treated with Ketek have better clinical outcome than treated with the older comparator drug will really provide substantial evidence.

What about risk? Can risk be managed? The sudden and rapid nature of the clinical toxicity over and beyond any of the numbers that we have been discussing really makes mitigation of risk very difficult.

We have heard, and I think the FDA agrees, that clinical clear communication of risk to the patient over and above clear risk communication to the prescriber is extremely important precisely because of this clinical manifestation.

Patients taking oral antibiotics do not think that they are going to get these sudden onsets of vision loss or sudden loss such as disturbance of consciousness. This is something that we need to really educate the patient as well as the prescriber.

[Slide.]

So, in total, we talked a lot about how we look at evidence for safety, the evidence for

safety, because we really cannot do hypothesis testing for the most part. It is really looking at the totality of the evidence. The totality of the evidence shows that there is a lot of concern regarding these highlighted safety events particularly because of the clinical nature of the toxicity, the rapid, sudden onset for this brief-duration drug, a 5-day drug really makes mitigation of risk very difficult.

So what we need to do is to really define the population that would actually benefit from taking this drug right up front so that we can justify the risk.

On the benefit side, we talked about, by law, we need to provide substantial evidence of benefit. We have learned this now and we need to move forward. Based on noninferiority trials without quantification of the control for the indications of AECB and ABS, it is uncertain as to what the drug effect is over and above the natural history of disease resolution.

For CAP, I think we all agree that there

is drug effect over and above the natural history of disease resolution but we still need demonstration of clinical outcome superiority over the older drug, not "no worse than," if we really want to show that this drug is better for resistance diseases caused by resistance pathogens.

[Slide.]

So does Ketek's benefit outweigh the risks for each of these indications. I would like to acknowledge the people up here on this slide that have helped me to put this overall summary for you today. Thank you.

DR. EDWARDS: Thank you very much. We have gotten substantially behind in our schedule. At this time, I am going to move to the Open Public Hearing. I do not want to truncate that so I am anticipating that we are going to have to delay the lunchtime probably approximately by a half hour, the time we go to lunch. We may also need to somewhat shorten the lunch time allotment.

So, I think we are going to move right ahead now into the Open Public Hearing.

Open Public Hearing

DR. EDWARDS: It is necessary for me to read a statement before we begin that.

"Both the Food and Drug Administration 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 sponsor, its product and, if known, its direct competitors.

"For example, this financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your audience 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."

We have a total of seven speakers. They have been assigned by random in order. I want to begin with Dr. David Ross.

David Ross, M.D., Ph.D.

DR. ROSS: Thank you, Dr. Edwards.

[Slide.]

Good morning. My name is David Ross. I am a board-certified infectious-disease physician and an active clinician. I served as the primary safety reviewer for Ketek during the first review cycle and was the Safety Team Leader during the second review cycle.

[Slide.]

I will present data showing that there was substantial evidence of fraud in this application. Aventis knew that there were problems but did not tell FDA reviewers. FDA managers knew but failed to tell this committee. FDA managers used the same

data to approve Ketek despite warnings from criminal investigators and reviewers about suspected systemic fraud.

Management was so bent on approval that I was pressured to "soften" my review by the review division director. Other reviewers were also pressured.

[Slide.]

In April, 2001, this committee requested a large Ketek safety study. After Study 3014 was submitted, FDA reviewers discovered serious issues pointing at fraud. Despite their concerns, FDA managers ordered 3014 presented to this committee omitting the problems. As a result, the committee recommended approval.

[Slide.]

Every 3014 site inspected by FDA before the investigation was dropped had major problems. By December, 2002, FDA managers knew of serious data integrity issues. They could have postponed the advisory committee or not allowed presentation of Study 3014. Instead, they ordered it presented

publicly.

Two months later, they told A.C. members about data-integrity issues in a closed session according to FDA managers. I was there. Pertinent data known to FDA managers was not presented to this advisory committee. A Senate Finance Committee report confirms that most of the 2003 A.C. members were unaware of these issues.

[Slide.]

Was this just a matter of a few bad apples? During the course of 3014, Aventis received warning after warning from its contract research organization about serious data integrity concerns including with its lead enroller. It did nothing.

Aventis failed to report these problems to FDA which found out only through its own inspections. Aventis finally admitted to FDA five months after submission of 3014 that it had known of problems at its lead enrolled but denied there were any other problems with the study.

[Slide.]

Aventis did not tell FDA reviewers what it knew. Six days before the 2003 meeting, I e-mailed the FDA manager responsible for Ketek about extremely serious data-integrity concerns known to the Review Division, Division of Scientific Investigations and Office of Criminal Investigations and copied the Review Division Director.

I asked about presenting these possible fraud issues to this committee. His response, "It wouldn't be productive to present the data-integrity issues. What would be useful," he said, "would be for Aventis to make their best presentation possible using postmarketing data."

[Slide.]

FDA managers instructed a reviewer to publicly present 3014. When the reviewer protested, he was ordered to disregard data-integrity issues and present the study.

[Slide.]

As a result, FDA managers listened as Aventis told this committee that they had obtained

virtually complete follow-up safety information on 24,000 patients, many of whom never existed. So misinformed, this committee voted to approve Ketek and Study 3014 is now being cited in the medical literature.

[Slide.]

The reviewers knew the real story. Prior to the meeting, an FDA safety reviewer wrote, "I just wish we could find even a single credible large enrolling site in 3014." CDER's Division of Scientific Investigations concluded that 3014 was useless. Thus, the questions asked by this committee in 2001 have never been answered. But Ketek is on the market.

[Slide.]

The criminal investigators knew the real story, too. In July, 2003, FDA's Office of Criminal Investigations told FDA managers that they needed to expand the investigation to determine Aventis' possible role in the fraud. An e-mail documenting this briefing has been turned over to the Senate Finance Committee.

[Slide.]

Despite these warnings, FDA managers used Study 3014. A senior FDA manager wrote that the Review Division used the data saying that they assessed those AEs that were identified to qualitatively assess patterns of toxicity.

I have two questions. First, what does this mean? Second, why does the FDA briefing package state five times that FDA did not rely on 3014?

[Slide.]

FDA managers even cited Study 3014 in January, 2006 in a Public Health Advisory, brushing aside reviewer protests.

[Slide.]

In July, 2003, FDA managers were warned by OCI about fraud with Ketek. They did nothing. In February, 2005, they received the first report of fatal Ketek-related liver failure. They did nothing. In February, 2006, they received written warnings from reviewers about fraud with Ketek and about pressure to change reviews. They did

nothing.

They received new OCI warnings two weeks later. They did nothing. Only after Congressional subpoenas and stories about 3014 fraud in major media, did FDA finally do anything. They reworded the label.

[Slide.]

In late June of this year, FDA reviewers, including myself, were summoned to a meeting with Commissioner Von Eschenbach in which he compared the FDA to a football team and told reviewers that if they publicly contradicted management about Ketek, they would be "traded from the team."

[Slide.]

In summary, serious fraud issues in this NDA remain unresolved. FDA has allowed fraudulent data to be presented publicly and has used it. The scope of the fraud remains undetermined and the Ketek team has been pressured to remain silent. At the same time, a number of patients have died after ingesting Ketek.

The study that was supposed to answer

critical safety questions was fatally corrupted. The postmarketing reports submitted in its place are no substitute for rigorous safety evaluation. It is up to this committee to demand that the applicant and the FDA provide real evidence of safety.

Thank you. The views presented here are my own. I have no conflicts to disclose. Your packets contain source documents for this presentation. I will be happy to answer any questions.

Thank you.

DR. EDWARDS: Thank you. We are going to move on to our next speaker, Mark Cohen.

Mark P. Cohen

MR. COHEN: Good afternoon. My name is Mark Cohen. I am the Food and Drug Safety Director for the Government Accountability Project. GAP is a 29-year-old nonprofit public-interest group that promotes government and corporate accountability by advancing occupational free speech, defending whistle blowers, sometimes lamplighters, and

empowering citizen activists.

Our clients include current and former FDA employees as well as employees of other government agencies and drug companies. I have no relationship to the sponsor of this drug.

Just so there is no mistake, I am a lawyer. I am not and M.D. or a scientist. While I have been following Ketek very closely for the last year, I still have found myself at sea over the last couple of days parsing some of the more technical details. So, if I make some mistakes in details, let me apologize.

But, that said, let me summarize what I think is the big-picture message of this meeting. 3014 extensive data-integrity issues mean that that study can't be relied upon to justify Ketek's approval. The foreign postmarket data on Ketek are hopelessly uncontrolled and inconsistent and can't be relied on.

The sponsor's 11th hour epidemiological studies lack validation or are not powered, so they can't be relied upon. Ketek has yet to be proven

more effective than doing nothing in treating sinusitis and bronchitis.

How did this drug ever get on the market to begin with? In 2001, your predecessor advisory committee was so disturbed by Ketek's safety profile that it recommended that additional studies be done. That led to the major clinical trial, Study 3014. But, as we have heard, that trial was rife with fraud and data-integrity issues.

