this stock interest falls below the de minimis exemption allowed under 5 C.F.R. 2640.202(b)(2), a waiver under 18 U.S.C. 208 is not required.

Lastly, Dr. John Bartlett has been granted a limited waiver under 18 U.S.C. 208(b)(3) which allows him to give a presentation but not vote, for his membership in unrelated advisory boards for four competing firms, for which he receives less than $10,001 per year per firm. Also, for his past unrelated speaking for a competitor, for which he received from $5,001 and $10,000 per year.

Waiver documents are available at FDA's dockets web page. Specific instructions as to how to access the web page are available outside today's meeting room at the FDA information table. In addition, copies of all the waivers can be obtained by submitting a written request to the

Agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

Thank you.

DR. EDWARDS: Thank you very much.

Could we now introduce the panel and I would like to begin there with your name, institution, and area of interest, please.

Introductions

DR. J. JENKINS: Good morning. I am John Jenkins. I am the Director of the Office of New Drugs, FDA.

DR. COX: Good morning. I am Ed Cox. I am the Acting Director for the Office of Antimicrobial Products at FDA.

DR. SORETH: I am Janice Soreth, Division Director for Anti-Infective and Ophthalmology Products at FDA.

DR. ALEXANDER: My name is John Alexander. I am a medical team leader in the Division of Anti-Infective and Ophthalmology Products at FDA.

DR. AVIGAN: I am Mark Avigan. I am the Director of Drug Risk Evaluation at the FDA.

DR. DAL PAN: Good morning. My name is Gerald Dal Pan. I am the Director of the Office of Surveillance and Epidemiology at FDA.

MR. LEVIN: Arthur Levin, Center for Medical Consumers. I am the Consumer Representative on the Drug Safety and Risk Management Committee.

DR. WIEDERMANN: Bud Wiedermann, Pediatric Infectious Diseases Physician, Children's National Medical Center, Washington, D.C.

DR. MARGO SMITH: Margo Smith, Infectious

Diseases at the Washington Hospital Center.

DR. KOSKI: Lee Koski, retired professor from the University of Maryland School of Medicine, where I was the head of the Neuromuscular Division for the past 20 years. I now work with the Guillain-Barre Foundation to better understand the diagnosis, management, and outcomes of inflammatory neuropathy.

DR. NORDEN: Carl Norden, University of New Jersey School of Medicine, in dentistry and infectious disease.

MR. MARCO: Michael Marco, International Center for AIDS Care and Treatment Programs, Columbia University, Mailman School of Public Health.

DR. EDWARDS: Jack Edwards, Harbor-UCLA Medical Center in Los Angeles, Adult Infectious Diseases.

DR. FOLLMANN: I am Dean Follmann, head of Statistics at NIAID.

DR. GUTIERREZ: I am Kathleen Gutierrez, Pediatric Infectious Diseases, Stanford University

School of Medicine.

DR. BRADLEY: John Bradley, Children's Hospital, San Diego, Pediatric Infectious Diseases.

DR. LEGGETT: Jim Leggett, Adult Infectious Diseases at Providence Portland Medical Center and OSU.

DR. HILTON: Joan Hilton, Professor of Biostatistics, University of California, San Francisco.

DR. PROSCHAN: I am Mike Proschan, a statistician at NIAID.

DR. MORRIS: Lou Morris. I have my own company that focuses on risk management.

DR. TOWNSEND: Greg Townsend, Infectious Disease, physician at the University of Virginia.

DR. HECKBERT: Susan Heckbert, Professor of Epidemiology and General Internist, University of Washington.

DR. WONG-BERINGER: Annie Wong-Beringer, University of Southern California, Associate Professor and Infectious Disease Pharmacist.

MS. SHAPIRO: Robyn Shapiro, Professor and

Director of the Center of Bioethics at the Medical College of Wisconsin, and a member of the DS&RM Committee.

DR. JANINE SMITH: Janine Smith, Deputy Clinical Director, National Eye Institute, NIH, Ophthalmology.

DR. EDWARDS: Thank you.

I would like now to introduce Dr. Gerald Dal Pan from the FDA, who is the Director of the Office of Surveillance and Epidemiology, to make some introductory comments, welcome, and clarify the exact purpose of this meeting.

Welcome & Introductory Comments/Purpose

Gerald Dal Pan, M.C., M.H.S.

DR. DAL PAN: Good morning to everyone. My name is Gerald Dal Pan. I am the Director of the Office of Surveillance and Epidemiology in FDA's Center for Drug Evaluation and Research. I would like to welcome all of you to today's Advisory Committee on telithromycin also known as Ketek.

We have members here of the Anti-Infective

Drugs Advisory Committee, the Drug Safety and Risk Management Advisory Committee, as well as other consultants with a wide range of expertise, to discuss the complex issues before us today.

Telithromycin is a ketolide antibiotic approved in the United States for three indications: acute bacterial sinusitis, acute exacerbation of chronic bronchitis, and community-acquired pneumonia.

The purpose of this meeting today is for the Advisory Committee members to discuss and vote on whether or not telithromycin's benefits outweigh its risks for each of the three approved indications and whether or not the available data support continued marketing for each of the three indications.

Over the next day and a half, you will hear presentations from FDA and its consultants, as well as from Sanofi-Aventis and its consultants, addressing the safety and efficacy of telithromycin.

Since telithromycin's U.S. approval in

April 2004, we have obtained a substantial amount of new safety information. Specific safety topics that you will hear about include hepatic adverse effects including the results of some additional analysis that have become available since warnings about liver failure and acute serious liver injury were added to telithromycin's label in June 2006.

You will also hear about visual adverse events, adverse events resulting in loss of consciousness, and exacerbations of myasthenia gravis.

You will also hear that the clinical trial design that was used to assess the efficacy of the telithromycin for each of its three indications, the non-inferiority trial design, has been called into question for conditions that have a high rate of spontaneous resolution, such as acute bacterial sinusitis and less severe cases of acute exacerbations of chronic bronchitis, because of concerns that non-inferiority trials cannot determine if the observed clinical success rate is due to the drug or to the natural history of the

condition being treated.

Finally, tomorrow afternoon, you will be asked to discuss and vote on whether or not telithromycin's benefits outweigh its risks for each of the three approved indications and whether or not the available data support continued marketing for each of the three indications.

You will be asked additionally to make recommendations about other steps that may be needed based on how you vote.

I would like to turn it over now to Dr. Cox, who will provide some more background information.

Once again, thank you for coming today and welcome.

Edward Cox, M.D., M.P.H.

DR. COX: Thank you, Dr. Dal Pan.

I am Edward Cox. I am the Acting Director for the Office of Antimicrobial Products in CDER/FDA.

[Slide.]

I would also like to start out first by

welcoming everybody and thanking you for coming here today. We will be talking about NDA 21-144, which is Ketek (telithromycin) Tablets and, as Dr. Dal Pan has mentioned, we will be discussing the overall benefits and risks based upon what we know today.

We will be reviewing the information in the original NDA and then also look at the additional information that we have since the drug was approved in April of 2004.

The primary purpose of the meeting today is to seek the Advisory Committee's advice on the overall assessment of risks and benefits for Ketek for each of its approved indications based upon what we know today.

[Slide.]

The review of the Ketek NDA was a very complex review. It spanned the course of three cycles which began in March 2000 and went through to the date of approval in April of 2004. It was also the subject of two previous Anti-Infective Drug Product Advisory Committees in April 2001 and

in January 2003, and Ketek was approved in April of 2004.

[Slide.]

The approved indications for Ketek include acute bacterial exacerbation of chronic bronchitis, acute bacterial sinusitis and community-acquired pneumonia for the organisms that are listed under each of the respective indications.

It is approved for treatment of these conditions in patients 18 years of age and older.

[Slide.]

I thought it would be helpful to provide some information about other oral drugs that are approved with similar indications. This list provides a representative list of other drugs for the same indications for which Ketek is approved in other related indications.

