our preclinical studies, our postmarketing visual commitments study and our two pharmacoepidemiologic studies.

These provide the basis for the strength of the evidence that we present today and tomorrow.

Thank you.

DR. EDWARDS: Thank you very much.

At this time, I am going to return to the FDA and ask Dr. Mortimer, who is from the European Medicines Agency, or the EMEA, to discuss the postmarketing ex U.S. studies.

Dr. Mortimer.

Five Years Postmarketing Ex U.S.

Orjan Mortimer, M.D., MPA

DR. MORTIMER: Thank you. I want to thank you for the invitation from the FDA to present the situation on the evaluation of Ketek in the European Union system.

[Slide.]

First of all, an outline, I will present for you the rather different system we have in Europe in comparison with the FDA and the U.S. for

one country and then the specifics for Ketek, the legal status, assessment of hepatic safety, renewal, which is a specific procedure we have with renewal this year in Europe, and assessment after the renewal, also summarize them.

[Slide.]

The European system, it is a decentralized network, so what you see here is a brief overview of the European FDA.

[Slide.]

We also have associated two, three more countries, but we don't discuss those today.

Here we are with the expertise. They are situated in the competent authorities, national competent authorities, so there we have the scientific teams.

Furthermore, we have as European administration located in Docklands, London. It is the European Medicines Agency. It has a staff I think about 400 people, and they are project team leaders, and so on, and they administrate, first of all, the centralized procedure, and I come back to

that.

They have scientific committees for human medicine of products veterinary area, often herbals and, in relation to those committees, you have a number of working parties down there that constitutes, so to say, the expertise in the respective area.

I am the delegate of the pharmacovigilance working party for Sweden. We also have two delegates per member states in this Scientific Committee for Human Medicinal Products. Furthermore, for these products they are authorized through this system. There are also alternative systems, so to say, for other products, but I will not touch on that because it's too complicated.

The delegate for countries is the rapporteur. Then, you can see an X is here for products. Ketek is authorized through the central system and Sweden is the rapporteur. We present safety issues, pharmacovigilance issues in the pharmacovigilance working party and discuss that

with the other member states and it is adopted by the committee here.

Above here you have the European Commission which takes the legal decisions.

Those countries mentioned here, Sweden, Germany, Netherlands, U.K. and France, we are those that have the largest number of rapporteurships. Wee are, so to say, responsible for most products among all these member states. Today, I think it is U.K. and Sweden together that are in the front of that. In France, for example, I think about 1,200 people employe. U.K. has about 1,000. Sweden has about 450. Germany must have over 1,000, as well, and Netherlands is about the size of Sweden I think.

[Slide.]

The European Medicines Agency, discussing then the role they have, they coordinate the evaluation and supervision of medicinal products throughout the European Union and the Agency brings together the scientific resources of these member states.

It is quite advanced networking. It's about 3,500 European experts that are, so to say, notifying us, taking part in the scientific assessment on quality, safety and efficacy.

This network by legislation was started in 1995 when the European Union member states were expanded from 12 to 15 and, now, in May of 2005, to 25 now. It is primarily only involved in the centralized procedure, the EMEA.

[Slide.]

The Committee of the Human Medicinal Products, they have a number of working parties. Here are some of them; biotech, pharmacovigilance, herbal, as well, safety, quality, efficacy. We have SAC, scientific advisory group, set up for specific matters for some therapeutic areas. As well, they are on a steady basis.

[Slide.]

The responsibilities on the Scientific Committee are, then, opinions on granting variation. Variation is an expression for procedure for updating the product information, the

SPC in Europe, suspensions, and so on, and opinion of any scientific matter concerning the evaluation of medicinal products for human use in the European Union, which then may be requested by the EMEA, by the member states, or by also the Commission.

[Slide.]

So they should formulate an opinion for these procedures and, when there is a disagreement in any procedure at national level or other levels of the procedures, they are then referred to the CHMP opinion by legislation. They also provide general guidance and provide guidelines that are developed by these different working parties.