FDA's Division of Scientific Investigations concluded the none of the data from 3014 could be relied upon with any degree of confidence. FDA's briefing document here is, at times, less categorical, calling 3014 "difficult to rely on." But we know that FDA did rely on 3014 even publicly citing it as late as January of this year in a Public Health Advisory in support of Ketek safety.

I can't say why Study 3014 got so out of control. How much was lax FDA oversight? How much was the fault of the contract research organization? What are we to make of allegations

that Aventis turned a blind eye or even coaxed the fraud? These are questions that need answers and they are clear signs that Congress intends to get to the bottom of this.

Now, I don't mean to sound dismissive or rude. But no one should be surprised when a sponsor spins data to promote approval of a drug. FDA's job is quite different. To weigh accurate data to ensure that the approval of drugs is based on good science considering both safety and efficacy. That wasn't done with Ketek.

The Food, Drug and Cosmetic Act makes clear the drug manufacturers must provide scientific proof that their drugs can be safely used before putting on the market. That didn't happen with Ketek.

FDA's briefing document acknowledges that your predecessor advisory committee in 2003 was not told about the serious data-integrity issues with 3014 even though those issues were daily being revealed to the agency.

FDA could have told you in a closed

session or not presented 3014 at all or postponed the meeting. Instead, FDA managers concealed the evidence and, with no knowledge of 3014, your predecessor panel recommended approval of Ketek.

In my world, the lawyer's world, this is called fraud in the inducement; that is, fraud going to the very making of the understanding. It is "bait and switch." That makes the entire contract voidable by the victim and you, the advisory committee, and the American public are the victims.

FDA managers knew at the time, the 2003 advisory committee, that 3014 couldn't withstand scrutiny. So they turned to foreign postmarket data in the language of the briefing document to augment 3014 and find a justification for Ketek's approval.

Yet, if the pre-3014 data was insufficient to prove safety and 3014, itself, was useless, as DSI concluded, then the foreign postmarketing data served pretty much as the sole basis for approving Ketek. As Dr. Graham asked yesterday, when has FDA

ever before approved a drug based exclusively on foreign postmarket data.

There are compelling reasons not to go down that road. As every speaker here has acknowledged, voluntary adverse-events reporting is a crapshoot. Gross under-reporting is the norm everywhere. So it is, in countries relied upon in the Ketek reports.

50 percent, I think it was, of the postmarket data, came from France. Did you know that a peer-reviewed study found that doctors in the Bordeaux region of France report only 1 out every 24,433 adverse drug reactions. What is more, the European data on Ketek at the time of its approval were eye-poppingly inconsistent. Italy reported one-fourth the rate of adverse events as Germany and the overall rate of adverse events in Europe was reported to be higher among people taking no drug at all than those taking Ketek.

Aventis claimed that, based on 2 million exposures to Ketek, not one single case of drug-related liver failure had been detected. This

all flunks the smell test.

Here is what we know from the U.S. experience. FDA's Division of Drug Risk Evaluation found in May that reporting rate for acute liver failure from Ketek was three to 10 times that of its three comparator drugs. That doesn't sound like a similar rate to me. The DDRE also noted a steady and worrisome increase in the rate of reported Ketek-associated ALF.

So here is where we are. The major safety study on Ketek your predecessor advisory committee requested was a sham. It is as if it was never done. The foreign postmarket data are utterly unreliable. The sponsor showed up last week with two as-yet unreviewed studies.

It falls on this committee to send Aventis and FDA a message that you won't be played the fool. You never did get the properly conducted Study 3014. You should insist on it and, this time, make it a superiority trial. Without it and proof of Ketek safety, this drug has no business being on the market.

Thank you for your time and attention.

DR. EDWARDS: Thank you. The next speaker is Dr. Helen Boucher.

Helen W. Boucher

DR. BOUCHER: Good afternoon.

[Slide.]

My name is Helen Boucher. I am a member of the Division of Infectious Diseases and Geographic Medicine at Tufts University, New England Medical Center in Boston. I practice clinical infectious disease focusing on transplant-related infections and I run our fellowship training program.

Today, I am here on behalf of the over 8,400 members of the Infectious Disease Society of America. We are mostly physicians and scientists interested in infectious disease, many of us, most of us, taking care of patients on a day-to-day basis.

[Slide.]

First of all, I will just disclose that I do have an interest in anti-infective development

and I provide advice and consultation to the companies listed here and in your handout.

[Slide.]

The reason we are here to talk to you today is more about a problem that involves all anti-infectives than the particular drug we are discussing today.

As we have talked about for the last two days, advances in clinical-trial design and our understanding of how to study and develop antibiotics has advanced a lot in the past 15 years. That is really good news. It has led to questions about what the best trial design is, what the best clinical development program is, not just any particular indication but how best to develop an antibiotic, how many studies would be required, how much PK/PD could be involved, and a number of questions have arisen. I think we all think that is a very good thing.

I think perhaps an unwanted side effect of this has been that there has been a growing uncertainty in the area of anti-infective

development especially among the sponsors who plan and execute these development programs.

A particular area I would like to focus your attention on is the lack of written guidance. I think that has been an issue that has been discussed for a long time and that contributes to what is the No. 1 reason we hear that companies are getting out of the anti-infective business.

We called it a "chilling" effect here on anti-infective drug development and some would say it is staggering.

[Slide.]

This agency, back in 2004, as part of the critical path, identified that we have a problem with "no drugs" in anti-infectives, particularly in antibiotics.

[Slide.]

I think that is reflected very graphically here in these bars that show the total number of antibacterials, now antibiotics, approved. This is from Brad Spellberg's paper in CID a couple of years ago showing what really reflects a drying up

pipeline, that the number of anti-infectives that are being developed and are being submitted to the agency is going down at a very alarming pace.

The data have been extended out to 2006 and we hope will be published soon. But what we see is that this steep decline continues. We are aware of more and more companies that are choosing to leave the anti-infective business despite the growing problems of resistance that I encounter every day in my practice whether it is patients with MRSA infections and the problem of community-acquired disease that Dr. Bartlett highlighted yesterday.

Our rate of community-acquired MRSA is going up by 50--that is 50--percent every six months right now, or multi-drug-resistant Acinetobacter infections where I have had two patients die in the last six months after giving them inhaled and I.V. Cholistin which is really a poison, an old drug but all we have in some of these cases.

[Slide.]

So a lot has been done about this and it has been a very good collaboration. Back in 2002, IDSA leadership worked with agency officials and the plan was to quickly move and publish adequate guidance for industry in anti-infective development.

I think it is important to emphasize what we mean by adequate. It is adequate advice that industry sponsors can follow but it is also adequate in terms of scientific basis for determining safety and effectiveness. I think we have heard a lot of that today and yesterday and that is great.

[Slide.]

In the meeting that was talked about earlier in November of 2002 at a collaborative workshop between the FDA, IDSA, PhRMA, five guidance documents were identified. They are shown here. They are for resistant pathogens, bacterial meningitis, acute bacterial sinusitis, otitis media and AECB. They were identified as sort of the top five in addressing industry's need for clarity.

[Slide.]

Since that time, there have been a number of very productive workshops in collaboration with agency, as I mentioned before. There have been meetings between IDSA and others in the agency as well as involvement of legislation at both the Senate and House level all of which led to an increase in commitment to publish these guidance documents to address our pressing need.

[Slide.]

Unfortunately, we still haven't seen these and that has led to what we are calling our concern, that, in the absence of these published guidelines, during the period of evolution, it could be seen that the agency appears not to have adopted a uniform approach for communicating or consistent time lines for implementing their new thinking.

We have talked about the recent events in the past two days meetings that are examples of this, I think.

[Slide.]

So, overall, there are a number of barriers to the development of safe and effective antibiotics. We just chose to focus on one today and that is the absence of clear FDA guidance on trial design that has been cited as the major barrier, the one reason, companies are giving up their anti-infective programs.

That means stopping discovery programs, getting out, going towards smoking, obesity, other drugs that we have heard about again and again. So we think it is the major barrier.

We, at IDSA, find the delay in the release of these guidance documents that we hear are completely mysterious, potentially detrimental to further drug discovery and, ultimately, harmful to our patients and our patients' children who so need and will need new antibiotics.

Finally, I would just like to emphasize our commitment to work with the agency in any way we can to help facilitate this process in any way that the agency would find helpful.

Thank you very much.

DR. EDWARDS: Thank you, Dr. Boucher. We will now move to William DuMouchel.

William DuMouchel

MR. DuMOUCHEL: Good afternoon. My name is William DuMouchel. I am a statistician by training, have been on the faculty of statistics departments at several major universities. My most recent academic appointment was as a professor of biostatistics and medical informatics at Columbia University.

For about the past decade, my research has focused on data mining and statistical analysis in the area of drug adverse events, both with spontaneous-reports data and clinical data.