We see that in this slide, there are a number of drugs listed here and they are generally grouped in descending order from penicillin, cephalosporins, macrolides and quinolones.

The goal here is not to look at each of

the agents. But we notice that there are a number for each and, if you look down lower, we also see that there is a different but related indication of lower respiratory tract infections.

This is an indication that used to be granted in the past that included both studies in patients with both AECB and community-acquired pneumonia.

Looking at the slide and thinking about the indications that we have here, in fact, I think what we are seeing some is the evolution of the science with regards to antimicrobial drug development.

In the past, drugs were studied for broader indications, such as lower respiratory tract infections. But, more recently, these broad indications have been split into their individual components, because of the differences in pathophysiology and natural history of these infections.

The other thing is if you look more closely at the drugs listed here, you will also

notice that there are some drugs you might expect to see that you don't, such as ampicillin, and you don't see the tetracyclines here.

Again, this echoes the issue of really the evolution of the science of antimicrobial drug development over time.

[Slide.]

If you look at the amoxicillin label, you will see an indication for infections of the ear, nose and throat. Ampicillin includes an even broader indication of infections of the respiratory tract.

Interesting to look at is the tetracycline and the doxycycline labels, which are very microbiologically driven and again have broader indications of respiratory tract infections and upper respiratory tract infections.

[Slide.]

This brings up the interesting point of the historical perspective of demonstrating efficacy and really that the science of clinical trial designs has advanced over time.

If we go back to 1938, the time of the Federal Food, Drug and Cosmetic Act, initially, drugs were first cleared for safety and pre-market notification was required, but an evaluation of efficacy was not required.

In 1962, with the Kefauver/Harris Amendments added a requirement that the drugs needed to be shown to be effective. It required a positive act of approval before a new drug could be marketed and required that the FDA review all drugs approved since 1938 for effectiveness.

The efficacy of the earlier antibiotics was evaluated under the Drug Efficacy and Study Implementation review and the available evidence with regards to efficacy for these products was what was reviewed in order to assess whether efficacy had been demonstrated.

[Slide.]

If we move beyond that, the period of 1962 and thereafter, in general, what we find in looking at antimicrobial drug applications are really broader studies that include patients with any of a

variety of different infections and it was through the review process, looking to see what types of infections had been enrolled in the study to actually lead to the indications for treatment of, say, community-acquired pneumonia or respiratory tract.

The studies were broad and included patients with a variety of different infections.

With the publication of the Points to Consider document in 1992 and the 1992 IDSA/FDA guidelines, there was a movement towards more indication specific trials, so CAP would be studied separately from AECB.

These guidelines also described that the studies should be designed to either show equivalence or superiority. In fact, looking back at these applications generally what is shown is equivalence or non-inferiority.

The 1998 draft guidances were similar in that they also had an indication specific theme across the different indications for which the draft guidances were written, such as

community-acquired pneumonia, acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, all separate indications, and also described that studies should be designed to show similar or superior effectiveness. Again, the studies showed non-inferiority.

In essence, looking back at antimicrobial approvals and even for the drugs that we have out there today for these indications, almost universally they have all been approved based upon showing non-inferiority, so that is, in fact, the standard of evidence that has been used to date with regards to, or to the point of recently with regards to the approval of antimicrobial drugs.

More recently, there have been questions on the ability of non-inferiority studies to provide informative data on efficacy in milder, typically self-limited infections.

[Slide.]

The studies supporting the approved indications for Ketek included a number of clinical studies across the indications of

community-acquired pneumonia, acute exacerbations of chronic bronchitis and acute bacterial sinusitis, and these were active controlled trials designed to show non-inferiority.

[Slide.]

If we look to the Code of Federal Regulations to see what it says about demonstrating efficacy, I will just read a couple lines here, and I think they are very instructive.

The CFR states that, "The purpose of conducting clinical investigations of a drug is to distinguish the effects of a drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation."

A couple of comments specifically to the issue of active treatment concurrent control trials. "They are typically used where the condition treated is such that administration of placebo or no treatment would be contrary to the interest of the patient."

One other consideration is the issue of if

you are intending to show similarity of the test and the control drugs, the report of the study should assess the ability of the study to have detected a difference between treatments.

Similarity of the test drug and the active control can mean either that both drugs were effective or that neither was effective and that the analysis of the study should explain why the drug should be considered effective in the study, for example, by reference to the results in previous placebo-controlled studies of the active control drug.

[Slide.]

The ICH E-10 guidance provides some additional information about this issue of being able to distinguish an active from an inactive therapy in the setting of trying to show non-inferiority. The term used here is that of assay sensitivity,

The assay sensitivity is a property of a clinical trial defined as the ability to distinguish an effective treatment from a less

effective or ineffective treatment.

If a trial is intended to demonstrate efficacy by showing a test treatment to be non-inferior to an active control, but lacks assay sensitivity, the trial may find an ineffective treatment to be non-inferior and could lead to an erroneous conclusion of efficacy.

The presence of assay sensitivity in a non-inferiority or equivalence trial can be deduced from two determinations. The first is historical evidence of sensitivity to the drug. This is based upon looking back at similarly designed trials and showing that the active treatment would have been able to distinguish itself from that of an inactive or ineffective treatment, such as a placebo.

Also important to consider in non-inferiority trials is that the trial was conducted appropriately; that is, that patients who are enrolled in the study actually had the disease of interest so that we can rely upon the previous information with regards to what we would expect the trial to be able to show with regards to

distinguishing an ineffective from an effective treatment.

[Slide.]

Now, I will try and walk through graphically what it is that I am describing here. What I have got here is a first case scenario where we have got a situation where there is a large treatment effect and a low spontaneous resolution rate.

So, in a non-inferiority study, we would be looking to compare the test to the active control and we would be looking to show that the test is not a certain degree, for the test drug is not a certain degree worse than that of the active control. That is described as the margin.

So, in this situation, we see the test drug performing similarly to the active control and within the non-inferiority margin.

We may not have this information directly from the trial and that is what the placebo control rate would be if a placebo had been included. In a three-arm study that had a placebo, you would have

this directly.

In a non-inferiority trial where you don't have a placebo included, you would be relying upon historical information to know, that there is a separation between the margin and how a placebo would perform if it had been included.

[Slide.]

Here is the second scenario. That is a situation where you have an unclear treatment effect and a high spontaneous resolution rate. Here, we see the test and the active aligned in a similar fashion and that the test drug stays within the margin. But here is a situation where if a placebo had been included in the trial, we would not be able to distinguish the effect of the placebo compared to what we had seen from the active or the test control.

[Slide.]

So, this is an attempt to graphically illustrate what I have just talked about. In this situation where you have got a large treatment effect and a low spontaneous resolution rate, a

non-inferiority study design is a perfectly fine way to assess how the drug performs.

In this situation down here, you can see how a non-inferiority study would not be informative, because it doesn't distinguish between placebo and alternative trial designs would need to be considered.

[Slide.]

We have had previous discussions about trial designs in acute bacterial sinusitis and acute bacterial exacerbations of chronic bronchitis. I would just like to briefly review some of the discussions we have had over time.

In October of 2003, there was a general discussion on trial design and acute bacterial sinusitis. The recommendations from this advisory committee was for superiority trial designs in acute bacterial sinusitis and a recommendation to consider placebo-controlled or adjunctive therapy controlled trials.

Also, another proviso put out was the issue of closely following patients and having

safety provisions in place for those patients who might experience progression of disease.

In 2006, there was a product-specific Anti-Infective Drugs Advisory Committee, which discussed a fluoroquinolone antibiotic gemifloxacin that was being considered for acute bacterial sinusitis and the study designs there were that of active controlled non-inferiority studies.

The Committee did vote on the question of efficacy alone, the Committee voted 4 Yes and 10 No against the efficacy and this hinged upon the issue of the non-inferiority trial design.