[Slide.]

For the centralized procedure, which is the procedure applicable for Ketek, when this is used, then, the companies submit one single application to all member states at the same time and a single evaluation is carried out, then, through the CHMP.

[Slide.]

If the committee then concludes that

quality, safety and efficacy of the medicinal product is sufficiently proven, then, it is a positive opinion adopted and then the Commission would make it valid in the European Union and all member states at the same time.

[Slide.]

To also present the scope of the centralized procedure, it is mandatory for biotech products for AIDS, cancer, neurodegenerative disorders, diabetes. It will add later on, in 2008, or so, for other disorders, viral diseases, also for orphans, where we have a specific committee, that prepares the status of the product for the CHMP and then it will go through the same kind of procedure as for other products.

It is also optional for other new active substances. Some generics may apply, as well, and biosimilars like for erythropoietin, for example, is a recent biosimilar product approved in Europe.

To look at the medical review process, then, the CHMP then issues its rapporteur and a co-rapporteur when you have the first application

for marketing authorization like for Ketek in 2001 when it was approved.

So, then, we make up two different--a rapporteur and the co-rapporteur assessment report on the quality, preclinical safety, clinical safety and efficacy.

There is also one member state making a peer review of the assessment. When you send out those assessment reports, you also add questions for clarification, outstanding issues, so to say, for clarification.

Then, there is a peer review in all member states, so they comment on the assessment and on the list of questions.

[Slide.]

Further in the procedure, which is 210 days, 7 months, with clock stops, but sufficient time, and so on. But the sufficient time, you have the assessment reports pooled and you have further responses to list of questions and further assessments within this procedure.

If it is down here, going to the CHMP,

then, they can choose then to not adopt a positive opinion and, then, in general, there is a withdrawal of the application. But the decision, their position is presented at the web site of the EMEA and, if it's okay, it's then adopted marketing authorization in Europe.

[Slide.]

To come into details, the rapporteur then, they have a scientific team, so we are looking into the files and meet with them as a presubmission and assessment of the marketing authorization application, as well.

Then, for the authorization, we have a life-cycle perspective and here we have a number of different tools by legislation then to follow.. We have periodic safety update reports that are six months during the first two years and then annual.

We have risk management plans by the new legislation set up one year ago. The risk management plans, they should in detail present a safety specification, which then take care of established risks, potential risks or missing

information.

Then, there you have a pharmacovigilance plan, which takes care of the potential and missing information, let's say, first of all. And you also have a risk minimization plan. So for each safety issue, you should consider if it's applicable or appropriate to propose risk-minimization measures like restriction or changes to the product information or communication, and so on.

We also have then follow-up measures that are conditions that may be related to updating, follow up of resistance for Ketek, for example. For clinical issues, there may be also the postmarketing studies, and so on, and to provide protocols and to have milestones when you should submit the results and so on.

Then, we have the renewal system, which is now the mandatory one, that you have, after five years, you have sum-up of all that has been assessed during five-year period since the first approval, and then you can adopt it for lifetime or for another five years. For example, I come back

to that for Ketek.

[Slide.]

Ketek was granted in European Union then in June 2001. The marketing authorization had the following indications. I think they are quite similar with approved in the U.S.

In patients aged 18 years or older, you have community-acquired pneumonia, mild to moderate, acute exacerbation of chronic bronchitis, acute sinusitis, and also as an alternative to beta-lactams for tonsillitis and pharyngitis in patients 12 years or older. This may be different with the U.S. I think this is approved in Canada, for example. The dose recommended is 800 mg once daily for 5 to 10 days.

[Slide.]

The usage in the European Union, totally, it is estimated to be 13 million courses, a large proportion then of the estimate of 27 million courses worldwide,which was the data log point for that I think was about July 2006 These are estimates, of course, provided by the MAH.