I am now the chief scientist at Lincoln Technologies which is a software and services firm headquartered in Massachusetts focusing on pharmacovigilance. We have supplied methodology and software environments to regulators such as the FDA and, in the U.K,, the MHRA.

These regulators and also several of the large pharmaceutical companies have adopted our

software for various pharmacovigilance purposes.

I have also been on two recent and somewhat relevant National Academy or Institute of Medicine committees. I was a member of the committee that was studying the postmarket adverse events for pediatric devices and another ongoing study right now on the privacy implications of datamining for counter-terrorism.

In terms of conflict of interest, our company does sell software and services to the FDA and to other regulators and to many pharmaceutical companies although, as far as I know, Sanofi-Aventis is not a user of our software.

Since the presentation by Dr. Levine yesterday relied heavily on the methodology and the software that we developed, I was asked to make myself available for questions and discussions in the use and interpretation of the disproportionality analysis of the AERS database. However, our company--we are not being paid for this appearance and the expenses of this trip--we are not being reimbursed.

In terms of the Levine and Szarfman analysis that was presented yesterday, it focuses on the relative frequency of reports of 16 drugs and 11 categories of reported medical events in the AERS database. This has to be studied in the context of about 33 million reports of about 3,000 medical ingredients and 10,000 MEDdra preferred terms.

So the analysis of so many frequencies certainly requires caution not only as the well-known fact that these reports do not really have a quality of scientific data, follow up is certainly necessary. The associations of disproportionality are certainly not necessarily causal and there is much confusion with indications for the drug and for complications of the disease in terms of these associations.

Another issue that is quite important is that fact that, as the data comes in, the drug names contain many mis-spellings and to process them automatically without human investigation for all 3 million reports is quite tricky. There are

also many duplicate reports that get submitted because the same incident can lead to reports coming from many sources.

However, our company has been working for going on to a decade with such data and we feel that we have a pretty good handle on the data-cleaning problem.

Finally, in terms of the statistical uncertainties, the ratios observed to expected in this kind of data are incredibly variable, especially when the counts and the expected values are small. Because of this excess variability, the problem of multiple comparisons is especially a worrisome because, if you start looking for the largest ratios when you are talking about thousands or millions of them, clearly, the variability can lead you astray.

In that regard, my main scientific contribution to this literature has been to develop Bayesian smoothing methods which help alleviate this multiple-comparisons issue. These methods have been reviewed in the peer-reviewed literature

and generally accepted.

The fact that this tradeoff, then, between the unreliability of individual values and the need to focus on the largest values is quite a bit alleviated by the smoothing methods that we have introduced in our methodology.

You saw the summary profiles of these different drugs across these major medical-event histories. I think that the fact that these methodologies have improved the statistical reliability does enable the big picture to be shown in terms of Dr. Levine's presentation.

It is also somewhat interesting that one of the MEDdra preferred terms is "drug infective" which was one of the things listed. Although, of course, that is nothing like a real study of efficacy, it is interesting that there is an internal--to the same database, kind of at least a hint as to the tradeoff between efficacy and the adverse events in that particular analysis.

I would be happy to answer any questions that anyone has about the methodology.

DR. EDWARDS: Thank you very much. We are going to move on to our next speaker now who is Dr. John Powers.

John H. Powers, M.D., FACP, FIDSA

DR. POWERS: Thanks, Dr. Edwards.

[Slide.]

Good afternoon. My name is John Powers. I was a medical scientist at FDA for the last eight years. The last five of those, I was the lead medical officer for the antimicrobial drug development and resistance initiative.

I am appearing here today as a private citizen. I am also a practicing clinician who sees patients and, prior to my time at FDA, I was an investigator on over 50 clinical trials. I also have published in the field of clinical trials in infectious diseases and I have written the chapter in Mandell's textbook on infectious diseases on interpreting the results of antimicrobial clinical trials.

Before my remarks, I would like to disclose that I am a consultant for MethylGene,

Cerexa and Takeda Pharmaceuticals.

[Slide.]

Since 1962, the law has required substantial evidence of effectiveness for drugs prior to licensure in the United States. Without substantial evidence of effectiveness, any adverse events in patients, no matter how rare, are not justifiable.

Congress, in court cases, also pointed out that the appropriate scientific standards outlined in the law are not meant to be applied prospectively only, a very important issue for today's discussion. There is no basis for previous agreements obviating appropriate analysis based on current understanding.

The standards in Europe are not the same as those in the United States and approval by other regulatory agencies does not obviate FDA from applying standards outlined in U.S. law.

[Slide.]

As Dr. Johann-Liang did not discuss, noninferiority trials do not show that two drugs

are equivalent or as effective as each other which makes conclusions like this one, on this slide, inappropriate. These trials are designed to rule out how much less effective a new drug might be compared to an old drug.

The amount by which the old drug is superior to placebo must be reliably known and must be reproducible from trial to trial. Pointing to a single placebo-controlled trial out of a body of evidence shows a fundamental misunderstanding of the data necessary to design and analyzes noninferiority trials. Reproducibility of results is a fundamental part of the scientific method even though we may choose to want to believe one out of a body of placebo-controlled trials.

This is neither statistical purism nor perfection but the basic information one needs to know if a drug is any more effective than no treatment at all. Without it, comparing a new drug to an old drug is meaningless. Meeting the definition of noninferiority for a trial does not necessarily mean the drug is effective.

Regulations since 1985 and the recent guidance ICHE-10 in 2000 outlines these issues. The advisory committee just discussed these issues three months ago.

[Slide.]

The issues with noninferiority trials go far beyond just picking a margin of noninferiority. If one enrolls patients in the disease who do not have the trial, as in the recent published telithromycin trial in sinusitis versus cefuroxime in which only 38.7 percent of the total enrolled patients were included in the bacteriologic per-protocol analysis and the European patients in that study actually had nasal endoscopies which we discussed at the previous advisory committee is not a valid way to determine that someone has the disease.

This data do not ensure that either the old drug or the new drug is any more effective than a placebo. Since noninferiority trials must be designed as similarly as possible to the placebo-controlled trials on which they are based

to ensure the constancy of the effect of the control, noninferiority trials also limit the ability to evaluate novel trial designs and endpoints.

IDSA's Bad Bugs, No Drugs white paper calls for FDA to evaluate novel trial designs but this cannot be done in the setting of noninferiority trials.

[Slide.]

Noninferiority trials are entirely appropriate in serious and life-threatening diseases where the benefits antimicrobials show on endpoints like decreased mortality are large and reproducible. Penicillin would be approved today for serious diseases and historical evidence shows a large decrease in mortality in diseases like severe pneumonia.

On the other hand, the results of previous placebo-controlled trials in acute bacterial sinusitis shows 12 of 17 trials failed to demonstrate a benefit of antimicrobials compared to placebo. In acute exacerbations of chronic

bronchitis, 9 of 14 trials failed to show a benefit of antimicrobials.

The placebo success rates in these trials vary widely from 19 to 95 percent. These vast differences in the trials mean that their results cannot be pooled.

You heard Dr. Bartlett yesterday discuss the issues with prior meta-analyses in these diseases. The perception that antimicrobials are already proven effective in these disease is based on the results from published meta-analyses that do not evaluate all of the clinical-trial pooled data across vastly different studies or evaluate only subgroups from these placebo-controlled trials.

For instance, the often-quoted Saint meta-analysis in AECB only evaluated nine of the 14 placebo-controlled trials ignoring over a third of the available data. One cannot calculate any number needed to treat from this data.

[Slide.]

Clinicians have already become aware that noninferiority trials do not provide the kind of

evidence that they need to make decisions for their patients. In a recently published trial of cefditoren compared to cefuroxime in AECB, a drug that was approved before telithromycin, the authors even note in the abstract of their publication that the trial does not ensure that either drug was any more effective than placebo.

[Slide.]

This graph shows that the results of noninferiority trials with telithromycin in sinusitis completely overlap with the effect of placebo in placebo-controlled trials. In fact, the Lindbaek trial that Dr. Ferguson talked about today still does not show that a 15 percent margin is justifiable as the confidence intervals cross that.

[Slide.]

The same applies to the three trials that were done with telithromycin in acute exacerbations of chronic bronchitis where the effect of the drug overlaps with that of placebo.

[Slide.]

At an advisory committee in September

related to acute bacterial sinusitis, some advisors felt that a drug that is being used in practice must be granted an indication so the clinicians will know about its adverse events.

However, FDA regulations already note that when a drug is previously believed to be effective but there is a lack of substantial evidence of effectiveness, the drug may be labeled as such while still describing the adverse events in labeling.

[Slide.]

I would like to now move on to talk about the ethics of clinical trials which seems to be a major objection to doing placebo-controlled trials. One of the fundamental principles in the ethics of clinical trials is equipoise; that is, is there uncertainty about the research question to justify putting patients at risk in a trial.

It is clear that there is still substantial uncertainty regarding the effect of antimicrobials in self-resolving respiratory-tract infections. It also seems incongruous to argue

that patients cannot provide informed consent to receive a placebo plus symptomatic therapies for diseases in which patients routinely decline to seek medical care. Not every patient with sinusitis goes to the doctor.