With regards to acute bacterial exacerbations of chronic bronchitis, there was an Anti-Infective Drug Products Advisory Committee in 2002 and there were general discussions recommending placebo-controlled studies in non-severely ill patients with acute bacterial exacerbations of chronic bronchitis.

We also had a regulatory briefing within CDER. It's a meeting of CDER senior management where we discussed the issue of acute bacterial

exacerbations of chronic bronchitis and trial design and it was felt that there was not adequate basis for non-inferiority trials in acute bacterial exacerbations of chronic bronchitis.

[Slide.]

To the issue of selecting between non-inferiority designs, superiority designs, active-controlled versus placebo-controlled trials, I will just mention some considerations here.

I will start out with essentially some historical perspective and that is that antibacterial drugs were first discovered many years ago and really represented a major advance in the field of medicine, being able to treat infections that previously, there were not therapies available to treat.

Because of this and because of the major advance in antibacterial therapies were, and still remain to be, antibacterial therapy was incorporated into clinical practice really before clinical trial design had become more sophisticated.

Some of the considerations that have to be grappled with, with regards to this question is in the setting of either delaying therapy or giving a placebo, there is a risk for progression or extension of infection. In those circumstances where an antimicrobial is given, there is also a risk of adverse reactions to the antimicrobial.

So, when designing a clinical trial, the clinical trial should not expose patients to significant risk, they should be informative and they should be ethical and acceptable based upon IRB review.

Another thing to think about, too, is that study design can actually impact upon the population that is enrolled in a study. This is done through the inclusion/exclusion criteria. But another consideration here, too, is the investigator's knowledge or awareness of what the patient may be eligible to receive if enrolled in the trial and the clinician's assessment of the patient's severity of illness may, in fact, influence whether the physician considers the

patient for enrollment in the study.

Other things to think about with regards to study designs are provisions for rescue therapy and considering the role of a DSMB especially in circumstances where they might be a placebo control and there might be a delay in the institution of therapy.

[Slide.]

Now, just to highlight a couple of items from the Ketek label, and I haven't reproduced all the label here but just some selected areas.

The Ketek label with regards to safety includes contraindications for patients who have had a previous history of hepatitis or jaundice associated with Ketek or any macrolide, contraindications against concomitant administration of Ketek with cisapride or pimozide.

Also, within the warning sections, it includes information on hepatic toxicity that was updated in June of 2002 that provides information on acute hepatic failure and severe liver injury, which in some cases has been fatal, and also a

strengthened warning with regards to exacerbation to myasthenia gravis that was strengthened in June of 2006, information on QT prolongation, pseudomembranous colitis that is included in all labels of antibacterial drug products, and it also includes precautions on visual disturbances and syncope, hepatic dysfunctions and drug interactions because Ketek is a CYP3A4 inhibitor and a CYPCA4 and 2D6 substrate.

[Slide.]

This slide is just to remind me that I haven't included everything in the previous label and for a complete listing of all that is in the label, there is a package insert included within your briefing package.

[Slide.]

Now, moving on to some other antimicrobials and what we have in the label for those products with regards to safety labeling and these are drugs from the macrolide class.

If we look at clarithromycin, we see that it has a contraindication against administration

with interacting drugs because of the concern for cardiac arrhythmias. Erythromycin contains similar information in the label with regards to taking terfenadine or astemizole because of the potential for cardiac arrhythmias.

Clarithromycin includes a warning that is specific with regard to use in pregnancy. All three of the drugs listed here include warnings about pseudomembranous colitis, as do all antibacterial drugs.

Clarithromycin and erythromycin include warnings about drug interactions and, if we look across the labels, we see that within the macrolide labels in one of the sections within the product labeling, there is information about hepatic adverse effects and also QT prolongation and arrhythmias.

[Slide.]

Just to keep in mind some of the other drugs that are used for treatment of these types of respiratory tract infections. I have also listed beta-lactams, tetracyclines, and the

fluoroquinolones. Again, I haven't listed everything that's on labels but just a couple of the adverse reactions that are well known to be associated with the group of drugs.

As for the beta-lactams, we have got penicillin allergy, allergies to cephalosporins, hypersensitivity reactions and again pseudomembranous colitis across all the drugs.

The tetracyclines include information on tooth development, the adverse effects on tooth development, on pregnancy and children, and also some information about photosensitivity.

The fluoroquinolones include information and warning about use in pediatrics, CNS disorders, hypersensitivity reactions, peripheral neuropathy, tendon effects, and also precautions on the potential effects of fluoroquinolones on the QT interval.

[Slide.]

While the focus of the meeting here today is to talk about the approved indications which are in the adult population, I will briefly mention

pediatrics.

First, Ketek is only approved for use in adults. The pediatric studies in acute bacterial otitis media, tonsillopharyngitis and community-acquired pneumonia were voluntarily paused by Sanofi-Aventis on June 8, 2006, so pediatric patients are not being enrolled in pediatric studies.

The discussions we have here today with regards to risk and benefit will help to inform any future discussions with regards to pediatric development.

[Slide.]

Now, just to run through briefly the broad scope of the meeting that we will be covering and the topics we will be covering over the two-day period. We will have a talk today from Dr. Bartlett about respiratory tract infections, treatment and epidemiology.

Then, we will move on to talk about the pre-market data and we will hear presentations both from the FDA and the sponsor, then the

postmarketing data will be discussed.

We will hear a presentation from the European Medicines Agency and also a discussion of data mining and then a discussion of hepatic adverse events. You will hear presentations both from the company, from the FDA, and then also from Special Government Employees, who have reviewed the information on the hepatic adverse events.

On day 2, we will continue on in discussing the post-marketing data and we will review the information with regards to visual adverse events, disturbances of consciousness and exacerbations of myasthenia gravis.

We will have some summary comments and then move on to the open public hearing and then move on to committee discussions and votes.

[Slide.]

I thought it would be helpful just to essentially run through the questions and the discussion points that we will be asking people to address on the afternoon of Day 2, so that everyone knows where we are going.

The first discussion point that we will ask the Committee to address is: Please discuss whether the benefits outweigh the risks for each of the approved indications for Ketek: community-acquired pneumonia, acute bacterial exacerbation of chronic bronchitis and acute bacterial sinusitis.

We will ask that the Committee take into consideration the current safety information specifically including hepatic, visual, loss of consciousness and exacerbation of myasthenia gravis adverse reactions.

We will ask that the Committee also consider the information supporting efficacy for these indications as well as the recent efficacy discussions on the use of non-inferiority trial designs.

We have three questions that we will be asking the Committee to vote on.

[Slide.]

Question 1. Based on your discussions of whether or not Ketek's benefits outweigh its risks,

do the available data support the continued marketing of any of the following approved indications?

We will ask you to vote separately for each of the indications: for community-acquired pneumonia, acute bacterial exacerbation of chronic bronchitis and acute bacterial sinusitis.

[Slide.]

Question 2. If continued marketing is recommended for any of the indications, please address the following:

Should any of the indications for which continued marketing is recommended be modified or limited?

Does the product label adequately describe the adverse reactions? We are asking you specifically address the issue of hepatic, visual, loss of consciousness and exacerbation of myasthenia gravis.

Then, the question of should any additional communication strategies or risk management programs be implemented to assure the

safe use of Ketek.

Then, ask if there are any recommendations for any additional studies to further define the benefits or risks of Ketek for each of its indications.

[Slide.]

The final question, Question 3. If continued marketing is not recommended for any of the indications, please address what evidence is needed to show that the benefits of Ketek outweigh the risks.

With that, I will close and thank you. Back to you, Dr. Edwards.

DR. EDWARDS: Thank you very much, Dr. Cox, for that very nice overview.

It is a great pleasure now for me to call on Dr. John Bartlett, who is Professor of Medicine at Hopkins, who will discuss respiratory tract infections. I am sure Dr. Bartlett is well known to everyone here and has a life-long interest in this topic.