France makes up over 50 percent of the use of prescriptions in Europe. But we also have very extensive use in Italy, Germany, Spain and Greece. This will reflect also the problem with multi-resistance in those countries. In Scandinavian countries and U.K., for example, the use is not as extensive and not either the problem with multi-resistance. But there emerged some multi-resistance problems in those countries, as well, of course.

[Slide.]

There are the most important product updates of product information. You recognize those interactions with rifampicin, which impairs the efficacy by interaction of the metabolism to p450 level.

There also has been an update regarding visual disturbances, aggravation of myasthenia gravis.

[Slide.]

In 2003 was updates concerning hepatic ADRs in the Side Effects section, anaphylactic

reactions and visual disorders. The Driving section has also been updated accordingly with the visual disorders.

[Slide.]

Monitoring of the proton beam time while patients are receiving telithromycin is also recommended in an update. Also transient loss of consciousness was added and a driving warning accordingly.

[Slide.]

Recently, then, after the publications in January 2006, like the situation was for the U.S. and the FDA actions, we issued warnings regarding severe hepatitis and liver failure, which may occur with short latency and, in most cases. were reversible. Patients should be informed of signs and symptoms, and we specified the signs and symptoms. That has been implemented by the company on request from the CHMP.

In September 2006, contraindication in patients with previous liver reactions during exposure to telithromycin, and also added that

fatalities have occurred with such reactions.

[Slide.]

We also had, during 2006, conducted a number of reassessments of hepatic safety and, in January, after the first preliminary one, the working party under CHMP considered the characteristics of serious hepatic reactions were not well described in the product information.

The short latency to onset of these reactions was of concern, primarily in primary care considering that the large proportion of use was in primary care and quite mild types of infections, respiratory infections, and an update of the product information was then requested.

[Slide.]

A further assessment was scheduled and the risk management plan tailored on hepatic safety was also to be requested, and an early suppression a concern to the company.

[Slide.]

This was designed as a follow-up measure, which is a procedural subtype of title then, and

most of the available data then, when we returned to that in May 2006, most of the available data on hepatic safety was considered consistent with the current labeling after the update in February with regard to hepatic safety.

No specific risk factors could be identified except a tendency then for patients with community-acquired pneumonia to be at high risk of liver reactions in line with what has been the impression in clinical studies perhaps because of longer duration of treatment or the problem to differentiate between what is the risk with the infection on the hepatic side and what is related to the treatment.

[Slide.]

In May, also, a risk management plan was considered satisfactory and there was a protocol for the U.S. study. That was all planned by the company here I think and that will be presented later today, the PHARMetrics and the Ingenix study. That has also been looked at, at the protocol in Europe. and the company has provided us with some

preliminary results.

The risk-benefit was still considered favorable after that assessment.

[Slide.]

The assessment of available data on hepatic safety in the European Member States was continued to say that was very important for us.

[Slide.]

Then came the renewal and that was submitted in parallel with the reassessment during the first half-year of 2006. So, in June, after the first reassessment, the CHMP considered the benefit-risk of Ketek to be continued to be favorable based on the review of available information from all parts of quality, efficacy and safety.

[Slide.]

Further then increased awareness of safety issues especially hepatic safety. The CHMP was of the opinion then that additional five-year renewal should be requested and that MAH should also continue to submit annual periodic safety update

reports. By legislation, after the first renewal, the next one is after three additional years. This is mandatory reporting by legislation normally.

[Slide.]

Assessment on cases of serious hepatic ADRs was also conducted in Europe by specifically requesting information from all competent authorities in Europe with regard to serious hepatic ADRs.

In summary, there were 49 cases. We have some application problems as usual but most of them were from France and Germany. We had 3 fatalities in Europe. This was done up to July 2006. All three of them were from France and they provided limited information. There were other explanations for the hepatic reactions in those three cases, so they could not be attributed to telithromycin according to the assessment, according to the assessment of the French agency.

[Slide.]

Furthermore, the reporting rate was about 4 to 10 cases per million courses. These data

again are in line with the current product information and did not alter the conclusions drawn by the CHMP in June. This was done in September, a quite recent one.