Several trials over the last year have shown that withholding therapy for a few days in acute otitis media did not result in increased adverse outcomes for children. The Declaration of Helsinki also outlines that placebo-controlled trials are ethical when, one, there are scientifically sound methodological reasons for their use in order to determine the safety or efficacy of a drug and, two, subjects will not be exposed to additional risk of serious harm.

Both of these conditions are met in self-resolving respiratory-tract infections and the irreversible harm, such as liver failure, may occur more commonly in the patients who receive active therapy, not placebo. Therefore, there may be benefits to patients who are enrolled in the placebo group.

Placebo-controlled trials do not mean that no treatment is given to subjects. Subjects can and should still receive appropriate non-antimicrobial symptomatic therapies. The proposed benefits of antimicrobials in preventing rare consequences of these diseases, like brain abscesses, has never been shown.

Even if antimicrobials do prevent these rare events, it is important to know the magnitude of this benefit to compare it to the magnitude of the adverse events. If an antimicrobial presents 1 in a million cases of brain abscess but 1 in 100,000 people die of adverse events related to the drug, then there is an overall negative effect from administering that drug.

This risk/benefit obviously does not apply in disease like severe pneumonia where there is a 30 percent decrease in mortality, therefore rare adverse events are justifiable.

However, using drugs in minor diseases where there is substantial harm from the drug violates the basic medical principal of, First Do

No Harm.

The noted medical ethicist Benjamin Friedman wrote in IRB in 1987 that, "for research in humans to be ethical, it must be scientifically worthy. A poorly or improperly designed trial that cannot possibly yield useful results related to the primary hypothesis is, by definition, unethical."

Friedman noted that, "A worthless study cannot benefit anyone, least of all the subject, himself. Any risk to the patient, no matter how small, cannot be justified." This concept is already incorporated in FDA's clinical hold regulations.

[Slide.]

Therefore, it is actually, as noted by these authors, inappropriate noninferiority trials that, themselves, are unethical since they expose subjects to harms without providing evidence of effectiveness. Institutional review boards are not protecting subject by allowing enrollment in inappropriate non-inferiority trials. This is an area for which education of IRBs is sorely needed.

[Slide.]

I would also like to address quickly the issues of resistance. There is a lack of clarity on the impact in humans of macrolide and penicillin resistance in the test tube as it is currently defined, even in diseases like pneumonia.

Since 10 to 15 percent of subjects in pneumonia trials will fail therapy even when are infected with susceptible organisms, case reports of failure are not evidence of lack of effectiveness of a drug. Even young healthy people die of pneumonia even though that rate is small.

In a recent trial by Fine in 1997, 0.1 percent of people who were young and healthy died of pneumonia. Several observational trials show no effect on outcomes in patients who are infected with macrolide-resistant or penicillin-resistant strains compared to patients infected with macrolide or penicillin-susceptible strains.

The mortality rate for pneumonia has not increased in recent years despite the emergency of

resistance in the test tube. This raises the issue that the definition of resistance in the test tube is most likely incorrect for both macrolides and penicillins since it does not accurately predict clinical failures in patients and overestimates the impact of resistance.

In fact, an article in the Journal of Clinical Microbiology in 1996 recommended lowering the break points for erythromycin based on no clinical data.

DR. EDWARDS: Excuse me, Dr. Powers. I am going to have to ask you to either stop here or briefly sum up to give time to the other speakers.

DR. POWERS: Thanks. We can and must do better clinical trials. Inappropriate trials expose patients to harm and approval of ineffective drugs actually compounds the problem of antimicrobial resistance. Also, taxpayers should not have to pay for drugs that have not been shown to be more effective than no therapy at all.

FDA managers should be leaders in advancing public health but leadership takes the

courage to do what is right even when it is difficult. The FDA reviewers I have had a honor and pleasure of working with are some of the most courageous public servants I know and I know that they can get out guidance that will help drug sponsors to develop drugs more effectively in the future.

DR. EDWARDS: Thank you very much. I would like to move now quickly to Dr. David Shlaes.

David M. Shlaes

DR. SHLAES: Thanks very much for the opportunity to speak to you today.

[Slide.]

I am highly tainted since I have been working in industry for the last ten years. Two companies have sponsored my trip. I don't have any specific relationship with Sanofi-Aventis. I might mention that before I worked in industry for the last ten years, I was an academic practicing infectious-disease physician. I still consider myself an infectious-disease physician. My area of research interest was antimicrobial resistance.

[Slide.]

What I would like to do is provide us today with a little perspective which I think is sorely lacking. I think just a few thoughts in terms of perspectives. Actually, my comments are actually going to be reminiscent of some of the things Dr. Bradley said yesterday and go back to the question Dr. Soreth asked at the very beginning of this meeting which is, compared to what, which I think is probably the most important question that anybody has yet asked.

So, in consideration of the risk/benefit for antibacterials, the agency could and probably should reflect on drugs approved previously including generic drugs based on efficacy data which they believe, in retrospect, are questionable.

Antibiotics with relatively low risk, in addition, but for which prescription volume is high, which includes many of the generic antibiotics, may be associated with higher absolute risk. If you looked at the prescription numbers

presented by the last FDA speaker, you will get an idea of that.

Then, as you already know, severe hepatotoxicity is not the only potentially life-threatening adverse effect in the antibiotic world. What I think would be more useful than looking at these adverse effects one at a time, in a way, would be to have some kind of a serious overall adverse effect index to better judge risk.

[Slide.]

Now, of course, there is a dilemma. This meeting actually poses a dilemma for both physicians and patients because, essentially, no antibiotic, as far as I know, has been approved by the FDA for acute bacterial sinusitis based both on bacteriology and with a placebo control.

That includes the first-choice antibiotics that people talk about in various guidelines, Augmentin or amoxicillin. The second-line antibiotics, in most guidelines, all have issues. Macrolides, and I believe there is accumulating evidence within the macrolide literature that

resistance leads to clinical failure.

There is very widespread resistance among tetracyclines. Same thing with Bactrim plus Bactrim is associated with common allergaic reactions. Then there are fluoroquinolones and others. The question I pose to the committee is do we no longer need other options. I would say the answer to that is no--that is, we do need other options.

[Slide.]

Again, as part of my campaign of perspective, if you look at the 10 million, and actually this wasn't a survey. This was actually the rate, I believe it is 23 now cases per 10 million prescriptions for Ketek resulting in serious liver toxicity and sometimes fatality. This included, as I said, the four deaths.

If you look at fatal anaphylaxis from penicillin, those rates vary from 1 to 35,000 to 1 in 100,000. So, in a rate for 10 million, it would be something like 100 to 285 deaths from anaphylaxis for the penicillin drugs.

Anaphylaxis is a toxicity that occurs suddenly. It is not predictable. It attacks young people, frequently. So I would suggest that this is a more dramatic, or as dramatic, an event as the acute liver toxicity and other toxicities you have been discussing for Ketek.

Even if you reduce the anaphylaxis numbers by tenfold to account for poor reporting, the event is still more common than hepatotoxicity, severe hepatotoxicity or fatal hepatotoxicity caused by Ketek.

[Slide.]

I did list prescription data in the U.S. but you have already seen that. So I will skip over that.

[Slide.]

The logical conclusion from my thoughts are that the FDA should withdraw approval of the penicillins as therapy at least for acute bacterial sinusitis. Congress should now inquire as to why the FDA did not move more expeditiously against the penicillins.

I say this recognizing that the problem with argumentum ad absurdum, which I believe is what this is, is that sometimes one finds the absurdity valid.

In conclusion, if we want efficacious new antibiotics for infections caused by resistance bacteria, we must be realistic and, I would say, consistent across all antibiotics about the risks we are willing to take and the standards we impose.

Thanks very much for the opportunity to address you today.

DR. EDWARDS: Thank you very much. Our last speaker is Dr. Prabhavathi Fernandes.

Prabhavathi Fernandes

DR. FERNANDES: Good afternoon, everyone. I have had over 30 years in antibacterial research. I worked in three major Pharma and now the fourth biotech company. I an not representing Aventis, have no relationship with Aventis-Sanofi. But I am interested in developing new antibacterials and my company does develop new antibacterials.

[Slide.]

So, in general, all of us here do have the same goals. We all want affordable--and nobody talked about the affordability of some of these clinical trials we are talking. Very few biotech companies could ever do a study with 24,000 people--affordable antibiotics that are safe and effective against, also, resistant bacteria. Success requires that we are all on this tablet.

[Slide.]

This tablet is currently broken. Patients and physicians say there are not enough safe and effective antibiotics. Pharma and biotech face lack of clear guidelines to develop antibacterials that make this financial risk too high. The returns on the investment for antibacterial development is too low. My investors tell me that.

FDA says we need extraordinarily safe antibiotics that are more effective than placebo and so does Congress.

[Slide.]