John, thank you for joining us.

FDA Presentation

Respiratory Tract Infections:

Epidemiology/Treatment

John Bartlett, M.D.

DR. BARTLETT: Thank you, Jack, and I want to express my gratitude for the opportunity to talk about this topic.

[Slide.]

This is who I am and this is my confessions.

[Slide.]

I am going to review respiratory tract infections including the three topics that Dr. Cox has already mentioned. I am not quite sure how to do this in a half an hour or so.

I will tell you in advance I am not going to talk about Ketek per se. I am going to talk about issues that I think are relevant to the discussion today and tomorrow, and those are some of the things that are listed here and are on the handout for people that can't see the slides.

It will perhaps seem a little

disorganized. But what I am trying to do is just cover bullet points of what I think are perhaps the most important issue.

[Slide.]

First of all, all three of these infections we are talking about involve the same bacteria. Most of them or two of the three are virtually almost 50 percent or more due to viral infections and then, in terms of bacterial infections, which we are talking about today, the organisms are the same but the relative frequency is quite a bit different.

[Slide.]

I am going to start off by talking about community-acquired pneumonia. That is probably the easiest one to start with because that's the one for which I think there is universal acceptance that antibiotic treatment is appropriate in almost all cases.

Here is a display of the pathogens and I think one of the first things we have to say is no matter how hard we try, we cannot fill in the pie.

There are a lot of blanks, and that is one of the things we have always struggled with. So if we do every diagnostic test we have, we still wind up with a number of enigmatic cases.

[Slide.]

In terms of the Infectious Disease Society guidelines, those are a product in evolution, are not quite ready to joint effort between the IDSA and the American Thoracic Society. But we can sort of guess what they are going to say.

They will not probably be different, much different from what they were in the previous rendition. So what it says is for walking pneumonia or outpatient pneumonia, the uncomplicated cases can be managed with a macrolide or a doxycycline and complicated would add to the list of fluoroquinolones.

Now, does that work? This is I think one of the best studies of walking pneumonia. It's another really good pneumonia study from Canada by Tom Marrie and his colleagues. What we did was to try to get people to follow an algorithm, which

they didn't do very well. But they did give the drugs that are on the list that I mentioned previously. I think the important part of it is the bottom line is that out of 700 cases, there were only 2 percent subsequently required hospitalization for failure to respond and half of those were for non-pneumonia related problems.

So, in other words, what has been advocated for walking pneumonia or outpatient pneumonia, for whatever reason, seems to work pretty darn well.

[Slide.]

Now, for hospitalized patients, it is a bit different because there is always mortality associated with community-acquired pneumonia sufficiently severe to require hospitalization.

These are the recommendations. It's fluoroquinolone alone or it's a macrolide plus a beta-lactam, and then if it's a patient admitted sufficiently sick to be admitted to the Intensive Care Unit, the recommendation is to cover the pneumococcus and legionella, the two outpatient

pathogens that kill patients. So that is the current recommendation.

[Slide.]

Now, where does that come from? Well, it comes from data that most people in the room would not consider particularly scientific. It's a retrospective analysis, a Medicare database, and the strength of it is the numbers.

I think what I would like to say this is, is kind of a signal, it's a signal of what we should be looking for and perhaps studying in order to do the proper science on this issue. We would all feel happier if this was a placebo-controlled trial.

What it shows is that if you take a cephalosporin like ceftriaxone or ceftaxime and use that as the bar by which all other drugs, combinations of drugs are compared in a database with more than 12,000 patients, and now actually, the more recent is 20,000 patients, what it shows is that with cephalosporin plus a macrolide there is a 26 percent reduction in mortality, perhaps the

most important endpoint of all and, with the fluoroquinolone alone, it's a 36 percent reduction.

That is really, quite frankly, the basis or the major study that impacted the guidelines.

[Slide.]

Now, in terms of diagnostic studies, this is a really disappointing slide or story, particularly disappointing to me and I think most of the people in the field. We would all love pathogen-directed therapy, but, as we go through the years with pneumonia CAP, the microbiology has gotten worse and worse and worse, and so what we have now is sort of you can do a sputum Gram stain and culture. But it is not expected and most people don't.

You can do a blood culture but probably only need to do it if the patient is going to the Intensive Care Unit. There is kind of universal acceptance of the urinary antigen for legionella.

If you look at the Medicare database, the number of people that have an etiologic diagnosis, about 6 or 8 percent out of blood cultures, and 5

percent out of anything else, so we are currently making the diagnosis somewhere between 10 and 15 percent of patients that have community-acquired pneumonia. So, in most cases, we just treat empirically.

[Slide.]

Now, I mentioned the gap in the diagnostic studies, could we do better. Well, I think we know we could do better and I think we know the technology is here to do it now. So this is one of the studies from the Netherlands, which shows the application of both bacteriology and PCR in patients with community-acquired pneumonia, and they identified a culprit in 74 percent of cases.

This is now being expanded. I think we all know that this technology is there, However, it is not inculcated into practice anyplace that I know of except on a research basis. So we think it is sort of ready for prime time but, nevertheless, it's awfully slow in coming.

When I have inquired about this, the answer is nobody wants to pay for it.

[Slide.]

Now, going to another bullet point, there is a curious observation with respect to community-acquired pneumonia and it is shown here; that is, what are the macrolides doing? They are controversial in two ways.

One is if you look at the major cause of pneumonia, the pneumococcus, it has a high rate of resistance. But if you look at clinical practice, like I did with the outpatients, it seems to work well. So there is this disconnect between the in vitro and the in vivo data.

Now, there are anecdotal cases that fail. We know that, but they are anecdotal in our population base.

This is another curious observation. So everyone in the room would say if somebody has pneumococcal pneumonia with bacteremia, it ought to be treated with beta-lactam if it's sensitive. So that is what they got, that's the analysis in this retrospective analysis.

[Slide.]

But what they found was that if you gave both the beta-lactam and a macrolide, notably, you reduced the mortality by 60 percent and that is shown in the Kaplan-Meier curve from the Victor Yu study, which was the largest study of pneumococcal pneumonia with bacteremia that was ever done.

Now, the question is, what is the role of the macrolide with the beta-lactam. I can tell you that people in Infectious Disease do not like these data. We don't want this phenomenon, because, first of all, we don't understand it.

Second of all, it represents a potential abuse of antibiotics. But, in terms of understanding the concepts of what we are doing with pneumonia, this is a fascinating observation that seems to be supported by at least six of six studies.

[Slide.]

Now, in terms of the pathogens that need help, I think probably the one that we would say is a deficit in our armamentarium of drugs is community-acquired MRSA or the USA 300 strain. It

is insufficient in numbers to be able to study, in my view, at least with an appropriate sample size. But it is a new bug and a devastating organism.

This is a review from the CDC of 17 cases. You notice the average age was 21. You will also notice the mortality was 30 percent.

I would have to say that in the process of doing a lot of clinical care of patients with pneumonia for a very long time, it is, in fact, very rare for a young, previously healthy adult to die of pneumonia. We have seen that for the first time in the last couple of years with this organism.

I am not sure that the data on other forms of Staph pneumonia, like hospital-acquired pneumonia, are applicable, because the mechanism of the pathogenic response may be different. This may be toxin or probably is toxin mediated and that requires it to follow a different set of rules.

[Slide.]

These are not subtle cases. I am not saying that people should be treated for suspected

MRSA USA 300 because they are clinically unique, and this is one of the cases we have that just shows massive necrosis of the lung.

[Slide.]

Another observation that has been interesting has been with penicillin-resistant pneumococci, and we view this as really the most important problem of resistance with regard to community-acquired pneumonia, and it may still be. But the vaccine, a pediatric protein conjugated vaccine, has made a huge impact.

[Slide.]

These are the data following its introduction in the late 1900s in terms of penicillin-sensitive strains. One of the oddities is that although it is only given to children, it has a big impact on penicillin-resistant pneumococci in the elderly or in older groups, as well.