[Slide.]

Taking global data then into consideration, the report of the fatal cases from the U.S. should be added to the product information and further evaluation and prescription and reporting of ADRs in the European Union is warranted. A full risk management plan on all safety issues with telithromycin is requested, and it has also been provided very recently, this week. So we have not looked into that yet. It will take some time.

[Slide.]

Some additional regulatory measures done in Europe, but we have introduced contraindication I think the same as in the U.S. Patients who have experienced a hepatic reaction during treatment with Ketek is contraindicated, of course to re-explore and add this information of fatalities.

[Slide.]

So, in summary, Ketek was authorized over five years ago in the European Union. The product information has been updated with safety information, all the safety issues we have discussed today and presented before.

[Slide.]

Reassessments of hepatic safety were made in parallel with the renewal, and the marketing organization was renewed by the European Commission in July, then, based on the CHMP opinion. The second five-year renewal will take place.

[Slide.]

We have annual safety update reports and several safety issues are closely monitored. The full risk management plan and the use of Ketek in the European Union is extensive and will be followed closely.

Thank you.

DR. EDWARDS: Thank you very much, Dr. Mortimer.

We now have time for questions prior to

the lunch break. I will open the discussion up for questions from the panel.

Committee Questions

DR. HECKBERT: Yes, I have a question for you, Dr. Mortimer, I may have just missed it. When you gave the estimated reporting rate based on the most recent information from the European Union, I jotted down 4 to 10 per million prescriptions, is that what you said, 4 to 10 per million?

DR. MORTIMER: Yes, 4 to 10, yes.

DR. HECKBERT: 4 to 10, but not per 10 million, per million, right?

DR. MORTIMER: Per million, yes.

DR. HECKBERT: Thank you.

DR. EDWARDS: Dr. Gutierrez.

DR. GUTIERREZ: I have a question for Dr. Jenkins, and it has to do with susceptibility testing for telithromycin. In your Slide No. 4-14, you say that in your erythromycin-resistant isolates, that 0.5 percent of those were resistant to telithromycin, is that correct?

DR. S. JENKINS: Yes.

DR. GUTIERREZ: The reason that I am asking the question is that there was an article that was published in Antimicrobial Agents in Chemotherapy in May of this year. This is from a group from Finland where they took 210 erythromycin-resistant pneumococci and they tested it by agar diffusion, which I understand is different than the way the PROTEKT study is testing isolates, and they found that actually, 13 percent of their isolates were resistant to telithromycin by this different method of susceptibility testing.

I guess the question I have for you is I just wondered if you could comment on this and I wondered if you could also comment on your methods of susceptibility testing and whether you would consider looking at agar diffusion in the isolates that you get in the PROTEKT study.

DR. S. JENKINS: Yes, the study you are referring to looked at disk diffusion susceptibility testing and what they found is that there was a small subpopulation of the organisms, in other words, you would have colonies growing

within the zone of inhibition in a smaller, in about I think you said 13 percent. I think that is pretty close.

When the MIC testing was done using the standard method, the Clinical Laboratory Standards Institute methods are considered those that are recommended all across the world including the EU and the United States.

The MICs of those organisms were not elevated, so there was a disconnect between what was being seen in disk diffusion testing versus that that was being seen using standard CLSI methodology, and how to interpret those results I think is impossible.

DR. GUTIERREZ: Thank you.

DR. EDWARDS: Dr. Follmann.

DR. FOLLMANN: I wanted to amplify on a comment that was just made about the rate for Dr. Mortimer.

You mentioned the rate of 4 to 10 cases of serious hepatitis adverse events, 4 to 10 per million. The FDA in their documents have reported

a rate of 23 per 10 million of acute liver failure, so the rates are a bit different.

I am guessing it has to do with perhaps the definition of what acute liver failure is in the U.S. and then whatever you are defining as serious hepatic adverse event to be.

I would just like to know the definition a little more clearly about the U.S. and the European definition of this serious adverse event.