So let's look at Ketek as an example only.

It is not the only problem, this particular drug, and see what is the cause of this problem. Antibiotics were developed for serious infections. However, they turned out to be pretty safe. Patients then demanded these antibiotics so patients are also at fault. They demanded these antibiotics for simple infections such as what we have heard, sinusitis, et cetera, and there are increased profits from antibiotic sales for simple infections which Pharma agreed, as well as patient demand, actually confounded.

Pharma then markets very aggressively for these simple infections, much more aggressively than for complicated because there is much more money in simple infections. There is increased patient exposure immediately after approval and increased reporting of adverse events and millions of patients are exposed immediately after approval.

This has now resulted with FDA, patients and Congress questioning use and safety of antibiotics and the question is where are the magic bullets.

[Slide.]

So thoughts which have arisen since Ketek was approved are should widespread use be discouraged to prevent selection of resistance bacteria. We are actually killing the goose which is laying the golden egg.

Should FDA protect the public from unnecessary exposure to antibodies that can result in harm? Should patients be using so many antibiotics for simple infections? Should physicians be writing so many antibiotic prescriptions?

Should Pharma sales reps promote antibiotics for simple infections? We are all at fault.

[Slide.]

There are unrealistic expectations. No drug, no antibiotic, is completely safe. Risk/benefit analysis is easier when you are treating complicated infections. It is impossible to detect every rare side effect in any size trial so there is no point in increasing the size of the

clinical trials and increasing, then, the cost of the drug.

We need preclinical toxicity, clinical safety in about a thousand patients but we also need mandatory--mandatory--submission of Phase IV data. I did like what I heard about Europe where they have to resubmit for approval.

There must be a ban on promotion for simple infections. I don't think I will be popular in Pharma for saying that, but there should be a ban on promotion for simple infections.

Waiting to get sufficient patients with resistant bacterial infections to prove efficacy in clinical trials is like waiting for insurance when your house is on fire. It is too late when you have a whole lot of resistance.

[Slide.]

So here is a proposal for clinical-trial design to demonstrate efficacy. I agree that, for simple infections, placebo-controlled trials are the only way to demonstrate that the drug is effective. Comparator controlled trials should be

used for serious or complicated infections to demonstrate efficacy.

About 200 cases per study for your drug should be used and the top two standard-of-care antibiotics should be used, not the worst-case antibiotic which has been previously approved.

Noninferiority studies for these compounds should be approved. An approval for organ systems of infections, such as respiratory, skin and skin-structure infections, should be used, using special areas like sinusitis, bronchitis and others when they are simple cases. If it works for complicated disease, it will work for the simple diseases and would reduce the cost of drug development.

In infectious diseases, the biomarker, which we have heard so much about, is isolation of the pathogen or PCR identification of the pathogen to demonstrate the pathogen and clearance. We have all forgotten COG's postulates.

A new antibiotic that has activity in vitro and in animal models against resistant

bacteria but is equal to or even slightly less active than a comparator, a proven efficacy comparator, could be then approved for the resistance bacteria.

[Slide.]

Now, encouragement for developing new antibiotics; clear FDA guidelines, which you have already heard about, to make drug development feasible is necessary. Two adequate, 400 patients each, perhaps, in comparator-controlled noninferiority studies for serious infections should allow a drug to be approved.

Approval on an organ-system basis to decrease costs of multiple clinical studies would be essential to get development of new antibiotics in place. Some diseases are rare. For example, endocarditis and guidelines should combine many rare deep-tissue organ infections into one claim.

The government should provide incentives to small companies who are addressing public-health needs for new antibiotics such as matching grants, et cetera.

With that, I thank you for your attention.

DR. EDWARDS: Thank you very much.

I would like to thank all the public speakers for making some very important comments. I am sure I speak for the entire commission here by saying that I don't think these important comments are going to simplify our deliberations this afternoon.

To that note, I want to preserve as much time as possible for the deliberations this afternoon and I am going to ask you to shorten your designated lunch period a bit.

I would like to resume the meeting at 1:40 this afternoon. So we will break now and return at 1:40.

[Whereupon, at 12:52 p.m., the meeting was recessed to be resumed at 1:40 p.m.]

A F T E R N O O N P R O C E E D I N G S

[1:45 p.m.]

DR. EDWARDS: I want to resume with the final portion of our meeting. I would like to begin that with the summary comments and charge to the committee which Dr. Cox will begin.

Summary Comments and Charge to the Committee

DR. COX: Good afternoon, everybody. I will just be making some brief comments before Dr. Dal Pan gives the charge to the committee.

[Slide.]

What I want to do is just briefly review where we have been over the last day and a half with regards to the topics we have covered.

[Slide.]

First, just to start out, we heard a talk about respiratory-tract infections, treatment and epidemiology, from Dr. Bartlett and then reviewed premarketing data with regards to efficacy, that which was available that supported the approval of the indications of CAP, ABS and ABECB.

[Slide.]

Then we went on and talked about the premarket safety database which included the controls and data from controlled and uncontrolled studies, data from Phase I studies and also we heard about the issues with regards to data from 3014 which was data that could not relied upon.

We also heard about the foreign postmarketing data that was part of the NDA approval. Then the Ketek NDA was approved in April of 2004.

Also, today, we have had some discussions about noninferiority trials, noninferiority designs, and started out by describing some of the earlier antibiotics and how the types of trials that we see submitted have changed over time.

We also talked the previous advisory committees and meetings that have talked and discussed the issue of noninferiority-trial designs, specifically in the indications of acute bacterial sinusitis and acute bacterial exacerbations of chronic bronchitis beginning with an advisory committee in 2002, in subsequent

committee meeting in 2003 and then, most recently, in the 2006 Anti-Infective Drugs Advisory Committee along with the regulatory briefing in 2005 such that, from the data that we have looked at, we haven't been able to reliably determine a margin for noninferiority studies in ABS and ABECB.

[Slide.]

We then moved on and started on the afternoon of the first day talking about postmarketing data. We heard from the European Medicines Agency with regard to their reassessment. We also heard about data mining, hepatic adverse events and then additional discussions, beginning this morning, with regards to disturbances of consciousness, exacerbations of myasthenia gravis and also the visual disturbances. Then we heard some summary comments on overall risk/benefit considerations.

Now we seek the committee's advice with regards to the overall assessment of the risks and benefits of Ketek for each of its approved indications based upon what we know today.

With that, with the Chairman's permission, I will turn the podium over to Dr. Dal Pan to read the questions and discussion points.

Thank you.

DR. DAL PAN: We have finished all the presentations now. I am going to go over what we would like the committee to discuss. It is really a recap of what I said in my opening remarks yesterday morning.

[Slide.]

The discussion we are asking you to focus on is the following. Please discuss whether the benefits outweigh the risks for each of the approved indications for Ketek, those indications being community-acquired pneumonia, acute exacerbations of chronic bronchitis and acute bacterial sinusitis.

We will ask you to please take into consideration the current safety information specifically including the hepatic, visual, loss of consciousness and exacerbation of myasthenia gravis adverse reactions that we have spoken about over

the past two days.

We would ask you also to please consider the information supporting efficacy for these indications as well as the recent efficacy discussions on the use of noninferiority trials.

Based on these discussions we would like you to answer a number of questions.

[Slide.]

First, 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 would like you to vote on this question and we would like you to vote separately for each of the indications, those being community-acquired pneumonia, acute exacerbations of chronic bronchitis and acute bacterial sinusitis.

[Slide.]

Following that, our second question is, 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? Again, we would like you to please specifically address hepatic, visual, loss of consciousness and exacerbation of myasthenia gravis adverse reactions.

Next, should any additional communication strategies or risk-management programs be implemented to assure the safe use of Ketek? If you think so, we would like to know what specifically you are thinking.

Next, please recommend any additional studies to further define the benefits of Ketek for each indication. Finally, please recommend any additional studies to further define the risks of Ketek for each indication.

[Slide.]

Our third question, 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 for those

indications.

Thank you.

DR. EDWARDS: Thank you. Before we actually begin the open discussion, because of the complexities of the issues we are facing today, I just wanted to let Sanofi-Aventis and the FDA in only a brief two-minute comment if they so choose to take a moment to respond to any points that have been brought up which they might want to address.

DR. GERRELL: Thank you very much, Mr. Chairman . My name is Richard Gerrell. I am the global head of Regulatory Affairs Development. I would like to take this opportunity to re-stress that Sanofi-Aventis takes very seriously patient safety. It is our highest priority.

We also take our ethical and regulatory responsibilities very seriously in all our actions including the conduct of clinical trials.

We have heard, over the last two days, some characterizations of Study 3014. We strongly object to the characterization that the company turned a blind eye or coaxed investigators or, even

worse yet, induced them to conduct fraud in the support of one of our studies.

This is simply false. We acted in good faith in the conduct of Study 3014. First, we did not ignore, we did not coax and we did not do anything unethical with our investigators. We do seek, as part of our routine clinical good clinical practices to exclude such investigators from our studies.