But it's like the balloon when you squeeze it, something has got to pop out. What popped out was a new strain 19A, which was, number one, not in

the vaccine and, number two, it's highly resistant to antibiotics so that there now seems to be a massive decrease in the amount of penicillin-resistant pneumococci. But an emerging resistant organism that may be a problem now in children, perhaps in the future.

[Slide.]

To conclude this part on the pneumococcus, the vaccine was introduced and it really took our resistance rates back 10 years, so we are where we were 10 years ago, which is quite extraordinary. But the 19A strain has come in and now is a big problem in children, it is not a problem in adults, as yet.

It is resistant to beta-lactams and macrolides. That notably limits the drugs that are available for pediatrics. It is almost always sensitive to fluoroquinolones and therefore, for adults, we are okay at least for the moment.

The thought is that the thing that is going to keep it good in adults is to keep fluoroquinolones out of children. That is

something that we really need to think about when we move forward with this.

There will be a vaccine that will include the 19A strain that is targeting somewhere between 2008 and 2010 for availability.

[Slide.]

The issues with regard to community-acquired pneumonia is a disappointing performance in terms of diagnostics, bad getting worse, yet frustrating because the technology seems to be there.

The antibiotic-resistant organisms that we need drugs for are the pneumococcus and MRSA, the USA 300 strain.

Some of the miscellaneous issues is the issues I raised about macrolides, the importance of pulmonary penetration, which is a signal that might be done in terms of testing drugs before they are put into people.

The time to administer, one of the things that the Medicare database has shown is that if you delay a few hours in the time you administer drugs,

antibiotics, it turns out to have a huge play in terms of mortality, hence, the rule that you have got to start the antibiotics within 6 hours, and the timing is probably an important part in any of the trials.

Finally are the mega databases, such as Medicare, and what role that should play in sort of deciding what kind of studies need to be done.

[Slide.]

Now, with regard to sinusitis, these are the recommendations from the American College of Physicians, the Centers for Disease Control, and the Infectious Disease Society of America. They are from 2001.

What they say is don't X-ray, don't culture, and the indications for antibiotics are those that are listed - symptoms for 7 days or serious disease.

What they also said was the greatest barrier to efficient antibiotic use is the lack of a simple test. I mean the fact is we just don't know when somebody has acute bacterial sinusitis.

[Slide.]

You can stick a needle into the sinuses and prove it that way. It may be realistic for some studies. It probably is never going to be inculcated into practice unless it gets much different.

This is the explanation for the 7-day rule. What is says is that sinusitis caused by viruses usually resolve in 7 days and therefore if they persist or get worse, then, 7 days is the time to give antibiotics because that is more likely to reflect a bacterial superinfection.

[Slide.]

There are a number of studies of sinusitis. One of them is shown here. It's a big study, a reasonably good study. It compares amoxicillin with placebo and what it shows is that it's a dead tie in terms of efficacy at least by statistical analysis. Of course, there were more adverse reactions in the group that got the amoxicillin.

[Slide.]

However, there are other studies that could be cited on and on and on, which have shown something different in terms of efficacy. This is the Cochrane Library Review, which was 49 studies and 13,000 patients including 20 blinded studies or double-blinded studies and 5 placebo-controlled trials.

They used radiology or clinical impression as the outcome parameter. What they showed is amoxicillin was better than placebo and there was no drug that could beat amoxicillin at least for this condition.

Now, that doesn't necessarily line up great with the organisms or the pathogens we recover when we aspirate the sinuses, but, nevertheless, that is the way the data fall when they are analyzed in the various trials.

[Slide.]

This is a different type of analysis. This is from Linder and his colleagues, an analysis of how people are evaluating sinusitis. The answer is that you can't use X-rays. I think everybody

agrees X-rays don't show that people are cured.

The clinical criteria that we use are terribly soft, and it is really a quality of life. I mean when is somebody better enough to go back to work, or when are they well enough to be functional in some way, and so forth.

[Slide.]

He reviewed the data on the various methods to evaluate the quality of life in patients that are treated for sinusitis. Here are all the tests that were used and then the number of studies that used them.

You can see that there is a huge number. Everybody is doing something, but it is quite different. The one I liked was the Sinonasal Outcome Test, the "snort" test, and there are several variations of that.

[Slide.]

The Linder review of this, his conclusion was there was no measure of outcome that has even minimal validation criteria. Virtually, all patients respond within 2 weeks, and, therefore, a

lot of the studies do is say is the patient better in 2 weeks, well, most patients are better in 2 weeks without anything and that seems to be pretty well established.

Meta-analyses of sinusitis do tend to show a benefit but it is kind of marginal and the question is whether it's better than the side effects, the tradeoff, the side effects of the antibiotic.

[Slide.]

In terms of sinusitis, what I wound up sort of concluding from this is we really need a test to know when bacteria are involved and I don't have an answer for that at all.

The second is probably the more important one is what are the criteria to say that someone is better, because the methods that are used at the present time seem to have inconsistency and no validation.

[Slide.]

I am going to go on and finish up by saying something about the third topic, which is

acute exacerbations of chronic bronchitis. I was also asked to comment on the guidelines for all three. So, for this, the latest guideline is from The American College of Chest Physicians, the ATS, and the Canadian Thoracic Society.

What they concluded is that antibiotics are recommended in patients with purulent sputum and more severe illness using the Big 3, increased cough, increased sputum, increased dyspnea.

Now, the FDA in 2002 said the antibiotic trials done over the past 40 years are flawed because the role of antibiotics is inconclusive.

[Slide.]

The guidelines said the antibiotic trials over the past 40 years are terrific because they have clearly shown that antibiotics work. What they cite is this study, which is the Saint study, which is a meta-analysis.

If you look at that, I mean what it clearly does is it favors the use of the antibiotics. The problem I have with it is if you look hard at the same study, it certainly does not

include all the studies that have been done in sinusitis, so there is some selection factor and, when you read the fine print, a lot of it is subset analysis.

If we are going to put a lot of weight on this study, I think we either need to sort of re-scrutinize this test or try to redo it in some way. Nevertheless, that is what has supported.

[Slide.]

One thing that was kind of surprising to me is that the document from the American College of Chest Physicians did say to use antibiotics but didn't say which antibiotics to use.

In terms of the Big 3 that I mentioned, everyone that gives the lecture on sinusitis goes back to this historic paper by Anthonisen, which was a large study, a randomized study with 3 antibiotics and a placebo.

What this shows is the frequency of response whether you had 1 of the 3, 2 of the 3, or 3 of the 3. This has sort of been marching orders ever since in terms of our evaluation of who needs

to be treated for acute exacerbations of chronic bronchitis.

[Slide.]

The endpoints are pretty nebulous. I mean for me, I don't practice chest medicine, so I don't do a lot of this and can't pretend to be an authority. There is others in the room that are.

However, to me, when I see somebody like this and they say, well, they are breathing a little bit harder or their sputum is a little bit greener or whatever, that is awfully tough to evaluate, and then to say that those things are getting better also becomes kind of tough.

This is an objective measure and it's the peak expiratory flow rate which did at least in the Anthonisen study tend to occur a little bit earlier in the group that got antibiotics.

[Slide.]

Now, there are studies which are placebo-controlled that are actually pretty striking in terms of their support of the use of antibiotics. This is one that was published in

Lancet a couple of years ago.

It randomized patients with ofloxacin and placebo. These are patients that were seriously ill enough to require hospitalization in the Intensive Care Unit. Other people were somewhat critical of putting this into a placebo-controlled trial but, nevertheless, you can see what they showed. The death rate was 4 percent versus 22 percent, and then the other parameters were also significantly different in the group that did not get the antibiotic.

[Slide.]

In terms of what we are learning about the disease, this is a topic which is now getting what I think is some serious science. This was an analysis by the Buffalo group. They are serious students of exacerbation of chronic bronchitis and have followed a cohort for a long time.