DR. MORTIMER: Most of these cases, of course, are serious by classical, they are hospitalizations in a way, so that is the criteria as such, or prolongation or life-threatening or fatalities.

So, when we come to looking at liver failures, then, I agree that is very difficult here to clearly specify what is the classification of acute liver failure, for example, made by the FDA or made by the company, or made in those studies that we are going to hear this afternoon.

Accordingly, the company, for example, applies encephalopathy as such as a prerequisite

for acute liver failure, and it depends. We must come somewhere here to really have the same criteria to compare the estimates we make. It's the only comment I have so far.

DR. AVIGAN: As you will see later this afternoon, you will get a rather expansive discussion about the case definitions, which are different, so we have actually sort of more segmented or fractionated the definitions which appear to be more encompassing in the case of the European, so I am not sure at the end that you wouldn't conclude that we are not that far apart. But let's see the data this afternoon.

DR. EDWARDS: Thank you.

Mr. Levin.

MR. LEVIN: My question is, is the sum total experience with ADEs postmarketing in the European community also dependent, as it is here, mostly on a spontaneous reporting system?

Are those centralized or are they maintained by the member states, the member nations, and are they mandatory or voluntary and

has anybody ever estimated the percent of unreported spontaneous event that maybe occur?

DR. MORTIMER: With regard to the system as such, each competent authority is responsible together with the company in its territory. Then, the national report within the territory then are electronically provided to the central European database for centralized approved products like Ketek.

It's a little bit messy, of course, because you have 25 countries. Some have a very developed system like France, UK, Sweden and Germany--Spain is one, and with a quite higher reporting rate. But underreporting, of course, is a problem.

There are a number of studies, of course, of underreporting and other factors that impacts on the spontaneous reporting in Europe, several countries, mostly with regard to skin reactions, overall serious reactions, and so on.

So there are a number of publications, as well, from Europe, from the U.S. I think it's

about the same, I would say.

DR. EDWARDS: Dr. Johann-Liang.

DR. JOHANN-LIANG: I wanted to offer a comment in response, shifting gears from Dr. Lonks' presentation regarding the translation of macrolide resistance in the lab to what is in the clinic, because I think it is such an important topic that needs more discussion as we move antibody trials forward.

The problem, I think that you have shown slides that there are case reports of macrolide-resistant treatment failures. The problem is that when we are trying to build a concordance between in vitro data to what is relevant for people for clinical outcome, I sort of think of as simplistic in a 4 by 4 table.

We are able to populate these upon case reports only really one cell, treatment failure based upon positive resistant pathogen. We are not able to really make good population of the other cells, so it is patients who are resistant/not resistant but result in treatment failure, or

patients who have success anyway regardless of what the drug is.

Probably a lot of that has to do with for diseases, and we think of it in diseases, for diseases with high spontaneous resolution.

The host immune response probably is able to take care of the burden of the pathogen whether it's resistant to an antibiotic or not, which brings us to some of the other topics that I think other speakers have talked about, what are the other risk factors, the severity of the illness, the fact that maybe there is an immune compromised state of the patient.

In those cases, perhaps having an effective antimicrobial that we really can account for the resistance will matter, because that patient needs that help.

Then, lastly, regarding the drugs themselves, maybe perhaps even in those patients with the underlying risk factors, the differences in the drugs, not just the antibiotic effect, and a pathogen effect actually by killing the bug. But

perhaps what Dr. Bartlett had alluded to regarding immuno-modulating effect, maybe that is why there isn't that exact concordance going from the in vitro to the actual clinical outcome of the patient.

I think there are many factors that we really need to account for rather than just trying to say the drug, you know, the resistance of the bug and therefore the concern translated and magnified, et cetera.

I think we will talk more about this in future topics but that is something that I wanted to offer as a comment.

DR. EDWARDS: Thank you.

Dr. Leggett.

DR. LEGGETT: A brief question for Dr. Mortimer.

In the application for the five-year renewal, was any of the 3014 data included?