As the court found in the sentencing of the one investigator in question, that this investigator committed "sophisticated fraud" to perpetuate her fraud against Aventis, the FDA and the public. At the time of the second advisory committee meeting, we believed that the GCP violations and deviations that had been conducted at this one study investigational site were to be remediated and that the data was going to be satisfactory.

It is important to note that the tools that we have at our disposal as a sponsor are different than the tools that the FDA and the

Criminal Investigation Branch has at their disposal to detect fraud.

To this point, we trust that the FDA and the Criminal Investigations Unit are continuing to do their investigations of Study 3014.

As you are aware, the FDA used ex-U.S. spontaneous reporting data as part of their review and approval process. Spontaneous reports that come from ex.U.S. have provided extremely valuable information for the safety profile of Ketek in detecting rare events as evidenced by the fact that myasthenia gravis exacerbations were noted prior to the approval in the United States through the Pharmacovigilance Reporting System in France.

Sanofi-Aventis takes patient safety very seriously. It is indeed our first priority. We have welcomed the opportunity over this last day and a half to present to you, to the FDA and to the public, the information that we know about Ketek, not only its safety but also its effectiveness.

Thank you very much.

DR. EDWARDS: Thank you very much.

Dr. Jenkins, do you care to make comments from the FDA?

DR. JENKINS: Yes. Thank you, Dr. Edwards. I think Dr. Cox got us started yesterday morning by reminding us that the review of the application for Ketek was very long and very complicated and raised very many complex issues.

Reminding you, there were three review cycles. There were two advisory-committee meetings. There was a request for the large safety study that was done after the first review cycle. There were the data-integrity issues, the fraud issues, the criminal convictions.

There was involvement not only of DSI who is a regular partner in helping us to assess clinical trials but also the Office of Criminal Investigations and others outside the agency that we don't deal with on such a regular basis.

Then, finally, there was the use of postmarketing safety data from Europe and other countries as part of the package to reach the decision that the product could be approved as

being safe and effective for its intended use.

So there is no doubting that this was a very complex review. Very many difficult and complex issues came up in real time over the course of that review. FDA was challenged with facing those issues with the information we had at hand as time evolved, which is very different, I think, and it is important to keep in perspective, than looking back at the entire totality of the information that is available to us today to raise questions.

You have heard one or more perspectives shared during the Open Public Hearing about what happened over the course of the review of the application. I would emphasize that is one perspective. There are many other perspectives within the FDA. There are documents and data that were not shared during that perspective.

So I don't want you to go away with the view that that is the only perspective about what happened during the review of the Ketek application.

The issue about whether to discuss the ongoing DSI investigations at the second advisory committee meeting has come up quite a bit. That was the subject of quite a bit of discussion within the agency in real time as we were preparing for that second advisory committee meeting in January of 2003.

There were reasons why the agency felt that we could not discuss that information at that January meeting and they certainly were not intended to be a means of deceiving the committee or deceiving the public. It was related to the fact that these were early results of the investigations.

The investigations were ongoing. At that time, we had no way of knowing what the eventual outcome of the investigations would be, going back to my comment earlier about it is easy now in hindsight knowing that we later decided that we could not utilize those data to question why didn't you know that in January of 2003.

Well, you may recall from the time line

that Dr. Soreth shared, we got the final memo from the Division of Scientific Investigations recommending that we not utilize Study 3014 over a year after that January, 2003 advisory committee. So there was a lot of ongoing work to evaluate the integrity of that data.

We are fortunate today in having Dr. Joanne Rhoads who is the former Director of the Division of Scientific Investigations at FDA who was in that position during the time that the Ketek was present with us. She was referenced in the Senate Finance Committee report and she would be willing to provide a brief overview from her perspective of the issues that were in play at that time if the committee would like to hear that.

FDA will formally respond to the Senate Finance Committee report. We received that on Wednesday, It involves the need to develop the response across multiple parts of the agency and to address issues about what we can say about investigations that may or may not be continuing.

So it will take, obviously, more time than

we have had to date to make that formal response.

I do think it is important for the committee to focus on the task at hand today that we are asking you, given everything you know today about the benefits and the risk of Ketek, what is your advice to us on how we should regulate this product going forward.

With that, I will stop. Again, if you would like for Dr. Rhoads to make a brief comment about her role and her thoughts about the decision not to present the data-integrity issues to the second advisory committee, she is here and happy to do that.

DR. EDWARDS: Thank you very much. Could I get a sense from the committee about whether they feel it would be of value for Dr. Rhoads to comment before we begin our deliberations.

Please, Dr. Rhoads.

DR. RHOADS: Hi. I am Joanne Rhoads. I am currently at the NIH but I was the Director of the Division of Scientific Investigation and was ultimately responsible for the contents of the

memoradum we sent to the Review Division about the 3014 study.

I can probably clarify for you two things. One is the context of the inspections and the limitations that we face, that we all face. One is that this was a large simple trial which was difficult. These are difficult studies to do and to monitor and to inspect.

As I recall, there were almost 25,000 subjects over almost 2000 sites. The sponsor had made an agreement with the Review Division to monitor on site certain--a percentage of sites. I think, ultimately, it was about 50 percent of the sites were monitored on site.

Part of the difficulty with these studies is, because you want to see what is happening in the real world, the investigators who were enrolled are real-world physicians who were not sophisticated in doing clinical trials. So you have a wide variation in the ability of the physicians to do the trial.

Just to make a point about the monitoring,

this was done by a fairly well-known group who does monitoring as a--it was contracted to them. Monitoring is highly variable. In my experience, even when fraud exists, monitors often don't find it. Even when serious programs exist, monitors often don't find it.

And there were problems definitely identified. But, considering the nature of the trial and the extent of the problem, we did not see direct evidence that this information was ignored by the company.

Having said that, I want to explain to you also the limitations of what the Division of Scientific Investigation can and cannot to. On average, we inspected, I think, two to three sites for large pivotal studies even for NDA applications. This was not in that category. Yet we ultimately, at the request of the Review Division, inspected eight sites.

The first three, we found significant problems. We referred those to the Office of Criminal Investigation. They, themselves, elected

to follow up on only one of those sites and the woman was subsequently convicted. The other two sites, they elected not to follow up on.

As a result of our analysis of the eight sites that we did in-depth inspections, we had to make an extrapolation of what this mean. Total, I think the number of subjects was about 1600. It was less than 10 percent of the number of subjects in the trial.

What we saw, though, was that the data at each site could not really be verified. We had one episode where we thought it looked like fraud and ultimately it was proven to be fraud. The others were not pursued by criminal investigation and fraud is a very, very high bar to prove. So we did not have conclusive evidence from any other site.

That is the situation we were left with having looked at what we saw, looking at clinical trials in general, if it is the quality of data that we normally see in a trial, we came to the conclusion that, look, out of four or five, because one study could not be completed, of the sites we

looked at, there were big problems.

That doesn't mean that we found adverse events specifically that haven't been reported. It was sloppiness. It was couldn't verify subjects when they came, if they were there. There were lots of problems that seemed sufficient to say, we can't rely on this information.

From that, we extrapolated. We said, look, if we can't verify--we have done as many inspections as we logistically could do. If we cannot have any confidence in this data, what can we say about the rest of the data? We can make no statement of confidence.

So that was the nature of the information we have the Review Division and the Review Division accepted our recommendation not to include the study in the label.

The other thing I would just like to say, in terms of what was revealed or not revealed to the advisory committee, all the time I was at DSI, Office of Chief Counsel was adamant, we could never reveal outside internal FDA communications in any

case that was not closed. As far as I know, even the disqualification letter to the woman who was in prison had not gone out and gone through the process by the time I left FDA last March.

So I think there were significant legal questions about what information could and could not be released.

If you have any questions, I am happy to answer them. But, from my perspective, it was a very difficult call. We made the most conservative call we could to say the data did not look robust. It did not look reliable. The Review Division accepted that recommendation.

DR. EDWARDS: Dr. Shapiro?

MS. SHAPIRO: I guess I am feeling entirely comfortable with how the FDA proceeded on this. I am struggling to get my arms around the relevance of this for our task at hand. To that end, I just have a--I have some assumptions that I would like confirmation of from the company and that is that the site investigators were not employees, that they were receiving only fair

market value, if anything, for what they were doing in promoting the study and that, when evidence came out about problems with them, there was no attempt on the part of the company to somehow hide that or keep them there or continue with the fraud, or whatever you want to call it.

DR. RHOADS: I will just say, from my perspective, I think from the evidence that you have heard here, is the study, itself, was never powered to find problems in the magnitude that it looks like they occur. So, even with a perfectly well-done study, with that design and everything else, with what you know now, it probably is not relevant.

But I think the main points are that we did not find deliberate hiding of serious adverse events. I think that is important to know. We just don't know what the quality of the information is.

MS. SHAPIRO: I don't mean even the relevance of the data that was discarded. I mean the relevance of the issue of this allegation of

pursuit of fraud. So, could I have my assumptions confirmed by the company?