What they are saying is Haemophilus influenzae is the number one pathogen, Moraxella is number two, and the pneumococcus is number three, so those were the numbers I showed at the

beginning. In exacerbations, they have shown in a series of three papers some observations that I think are awfully good in terms of deciding what the role of antibiotics may be.

[Slide.]

This is the molecular typing of sputum isolates of Haemophilus influenzae. What they showed is that there may be--many of you are familiar with the old studies that showed the bacteriology never changes--what this says is that the bacteriology is not changing but there is a new strain of Haemophilus influenzae more frequently than in a control group and the strain change may account for the exacerbation.

[Slide.]

Pursuing that one step further, they have shown there, there is an antigenic or an immune response to that new strain. Now, I think adding additional data to support the role of Haemophilus influenzae as a cause of at least some exacerbations of bronchitis or exacerbation of chronic bronchitis.

[Slide.]

Some of these new methods, which would be awfully nice to incorporate as we move forward and trying to figure out who to treat and how to evaluate outcome are the role of bronchoscopy in terms of determining the pathology of the lesion, the molecular epidemiology which I talked about, the immune response which I talked about, and also the evidence of airway inflammation, possibly IL-8, as a measure of knowing when a bacterial infection is responsible for the disease.

[Slide.]

So, in terms of acute exacerbations of chronic bronchitis, the issues I have pointed out are that the issues to treat and evaluate are crude at the present time. They may in the future inculcate time of response but that might require measurements on many times points, the time to next exacerbation which has become popular--but I am not sure of the science behind that--and what I said about sinusitis. Maybe the most important thing is quality of life for a person who is suffering from

chronic cough.

The goal I think should be to apply some of the next technology into the trials in order to see if there is a marker that could be used to either diagnose or evaluate response to therapy, such as IL-8, for example.

There has always been the suggestion that a placebo-controlled trial would be good to do but a response that nobody will do that--and my understanding is there now are a couple of sponsored studies with a placebo control.

Finally, as something that Tim Murphy from Buffalo told me in a conversation yesterday, that I found fascinating, he said, you know, with Haemophilus influenzae, 40 percent of what we call Haemophilus influenzae is actually Haemophilus hemolyticus, a total non-pathogen, and that does not cause disease and is a common mistake accounting for 40 percent of the H. flu, another kind of curious twist in the role of Haemophilus influenzae.

So I will finish there. Thank you very

much for your attention.

DR. EDWARDS: Thank you very much, John. I think all of us realize what a tremendous challenge it is to discuss this topic in such a brief period of time. That was a very nice overview, we appreciate it.

I am going to move on now to Mark Moyer from Sanofi-Aventis, who will coordinate the presentations from the sponsor.

Sponsor Presentation

Introductory Remarks

Mark Moyer, MS

MR. MOYER: Good morning, members of the Joint Advisory Committee, FDA, and our audience.

[Slide.]

I will be providing some introductory remarks regarding our product telithromycin today.

[Slide.]

My name is Mark Moyer. I am from Sanofi-Aventis' Corporate Regulatory Affairs Department.

[Slide.]

Telithromycin, as you have already heard, is first in a new class of antimicrobial agents, the ketolides.

This product was selected to overcome erythromycin resistance in Streptococcus pneumoniae isolates. It was structurally changed to add a 3-keto function which provides its unique characteristics, as well as its name, the ketolide class.

Part of this unique aspect of this product are its ability to bind to two sites on the bacterial ribosomes versus macrolides which are able to bind at one site. This has the potential to avoid resistance then because of these site bindings.

It also is focused on a spectrum of activity against common and atypical bacterial pathogens that cause respiratory tract infections, including multidrug resistant Streptococcus pneumoniae.

It also has uniqueness of limited activity against non-respiratory pathogens which have the

potential to avoid complications that often occur with treatments of bacterial infections.

[Slide.]

The product has been approved in over 90 countries for the treatment of respiratory tract infections in adults. This includes Europe, Canada, Japan and the United States in April of 2004.

The European health authorities just recently this year reapproved the product based on a five-year renewal process in the review of the safety data which you will have available to you today in our presentations.

There is an estimated worldwide exposure of 28 million patients since it was first launched in Germany in October of 2001, and there is an estimated U.S. exposure of some 6 million courses of treatment.

[Slide.]

We have an extensive list of presentations as the sponsor. Our goal in this to ensure that you have all the information and the data available to you to accurately discuss and make

determinations on the questions that are presented before you by the Food and Drug Administration.

This includes a presentation on the medical need due to the resistance of antibacterial agents. We will have a review of the approval activities and the data that was available to the Food and Drug Administration at the time of approval.

We will go over the post-approval, microbiology surveillance that the company has supported to demonstrate the ongoing need for antibiotics in these infectious areas.

The clinical importance of erythromycin resistance in Streptococcus pneumoniae. We will also go over the clinical safety that is available to date including the postmarketing surveillance and also later on in our presentations, you will hear about two epidemiologic studies that are unique and provide an enhanced way of looking at one of the adverse events of special interest, hepatotoxicity, in which in the afternoon presentation, we will have several presenters go

over the topic of what is the potential risk for hepatotoxicity related to telithromycin.

That will include a complete safety overview of the data available to us, an expert review by Dr. Lewis, epidemiologic investigation from the PHARMetrics database, another epidemiologic investigation from Ingenix database, and then a review of the epidemiology and putting this all into perspective for us.

[Slide.]

Our second day's presentations tomorrow will include again the adverse events of special interest. These adverse events of special interest were either identified due to the pharmacology of the classes, such as macrolides, the clinical development program, or the postmarketing surveillance that provided signals that we need to investigate further.

Those presentations will include the visual adverse events, the exacerbation of myasthenia gravis, syncope and loss of consciousness. We will have a complete

presentation on the safety data, a review by our expert on the visual and a review by our expert on the myasthenia gravis.

The treatment options for respiratory tract infections and the role that telithromycin plays will be reviewed by indication, an overview of community-acquired pneumonia, acute exacerbations of chronic bronchitis and the antibacterials in acute bacterial sinusitis, and then we will sum up and provide you an overview of all the information you have heard over the last day and a half.

[Slide.]

We also have with us several experts that will be available to you to address questions to provide their perspective. This includes an ophthalmologist, hepatologist, neurologist, a cardiologist and our pathologist that have looked extensively at the data that you will hear about today, and the Food and Drug Administration has also had access and reviewed extensively.

[Slide.]

We also have clinical experts including adults and a pediatrician that was responsible for our review committee, Dr. George McCracken, who will be with us tomorrow only, so we will have to have any questions for him during our second session tomorrow.

[Slide.]

In addition, we have epidemiology experts in attendance and they will be able to provide their perspectives on the epidemiology and how we can utilize epidemiologic studies to enhance our evaluation of signals that we have observed in postmarketing surveillance data.

[Slide.]

We also have presenters and a cohort of experts on microbiology and biostatistics.

[Slide.]

What we will provide over the two days is demonstration that there is a microbiologic surveillance that demonstrates an ongoing need for products such as telithromycin, that there is actually a positive benefit-risk across all

indications that have been extensively studied, not only in the initial approval but also in some of our Phase IV studies that are now coming to fruition databases, and we will be providing them to the Food and Drug Administration over the coming months and years as that data becomes available.

We also have postmarketing safety data that have led to labeling modifications and also has included enhanced communications to the company as performed to ensure that medical providers are appropriately informed of the risks to make prescribing decisions for their patients.

Safety signals are more definitively evaluated through the epidemiologic studies in which you will hear about two of them regarding the potential for hepatic toxicity.

We continue with our risk management program and we will continue to make enhancements to that to ensure that health care providers are appropriately informed to make important treatment decisions.

[Slide.]

When we review each of the indications, you will hear about the efficacy demonstrated in community-acquired pneumonia. We will demonstrate that there is a broad range of comparators that we have looked at.