DR. MORTIMER: I cannot give you the exact, but I assume we have the same files at this time. I think you should perhaps ask the company.

DR. LEGGETT: We will.

DR. EDWARDS: Thank you.

Dr. Wiedermann.

DR. WIEDERMANN: I had a couple of questions, first, for Dr. Jenkins, referring to your Slide 15 where you had the six countries aggregate data on that red line.

I am wondering if you look at individual countries, especially ones that started earlier, like Germany, is there a difference in the numbers of isolates you have among those countries and would the curve look any different if you looked just, say, at Germany, the ones that started sooner?

DR. S. JENKINS: We didn't specifically look by country in this analysis. That having been said, it is actually quite easy to go back and do that. I am not sure if this is something we can even do during the lunchtime period to cut the data by country but it can be done with the software that is available to us. But, at this point in time, I have not seen those data, so I really can't

answer the question.

DR. WIEDERMANN: Thank you.

May I do my second question for Dr. Lonks, a little similar to that previous question. With your Slide 4 that had the CDC studies and then the case reports, and I assume your references that you had at the end referred to that slide.

I just wanted to clarify, these are all U.S. studies, so you did not look at anything outside the U.S.?

DR. LONKS: If I can just step back for a minute, at the beginning these were case reports. Then, there were case-controlled studies. The controls were patients with susceptible isolates.

A study I was involved in was multicentered, two hospitals in Providence, Rhode Island, one in Boston, one in Barcelona, Spain, so they were population based. We also had controls. We tried to match two controls per case and, in our particular study, there were no failures with the susceptible strains.

Dr. Low is here and if he can comment on

his study, they had a broader look at the susceptibles. They didn't do matching or controls. They actually looked at all susceptibles and did find a couple of treatment failures in the susceptibles but it was still statistically far more likely to occur with resistant strains.

Overall, the majority of this data is from the United States and Canada. If you want to just take the grand total, 4 from Belgium you can subtract out, and Spain was about 12 that you can back out of this particular data. But most of this here, the treatment failures are from the United States. The CDC study that was published also looked at susceptible, as well as resistant isolates.

What I wanted to do here, my point was just to show that the resistance problems are affecting patients. These patients were treated as outpatients, they failed. They were hospitalized and there were deaths among these patients.

Seeing Dr. Musher just a little earlier reminded me there was a 20 some-odd-old patient,

who was a very healthy male, went into the hospital, got IV azithromycin and died because he received azithromycin, azithromycin-resistant isolate, so these are not just benign failures and there have been controlled studies taking a look at susceptible isolates, as well.

DR. WIEDERMANN: Was there a systematic literature review, systematic approach to selecting the studies you included in that, or were these just things you were aware of?

DR. LONKS: I started in this particular area in 1991. I did an extensive literature search and only found a couple of case reports going back to the 1960s, trying to look at this issue of resistance.

As you saw up in the slide, there is only a couple of case reports. Then, there was a case where I had a healthy 32-year-old gentleman who came into the hospital.

He had gone to an outpatient department, had an X-ray done, and had a right lower lobe pneumonia. He was treated with erythromycin. Two

days later he went to his internist because he was feeling no better, a colleague of mine.

A sputum Gram's stain was done in the office. It was very remarkable. He still saw some gram-positive cocci and told the patient to wait until the next day to see if he had a response. That night he became confused, started hallucinating. The next morning was brought in to the hospital. This has been published in my publications, as well, describing this case.

The gentleman then came in, he was very sick. We saw the gram-positive cocci in the sputum. Because of the hallucinations and also the fact it required a lumbar puncture to make sure that he did also did not develop meningitis. This is a healthy guy, he had received no antibiotics.

The other point that was brought up is, you know, with the case-controlled study, there is a host response. Well, if you take a look at the study I published in CID a couple of years ago, we also included all their comorbidities. If you look at the table in that publication, you will find out

that there was really no difference between the cases and controls and those that failed as far as their medical illnesses. That it is really not a host response but a resistance issue.