DR. EDWARDS: Sure.

MR. GERRELL: You can have your questions confirmed. They were not employees of the company and they were, indeed, paid fair market value.

DR. EDWARDS: Thank you very much.

Committee Discussion of Overall Risk/Benefit

DR. EDWARDS: Now we are beginning our open discussion. I wanted to describe the format which I believe we will be following. It is basically going to be divided into two parts. We are going to have an open discussion, let each of us give our opinions and contemplations about the issues we have been asked to focus on.

We will take a break and then we are going to allow at least an hour--it will probably take a bit more than that--for us to actually do the voting.

Now, we have been asked to vote on three separate issues. So we will do that and will consider the community-acquired pneumonia,

bronchitis and sinusitis individually. We will take a vote on those three entities in an individual way.

Unless there are any objections, and I am certainly open to suggestion on this, I am going to use a slightly different format. My rationale for using the format, which I will describe in just a minute, is that this is a mixed committee of two different basically disciplines. We are the Anti-Infective Advisory Committee and then the Drug Safety Committee. So, for this particular voting period, we have got this combination of expertise.

What I would like to do is this; for each of the individual entities, have each one of us individually give our vote and then definitely give our rationale for that vote.

After we have heard everyone's vote and rationale, I am going to offer the opportunity for anyone who wants to to change their vote to a final vote. This will allow each of us to hear the thinking processes of each of the individuals. So, at the end, we will then have a final vote.

One of the reasons I am interested in pursuing this is to eliminate, as much as possible, the sort of herd effect that can occur with voting in this kind of a structure and, secondly, to allow our cross-disciplines, if you will, to have an opportunity to have the rationales displayed.

So, if there are no objections to that mode of procedure, that is the way we will follow.

MR. LEVIN: This is not an objection, just a point of information. There are really three categories here of voting members. There are the Anti-Infectives, the Drug Safety and Risk Management and the consultants to FDA that are voting. So it is an amalgam of three different constituencies.

DR. EDWARDS: Thank you. The questions that we see on our agenda after the three entities--that is, "If continued marketing is recommended for any indications, please address the following." Those issues we are going to address in a more or less open-discussion fashion although, if we identify areas where a tally needs to be

taken--that is regarding a specific change in packaging or something like that--then we will have a vote to give the FDA a sense for the committee's inclination to go in a particular direction on a particular issue there.

I will be asking them to guide us to call for those types of tallies. So that means, when you vote, if you, for instance, vote "yes" for community-acquired pneumonia, we are not going to have you give specific recommendations about each of the points under there. So, again, that will be more in the discussion format.

Are there any questions about the general plan to proceed here? Then I think we will--yes, Dr. Norden.

DR. NORDEN: I guess I have one other question for the FDA, I think. We are talking only about Ketek today. Whatever actions we proposed, Ketek should or should not be influenced by potential actions or other drugs in the same class or other classes.

DR. COX: You are correct, Dr. Norden.

The subject of today's meeting is to discuss Ketek.

DR. EDWARDS: Thank you. I also did want to add that we do have the opportunity to ask questions further if further points of clarification need to be made from both the FDA and Sanofi-Aventis. So we have that flexibility.

Again, I will emphasize what I think has been brought out on many occasions so far, that our focus really is on determining whether the benefits outweigh the risks for these indications, the process of the FDA and the entire process of drug-safety evaluation are not the focus of this meeting today. It is this specific question, issue, that has been raised about this specific drug.

Would anyone like to begin. Dr. Leggett? We are on community-acquired pneumonia for the most part.

DR. LEGGETT: I have offered to go first even though I didn't want to because I was the Chairman of that infamous 2003 meeting. So I should get what I deserve.

For the first time even in one of these meetings I actually spent some time writing down things so I would at least try to get them a little bit right.

As far as I can tell from outside the FDA, an advisory committee never hears the whole of any story about any drug. We are asked to comment on parts of the puzzle. The FDA is the one that makes the final drug approval and oftentimes receives other information from the company after the meetings. So I didn't find that very unusual.

The major issues underpinning the convening of this joint advisory committee remain the same as in 2001 and 2003 and much of the discussion of these has followed a similar pattern even though the specific data have evolved.

Benefit/risk has been the major theme in all of these three meetings. If efficacy had not been shown in 2003, then any risk now is too much. However, it was the FDA's opinion at that time that the drug was effective in a noninferiority trial during a time of transition to recommending

superiority trials.

It has been my anecdotal observation that advisory meetings are always more difficult when there are safety issues because, in good part, easily detectable toxicities such as what would be seen in a normal-size clinical trial dooms a drug long before we would see it and we don't have the same reliable statistical methods or surrogate markers for rare toxic effects to help guide our recommendations to the FDA.

We are working in an imperfect, resource-limited world where we need new antibiotics that are, in turn, among, if not the least, profitable products for the pharmaceutical industry that currently produces these agents in less and less fashion.

The advisory committee in 2003 recommended approval and I have not seen data presented in these two days that contradict our committee's 2003 efficacy opinion. We have heard that the EMEA did grant a five-year renewal which I found interesting and should be, hopefully, profitable for the FDA

going forward.

The FDA has been evolving its trial-design guidance for some time and has been holding advisory meetings well before Dr. Woods' New England Journal of Medicine proposal for radical changes in the drug-approval process published this year.

However, I don't believe that an FDA advisory committee should recommend a new standard for a previously approved drug using a new standard if the FDA cannot do it anyway which is what I had been told in the past when I was so brash as to suggest that.

I think, for the indications with no clear hard endpoint or with a relatively high spontaneous-remission rate such as AECB, which is not the most severe type, or ABS certainly would benefit from superiority placebo trials. If these trials can be requested, I would favor that both of these latter trials be redone. They would certainly not be as costly to the company as 3014 was.

I am sure, in this regard, that the pollyanna effect that we have discussed in the Anti-Infective Committee several times before for otitis media is just as true for these two latter indications as it appears to be for acute otitis media. Thus, to me, the major issue is whether new safety data is sufficiently disquieting to reverse or modify our previous 2003 recommendation.

So, what do I see in conclusion here? There were hints of rare toxicity that surfaced at the 2001 meeting that I attended. There have been several toxicity issues that appear to be fairly well clarified by the time of the 2003 meeting. There have, thus, been postmarketing--AERS has providing more information about rare toxicities from initial data mining to detecting signals to pharmacoepidemiology to focused case-by-case review to better quantify the risks.

I also wonder, in this regard, whether there might not be some significant class effect or on top of everything that was talked about up to this point.

Now, in terms of the specific toxicities--do you want me to discuss that part at this point?

DR. EDWARDS: Yes, Jim.

DR. LEGGETT: I am done with that.

DR. EDWARDS: I really appreciate your starting out. You are bringing up an issue that I think all of us on the Anti-Infective side are going to want to hear the safety people talk about.

DR. LEGGETT: Exactly.

DR. EDWARDS: I am hoping they will volunteer. If not, I am going to put them down.

DR. LEGGETT: Great. I would like that.

DR. EDWARDS: But if you wanted to express some thoughts about the toxicity now, that would be fine.

DR. LEGGETT: Here is an ignorant I.D.'s version of what is going on. First of all, I am neither a toxicologist nor a pharmacoepidemiologist. The committee meetings I have attended regarding safety issues have always been the most difficult ones I have dealt with. On

the other hand, I am a practicing physician and a member of the IDSA who has lectured in a similar vein to the presentation by Dr. Boucher. I do want to see drugs that will help me treat people.

Regarding hepatotoxicity, specifically, the FDA's data mining shows a spike but I wouldn't consider any of these toxicities in isolation nor would I limit a comparison only to similar class. I didn't think that was correct because, in the presentation, spikes showed in different classes at different places.

We often prescribe first, say, a macrolide and then a beta lactam and then maybe a fluoroquinolone to the same patient over a brief period of time. So I think it is important to not only compare within, say, ketolides to macrolides. We need to include the toxicities of those other classes.

Moreover, I think that trimethaprim sulfamethoxazole, for instance, and penicillin are also toxic such as with Stevens Johnson, anaphylaxis, cytopenias, et cetera. So, in terms

of the hepatotoxicity, I do not think that that should modify our stance in community-acquired pneumonia. But we can talk about other things to spruce it up as the next step.

DR. EDWARDS: Thank you very much. Probably most of us on the anti-infective side listening to the toxicity discussions today feel that there is somewhat of a disparity in the presentations and the quality or the quantity of the toxicity.

It would be very helpful, I think, certainly for me personally but probably for the rest of us, if we could hear people from the safety side reflect on this somewhat different perspective.

Dr. Morris.

DR. MORRIS: I certainly have that same--I mean, that is my glowing issue right now is what we heard about the--well, there are lots of issues in safety. Let me just define one and ask for some discussion about it and that is the disparity in the concept that the risks for hepatotoxicity are

unique or not unique. We have two very different views.