It actually works against common and atypical bacterial pathogens. We have data that supports that it works against multidrug resistance and in outpatients that are at risk for complications including the elderly, with safety that is comparable to other antibiotics for this indication and, as you heard this morning, each of the antibiotics in these indications has its own unique safety profile. Telithromycin has its own unique profile but it is also comparable in the overall risk associated with this indication.

As far as acute exacerbation of chronic bronchitis indications, we have also demonstrated versus a broad range of comparators the efficacy against key common bacterial pathogens and again in at-risk subgroups, the elderly, and risk factors for comorbidity and including airway obstruction..

The safety profile is comparable also in this indication to other antibiotics.

[Slide.]

Acute bacterial sinusitis indication. Again, we have looked at several standard antibiotic treatments and demonstrated the efficacy versus those, against key common bacterial pathogens in this indication, in subgroups of interest, such as severe infection per the investigator, documented pathogen at entry and total opacity on the sinus X-ray.

Again, we believe and support, the data will support the safety is comparable to other antibiotics for this particular indication.

[Slide.]

I would now like to take the opportunity to introduce our first presenter that we will be presenting on behalf of the sponsor on the Antimicrobial Use for Respiratory Tract Infections, Needs and Consequences. This will be presented by Dr. Donald Low. He is the Medical Director of the Ontario Public Health Laboratory and is a professor

at the University of Toronto.

Dr. Low.

Medical Need and Resistance

Don E. Low, M.D., FRCPC

DR. LOW: Thanks very much and good morning.

I will speak to you today about the need for antibiotic agents for the treatment of community-acquired respiratory tract infections that have a narrow spectrum, targeted spectrum of activity, yet remain active against resistant strains.

Some of which you will hear, as Yogi Berra said, is deja vu all over again because of John's presentation, but if you will bear with me, these are important points to make and I think they bear repeating.

[Slide.]

As you have heard, the Streptococcus pneumoniae is an important pathogen in the respiratory tract. It is the most cause of community-acquired pneumonia. It is associated

with a mortality rate of 12 percent. Two-thirds of all fatal cases of community-acquired pneumonia are due to the pneumococcus.

[Slide.]

During the 1990s, what we witnessed was the rapid emergence of penicillin resistance in the pneumococcus from less than 2 percent in the late 1980s to 15 percent by 2004.

[Slide.]

During that same time period, we saw the emergence of macrolide resistance again from less than 2 percent in the 1980s to 25 percent by 2004.

[Slide.]

Even more disconcerting were reports of resistance to other classes of antibiotics used to treat respiratory tract infections and also the recognition of the appearance of multidrug-resistant strains. Gary Doern reported from his U.S. surveillance program of 2002-2003 that, in fact, 25 percent of all isolates were multidrug resistant.

[Slide.]

Now, as Dr. Bartlett pointed out, we have recently seen the benefits of the new pneumococcal conjugate vaccine that was introduced in 2000. Our colleagues from the CDC reported that penicillin nonsusceptible in base of strains in pneumococci peaked in 1999 but significantly have decreased by 2004.

[Slide.]

However, it is important to recognize that there were no significant changes in the proportion of isolates that were resistant to macrolides or the fluoroquinolones, levofloxacin in particular.

[Slide.]

In addition, again as Dr. Bartlett has pointed out, there was a recognition of the appearance of a strain of serotype 19A, a serotype not covered by the vaccine.

This serotype was found to be multidrug resistant including being nonsusceptible to amoxicillin and ceftriaxone but Ketek, telithromycin, is fully active against the strain. Of course, concern that this replacement disease,

as it is referred to, has the potential to reduce the overall benefit of the vaccine against resistant strains.

[Slide.]

In addition, we have also seen the emergence of resistance to other common causes of respiratory tract infections including Haemophilus influenzae and Moraxella catarrhalis.

[Slide.]

So what is the evidence that resistance actually makes a difference?

[Slide.]

In fact, there are many that believe that there exists a discordance between reported in vitro resistance and clinical success in vivo. So why have clinical studies not been able to sort out this paradox?

One is doing outcome studies are very difficult to do, as again Dr. Bartlett has pointed out. Even using the best diagnostic techniques, an etiological agent is only identified in about 50 percent of cases.

Secondly, measuring the impact of discordant therapy is difficult. In the community, patients are treated empirically, specimens aren't sent, isolates aren't identified, susceptibility testing is not done.

In the hospital, patients are seriously ill, often using multidrug therapy. Mortality is an insensitive measure of outcome and, in fact, high-risk patients will often die despite the use of appropriate antibiotics and low-risk patients will often get better even in the absence of antibiotics.

Finally, MICs do not necessarily reflect drug levels that are found in vivo. Thus, substantial numbers of clinical infections are mislabeled as resistant to common antimicrobial drugs, such as the penicillins and, therefore should not be expected to fail therapy with these drugs.

[Slide.]

The clinical impact of penicillin resistance on the outcome of pneumococcal pneumonia

has recently been reviewed by Lance Peterson in Clinical Infectious Disease. He found the documentation of penicillin treatment failure particularly with the aminopenicillins remains virtually nonexistent.

[Slide.]

However, pneumococcal isolates were rare that had MICs of greater than 2. With the exception of some of the older cephalosporins, the PK/PD properties of most beta-lactams ensure activity against the vast majority of beta-lactam-susceptible, -intermediate, and -resistant strains.

[Slide.]

However, he did find numerous well-documented reports of treatment failure with the macrolide class of antibiotics in the treatment of pneumococcal pneumonia.

[Slide.]

Our group has been able to contribute to the understanding of this problem as a result of data that we have generated through our

population-based surveillance program of invasive pneumococcal disease that has been in place since 1995.

We defined a macrolide failure as when an oral macrolide was prescribed and Strep pneumoniae was isolated from a blood culture while on therapy or within 2 days of completing therapy.

1,696 episodes of pneumococcal bacteremia were detected. Of these, 60 represented failures of outpatient macrolide therapy including with clarithromycin and azithromycin.

[Slide.]

Macrolide failures were significantly more common among patients with pneumococcal bacteremia, with isolates exhibiting an erythromycin MIC of 1 mcg/ml compared with isolates exhibiting MICs of less than or equal to 0.5 mcg/ml from patients that didn't fail macrolide therapy, a susceptible category.

[Slide.]

Increases in the MIC greater than 1 mcg/ml were not associated with further increases in the

likelihood of macrolide failure.

[Slide.]

Similarly, Grant & colleagues from the CDC reported recently at ICAAC the association between macrolide treatment failures and resistance with pneumococcal bacteremia.

Of those patients that failed therapy, isolates were more often resistant as compared to those that didn't and, as we found, failures were just as likely to occur with low-level resistance as with high-level resistance.

[Slide.]

We have seen other consequences of antibiotics with broad spectrum activity used for the treatment of community-acquired respiratory tract infections including the emergence of resistance in enteric gram-negative rods and antibiotic-associated colitis.

[Slide.]

Several studies have documented the emergence of resistance in gram-negative rods causing urinary tract infections in the community

to a number of antimicrobials including fluoroquinolones and amoxicillin-clavulanate.

[Slide.]

C. difficile-associated disease is increasingly recognized among residents of long-term care facilities and among persons living in the community. MacDonald & colleagues from the CDC described a new strain of C. difficile and implicated a possible role of fluoroquinolone use as driving the emergence.

They analyzed 187 isolates obtained from patients with C. difficile-associated enteric disease from 8 outbreaks at U.S. health care facilities occurring between 2000 and 2003.

The epidemic strain they identified from recently collected isolates was positive for the binary toxin and was universally resistant to the fluoroquinolones.

[Slide.]

In summary, RTIs are a frequent cause of disease in the community. Strep pneumoniae is the most common bacterial pathogen and the one

associated with the greatest morbidity and mortality.

The relevance of resistance is now better established in some classes of antimicrobials including the macrolides.