DR. EDWARDS: Dr. Lonks, based on modeling, can you estimate the magnitude of that publication lag artifact from 2004 on?

DR. LONKS: The study done in Toronto, that was a surveillance-based study, was between 2000 and 2004, was not published until the summer of 2006, so there were failures in 2000 that did not get into the published literature until 6 1/2 years later.

The CDC study that was just presented as an abstract at ICAAC this year was patients from 2001 to 2003, so you are looking at a time lag of 3 to 5 years on when that gets presented, and that is yet to be published.

DR. EDWARDS: Thank you.

Dr. Bradley.

DR. BRADLEY: Thanks. I have got a general observation and question of the FDA to

clarify the charge that you have to the Committee during these two days.

We have certainly heard information presented by Dr. Alexander that reflected presentations to the Committee over three years ago, and I had the pleasure of being here at that time and saw the data.

Based on a non-inferiority trial design with the issues of AEs that were discussed, we voted for recommending approval. As we go through current risk assessments, both in the U.S. and in the European Union looking at postmarketing surveillance with spontaneous reporting, clearly, postmarketing surveillance won't give you as accurate a view of adverse events as prospective collected data where all of the AEs are nicely defined and you have a beautifully captured population that you can follow.

Some of the differences in definition in hepatic toxicity have certainly already been discussed. So I think looking at risk assessment now with telithromycin, and comparing it with

something like erythromycin, has some inherent dangers.

I don't know if the erythromycin AE reporting rate in 2006 will be the same as telithromycin.

In terms of clinical trial design, the non-inferiority clinical trial design for sinusitis and acute exacerbation of chronic bronchitis, which was felt to be appropriate in the late '90s, when these studies were started and upon which we based our votes in 2003, has certainly been reassessed just a few months ago with gemifloxacin.

With a superiority trial design, that recommendation for approval was not made based on guidances that you have within the FDA that you discussed with the company, which we still are hoping to see soon. But now the fact that telithromycin in your discussions with the sponsor had an approved non-inferiority clinical trial design, now raises the question that for each of the 12 drugs that Dr. Cox had presented, that are currently approved and used for sinusitis, and 18

for acute exacerbation of chronic bronchitis--and I presume all of these were approved on a non-inferiority trial design--if we are going to hold telithromycin up to a superiority trial design standard, we should do the same for all of these drugs and assess each and every one in the context of the risks and benefits that one might see for all of these drugs.

In that context, we might see a drug like trimethoprim sulfa with its Stevens-Johnson side effect actually being withdrawn from the market for lower respiratory tract, upper respiratory tract indications.

I am hoping to look to the Agency to help us define how it is that you want us to look at these issues, because if you are going to go back and look at every drug this way, and we would certainly support it, you will need to increase your staff by two- or threefold, it will be a pretty large job.

But if the scientific community and the Agency and the political community all believes

that in order to protect the population, both of the U.S. and the EU, that we now have a new standard, then, just like in 1962, with the Kefauver-Harris amendment that said drugs need to be effective and every drug that was approved needed to show efficacy before it could still be marketed, we may be at the same momentous point here that when you come up with a new approval bar that is higher than before, that every drug that has been approved previously now needs to go through a re-evaluation.

Again, I am happy to support that effort. But to go back and pick on a single drug which was approved by non-inferiority trial design, and particularly pick on a drug that is still branded and has a sponsor where there is money to do the trials compared to trimeth sulfa, I think it is making things more confusing for all of us. I believe we need consistent scientifically-based and transparent criteria to be applied to all antibiotics for all indications.

Thanks.

DR. EDWARDS: John, I assume that was a comment, not a question.

DR. BRADLEY: Both, Jack.

DR. EDWARDS: Not to in any way diminish the magnitude of the issue you are bringing up because it really is a major problem for us all, that we are all trying to wrestle with here. But I think we are going to touch on the issue over and over again during the discussions. I am not sure that we want to do it at this moment unless--I sort of am getting the affirmative nod--we are really beyond the moment we are supposed to break for lunch right now.