I guess the way it occurs is when you look at spontaneous reports, you are supposed to think of them generating hypotheses. I thought that FDA did a really great job, that Dr. Brinker did a terrific job, and his colleagues, in defining the hypothesis much better than I would have ever expected.

But it is an hypothesis. Then we looked to other studies and we had two from the sponsor one of which I think had problems in its narrowness of its definitions whereas the PHARMet study actually did find a number of risk percent that was somewhat similar to the percent we heard, I guess the 1 in 20,000 to 30,000. If I understand the PHARMet study, it is like 1 in 137,000. But even the PHARMet study is just unique cases or unconfounded cases, I think is the way it was explained.

So there is a similarity but the disparity exists as to whether it is a unique problem or it

is a very similar problem. In the PHARMet study, we heard it is about the same as other drugs. But we just heard from FDA that it is a very unique problem. Looking at that FDA data, it looks as if that analysis comes from this controversial issue of dividing by time and it is an area I have never seen before.

I know the sponsor had some questions about it. FDA seemed to say that it was okay. I mean, I heard two things from FDA, one from Dr. Dal Pan which said there are questions and one from the presenter who said that, this is it. I don't know what FDA's position is on this or if there is a single position within FDA. So maybe first FDA can clarify what it believes and then we can go talk about--some of the epidemiologists and statisticians could talk about that analysis.

DR. DAL PAN: Let me just clarify. There are differences of opinion in FDA as to the slide Dr. Johann-Liang showed this morning where the person-time method is used. I explained that yesterday. So you have heard both positions from

Dr. Graham yesterday.

DR. MORRIS: But that was presented as FDA's position. I mean, that was my understanding.

DR. DAL PAN: I think Dr. Johann-Liang qualified it by saying that there were differences, there were methodologic issues in quantifying things. So I think that it is not my opinion that that is the right method to base a comparison of telithromycin against bromphenac or triglidozone or a trovofloxacin.

I think her point from that slide was really the rapid onset of the syndrome which I think we all agree on. I think that is one of our big concerns for all of us who are looking at--

DR. MORRIS: That was a separate concern.

DR. DAL PAN: Yes.

DR. MORRIS: But just that one slide, I thought you were saying this is unique and this is a unique antibiotic that is only comparable to other antibiotics that were removed from the market.

DR. JOHANN-LIANG: I can respond. The

point of this slide, just like Dr. Dal Pan said, was an illustration of the clinical manifestation that I was talking about, like you said, the tempo, the rapidness, the suddenness, because what you are seeing there, when you look at--when you factor in time and you are sort of looking at those drugs and filling in the time factor to look at them sort in a consistent manner, in a way.

What you are seeing is that the numbers--even though Dr. Brinker's analysis which is just looking at exposure in the denominator shows that numberswise, it is less than trovo, let's say. When you account for the time, you are seeing a number that rises for Ketek.

Simply, that is to illustrate--from my perspective, that was just a number demonstration to show that that risk of hepatotoxicity becomes right up front for the drug Ketek. That was really it. If you need further--

DR. MORRIS: But that is what I am objecting to. That analysis suggests that, if you divide--because we are dealing with an antibiotic

relative to a chronic drug, is that the way we assess risk for an antibiotic? I had never heard that before.

DR. DAL PAN: I guess it was my point that, because of the variable durations that people take the drug for, and the variable occurrence of risk over the time period, which is an assumption of the person-time method, that the risk is constant across the time which I didn't feel was met for the comparator drugs, that that method didn't work.

That was my point. When you look at the simple reporting rates which are problematic as well, for the four drugs posted on that slide, in fact, Ketek was lower than all of them. So I think that those simple reporting rates were actually not on the slide. But we have other data to show that.

I think that that was my concern with that particular analysis. But it doesn't mitigate any concern I have that Ketek is hepatotoxic or that it has a very rapid onset.

DR. AVIGAN: Can I just add a little bit

about this. I did participate in the expert panel. We are confusing, I think, apples and oranges. There really are two measures. One is at the population level which we have heard about from the epidemiologic studies. But where there was some limitation, perhaps, is in the careful case review about causality and learning more about the clinical differential diagnosis which is very important to know what you end up with which is linked to the drug because the phenotypes of these liver events have to be excluded for other etiologies.

That is a very important point. What we did, I think, as you heard yesterday and we went through this step-by-step, is a case-level or patient-level analysis to show you what the nature of this clinical syndrome is and to assign causality.

The point about all of this is a subset of the universe of cases and it is a spontaneous reported subset. In that subset, we were struck by the clinical characteristics of rapid onset in an

opportunity to actually risk-manage this when this event occurs because these events are catastrophic and not predicable. They are random. So, at least as far as we can tell, there is more to learn about susceptibility factors in patients in the future.

The outcomes in this group were relatively severe. In this group, there was about an over 80 percent rate of either hospitalization or death or transplant. So we were struck by--so here the signal really has more to do with the clinical phenotype when it occurs rather than the incidences.

Both measures are complementary. With regards to an epidemiologic study, in my opinion, and I think many would agree, that the medical-record analysis and determination of what those ICD-9 codes, or those codes that are billing codes, how they translate to differential diagnosis to allow for a careful assessment of the cases and appropriate exclusion and inclusion, is really critical.

So that is something we need to review.

We haven't actually looked at that data yet. Nonetheless, there is clearly a risk of some kind of a rare event where, in certain susceptible patients--we don't know what those susceptibilities are. We know females, perhaps more aged patients and maybe there are genetic susceptibilities, who may be at increased risk above what we see in the generic background.

We have more to learn about this and I think we heard about that from Dr. Seefe and Dr. Lee. So there may be some individuals out there in the real world who are at, perhaps, greater risk than the 1 in 100,000 or whatever that number is for acute liver failure.

DR. MORRIS: My question is, is there a unique risk to this drug that is greater than other antibiotics.

DR. JOHANN-LIANG: In response to that, the only other antibiotic that was restricted or withdrawn that was on the table was trovofloxacin regarding the specific issue of hepatotoxicity. So, in that way, we were trying to--since we are

looking at Ketek right now, we could look at across--we could look at cefditoren because there were already the other comparators. We could look at gemifloxacin with this issue.

But we chose to present only those drugs in the past that had an issue with this regarding hepatotoxicity and trovofloxacin and antibiotics.

The second point that is important to remember--it is so hard for us, at this point, and we will review the epi studies that have come in from the FDA. We haven't had a chance to do so.

But, at this point in time, again, as I have said before, trying to quantify with numbers whether using this database is very difficult. So we still come down to, what was the clinical picture of the hepatotoxicity which was discussed at length.

The thing that is really important in addressing Ketek's benefit to risk is that, of those 12 acute liver-failure patients, only two took the drug according to the reports for pneumonia. The rest took it for sinusitis,

bronchitis, upper respiratory infections. So you really need to keep that in mind; what was the indication of use that resulted in the acute liver failure.

DR. AVIGAN: I will just try to say one thing about that. We don't have a side-by-side comparative analysis of the incidence of catastrophic acute liver failure. That is actually difficult to ascertain from the kind of data sets that you heard about that we are using.

But one thing I do want to point out to you is that, although the target organ may be the same for various kinds of drugs, for different drugs for liver toxicity, the ranges of injuries that you get for different drugs actually are potentially distinct.

The point here, again, is that, for some antibiotics, you get this immunoallergic rapid-tempo sort of injury which is distinct, perhaps, than some other antibiotics.

DR. MORRIS: Can I try this one more time? The sponsor maintains that the risk of

hepatotoxicity is the same for Ketek as for other drugs. You can agree, disagree or I don't know. Can I have an answer?

DR. AVIGAN: I think that we concluded from Allen's talk that the reporting-rate difference that was seen between the comparators, which were the floxacins, and his analysis of Ketek that that reporting rate of 23 versus 6 for the other antibiotics was within a range where we could not say that the incidence is different. We couldn't conclude that because the data, itself, is too granular to make such a conclusion because of the secular reporting trends.

So we are concerned but we don't have a precise enough measure to say that that represents a true difference in incidence.

DR. EDWARDS: Dr. Follman.

DR. FOLLMAN: I had my mind made up a little more before I came here today. One of the things I am struggling with now is the level of evidence for efficacy. Dr. Johann-Liang, in her talk, discussed how the ground rules or the

landscape has shifted in terms of clinical trials and not noninferiority trials are not viewed in the same way that they were when this compound was licensed.

She provided some data that suggested--well, she provided some conclusions, I guess, that panels had decided, that the FDA-sponsored panels decided, that the state of a evidence now is that efficacy trials are needed.

So my concern here now is whether this should sort of be grandfathered in in terms of efficacy and say, well, the noninferiority trials that they passed are good enough. Should I accept what the FDA seems to be saying for acute sinusitis and acute exacerbations of chronic bronchitis or should I make a decision now about what I really think about the noninferiority- versus efficacy-trial questions.

So, in my mind, I am not real clear about how I view the efficacy of this product yet. So I would like a little more comment on FDA's part about what is their view about the state of