The use of broad-spectrum agents for the treatment of community-acquired respiratory tract infections may not only result in resistance in bystander organisms but may lead to an increase is antibiotic-associated colitis.

Finally, there is a need for antibiotics with efficacy against resistant pathogens and targeted antibacterial spectrum.

Thank you.

Overview of Approval Activities

Helen Edelberg, M.D., M.P.H.

DR. EDELBERG: Good morning.

[Slide.]

I am Helen Edelberg from Corporate Regulatory Affairs.

[Slide.]

I am going to provide an overview of the

FDA approval process for telithromycin starting with the current status and approval timeline, followed by a summary of the data submitted to support the approval of telithromycin, and a brief discussion of postapproval regulatory activities.

[Slide.]

I will start with the current status of telithromycin and the timeline for FDA approval.

[Slide.]

In the U.S., telithromycin is indicated for the treatment of mild to moderate community-acquired pneumonia due to bacterial pathogens that are common including multidrug-resistant Streptococcus pneumoniae or atypical, as well as for acute exacerbations of chronic bronchitis and acute bacterial sinusitis in adults 18 years of age and older.

[Slide.]

This timeline starting with submission of the investigational New Drug Application in 1998 shows that data to support the FDA approval of telithromycin underwent extensive review by the FDA

and were the subject of two meetings of the Anti-Infective Drugs Advisory Committee.

[Slide.]

The New Drug Application for telithromycin included a total of 36 Phase I studies and 10 Phase III studies, 8 in the approved indications.

Based on review of these data, the Advisory Committee recommended approval of telithromycin for the treatment of community-acquired pneumonia, as well as collection of additional efficacy data on antibiotic-resistant Streptococcus pneumoniae and collection of additional safety data from a larger sample of patients, particularly from older adults and from subjects with comorbid medical conditions.

The FDA issued an Approvable letter for community-acquired pneumonia, acute exacerbation of chronic bronchitis and acute bacterial sinusitis. Tonsillar pharyngitis was deemed Not Approvable.

[Slide.]

We filed a complete response to this FDA Approvable letter including pharmacokinetics data

from an additional 7 Phase I studies, clinical efficacy data from an additional 4 Phase III studies, ex-U.S. postmarketing safety data, following an estimated 1.5 million patient exposures mainly in Europe, as well as additional safety data from a large, 24,000 subjects, 12,000 of which were telithromycin-treated safety evaluable, comparative study in a usual care setting. These data were not relied on for FDA approval or are referenced in the U.S. prescribing information.

A second Advisory Committee recommended approval of telithromycin for the three indications. But, following up on concerns over data integrity in Study 3014, the FDA requested additional analyses and information relating to pre-approval studies and postmarketing experience from other countries.

During a closed door session, the FDA briefed the Advisory Committee on these data integrity issues and on the approvable action that was taken for telithromycin.

[Slide.]

Ten months later, we submitted a complete response to the second Approvable letter including requested documents from Study 3014, a comprehensive review of visual effects, which is called the "Integrated Overview of Visual Events," and will be described later, clinical trial data from an additional two Phase I drug-drug interaction studies, 2 Phase III studies, one of which was an open label community-acquired pneumonia study that was enriched with antibiotic-resistant Streptococcus pneumoniae isolates, as well as ex-U.S. postmarketing safety data from an interim report of a German postmarketing observational survey, and an estimated 6 million patient exposures as of December 31st, 2003.

Let me just point out that the number that is referenced by the FDA of 3.7 million was the number that was submitted in our initial complete response in October of 2003. That was followed by 2 safety update reports, the last of which prior to

approval included data on the 6 million patients.

[Slide.]

After review of this additional data and information, the FDA approved telithromycin for these indications in April of 2004.

[Slide.]

Next, I will highlight the key Phase I microbiology, clinical efficacy and safety data that were used to support the FDA approval of telithromycin.

[Slide.]

The clinical pharmacology of telithromycin has been extensively studied including plasma and tissue pharmacokinetics, the effective impairment of elimination pathways on exposure to telithromycin and the effect of telithromycin on exposure to other drugs.

Of note, there was no increased exposure to telithromycin in subjects with mild or moderate hepatic impairment. That is to say, there is no need for a dose adjustment in these patients.

Telithromycin was shown to increase the

concentration of drugs metabolized by Isoform 3A4 of the cytochrome p50 hepatic enzyme system, a finding which is reflected in the labeling as was mentioned previously.

[Slide.]

In vitro microbiology studies demonstrated that telithromycin has a focused spectrum of antimicrobial bacterial activity against the common and atypical pathogens that cause most community-acquired respiratory tract infections including activity against antibiotic-resistant Streptococcus pneumoniae by the novel dual binding mechanism which will be further discussed by Dr. Stephen Jenkins.

Telithromycin has limited activity against nonrespiratory pathogens, which means that it has a limited impact on the usual bacterial host flora.

[Slide.]

Pivotal Phase III efficacy and safety studies in the approved indications included 10 randomized controlled and 4 open label studies, 3 of which were performed to increase the yield of

pathogens of interest and were enriched for Streptococcus pneumoniae based on specific study inclusion criteria.

This study design and primary efficacy parameters were consistent with U.S. and other worldwide regulatory guidelines for anti-infective drug development, which at the time recommended randomized controlled non-inferiority studies to demonstrate clinical efficacy.

[Slide.]

Pre-approval clinical efficacy data in community-acquired pneumonia included a total of 2,016 subjects in 4 randomized controlled and 4 open label pivotal Phase III studies. These data demonstrated that telithromycin is effective in treating community-acquired pneumonia due to key common and atypical bacterial pathogens including multidrug-resistant Streptococcus pneumoniae.

It is also effective in outpatients who are at risk for complications, for example, older adults and subjects with bilateral pneumonia or pneumococcal bacteremia.

The next two slides include some of the key data that were used to support the efficacy of telithromycin in the treatment of community-acquired pneumonia.

[Slide.]

This table shows that clinical cure rates for telithromycin were comparable to those for high-dose amoxicillin or clarithromycin in two different studies.

Study 3009 was terminated early due to FDA restrictions on trovafloxacin and did not reach the targeted sample size.

[Slide.]

This table which shows clinical cure rate by pathogen demonstrates that telithromycin is clinically active against pathogens of interest and in particular against Streptococcus pneumoniae.

[Slide.]

This table shows that telithromycin is active against antibiotic-resistant pneumococci.

As mentioned previously, the sizable number of Streptococcus pneumoniae isolates in the

telithromycin treatment groups was achieved with these additional open label studies.

[Slide.]

Finally, this table of clinical cure rates by risk subgroup in community-acquired pneumonia demonstrates the effectiveness of telithromycin in subjects who are at increased risk of morbidity and mortality including those with bacteremia, a number of whom had blood infections due to multidrug-resistant Streptococcus pneumoniae, older adults, and those subjects with a PORT score greater than or equal to III--that is, patients who are at increased risk of death due to pneumonia based on this prediction rule.

[Slide.]

Let's turn now to the pre-approval clinical efficacy data in acute exacerbation of chronic bronchitis.

These data, including a total of 480 subjects in 3 randomized controlled pivotal Phase III studies demonstrated that telithromycin is effective in treating acute exacerbation of chronic

bronchitis due to key common bacterial pathogens and in outpatients who are at risk for complications, again, for example, older adults and subjects with multiple comorbidities or underlying airway obstruction.

The following three slides will include some of the key data that were used to support the efficacy of telithromycin in the treatment of this particular respiratory tract infection.

[Slide.]

This table shows that clinical cure rates for telithromycin were comparable to those for amoxicillin/clavulanate, cefuroxime, or clarithromycin.

[Slide.]

This table shows clinical cure rate by pathogen.

In the acute exacerbation of chronic bronchitis studies, the efficacy of telithromycin against Haemophilus influenzae was lower than was demonstrated in the community-acquired pneumonia pivotal Phase III studies.