I think we will definitely come back and re-talk about this issue as the discussions go on.

Dr. Jenkins, did you want to make a comment?

DR. J. JENKINS: I will just make a brief comment on that point. It's a very good one that Dr. Bradley is raising. In the natural course of regulating drugs, the standards for approval, the clinical, scientific standards change over time,

not just in antimicrobials but in all areas.

You are right. It would be a monumental task to go back and reassess everything that has been done before and we generally don't do that at the FDA. What we do is we look back when there is a reason to look back, so if there is a new safety signal that may throw out of balance the previous risk-benefit assessment that was made at the time of the original approval, then, that is a trigger to go back in a selected fashion and look.

So, that is why we are looking at Ketek today, is because of the safety signals that have arisen since it was marketed. You are right, you could do the same thing for all those other antimicrobials that are used for the same indication.

A similar situation came up a couple years ago when we were looking at the Cox-2 agents and the nonsteroidal agents. The databases that we have for the approval of Cox-2 agents is much more extensive than the databases we had at the time of approval for the traditional nonsteroidals.

We have not gone back and tried to require or reassess the old nonsteroidals. You could argue scientifically that would be optimal. But, pragmatically, it is very difficult and very burdensome to try to think about how to do that.

We generally look to look back at the risk-benefit assessment when something new comes to light, generally on the safety side.

DR. EDWARDS: Clarify, Dr. Jenkins. We think or we are debating the issue of whether there is a signal here regarding safety, so we are selectively going back with this particular agent. But in materials we have been sent prior to this meeting, we have been asked to consider the risk-benefit ratio in light of recent discussions which have been centered on non-inferiority trial design in certain of these indications. Is that correct?

DR. J. JENKINS: That is correct. We certainly don't want you to exclude the evolution of science that we now have a more thorough understanding of non-inferiority and we are trying

to take a more rigorous scientific approach. We certainly don't want you to exclude that evolving science and that evolving approach and we wanted you to factor that in as you are making your assessment of benefit-risk.

I was just responding to Dr. Bradley's point that you could make the same approach for the 12 and 18, I think you said, other antimicrobials that are currently approved for the same indications.

Ketek is being triggered because of the safety concerns that have arisen. If one of those other 12 or 18 had a safety concern, a new one that developed, we would do the same thing.

DR. EDWARDS: Thank you.

I am going to do the unpopular thing of obviating about five more questions, which I had on the list here of people interested in asking, and I am just going to I am afraid have to do that, so that we are able to keep as much on schedule as possible.

At this point we are going to break for an

hour roughly, and we are going to return at 1:30 to resume the meeting.

Thank you.

[Whereupon, at 12:40 p.m., the proceedings were recessed, to be resumed at 1:30 p.m.]

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

[1:35 p.m.]

DR. EDWARDS: We are going to proceed now and it is a pleasure to introduce Dr. Jonathan Levine, who will give our discussion on the data mining evaluations of the AERS.

Data Mining Evaluation of AERS/Multiple Antibiotics

Jonathan G. Levine, Ph.D.

DR. LEVINE: Good afternoon.

[Slide.]

I am going to talk about a data mining analysis that Dr. Szarfman and I did of multiple AERS antibiotics. This was requested by the Division of Anti-Infectives and Ophthalmology Products last spring.

[Slide.]

Let's start off talking about what is data mining. To my mind, data mining is statistical analysis applied to large databases where there aren't any a priori hypotheses. So it's looking for answers without necessarily having the questions set up ahead of time.

We didn't do millions and millions of statistical techniques on a large database. Instead, we used a specific technique, the MGPS algorithm, to analyze all suspect drug and adverse event pairs in AERS.

I am going to briefly discuss AERS and the MGPS algorithm. The details are in the briefing package.

[Slide.]

So, what is AERS? Computerized adverse events case reporting system. Voluntary reporting by health care workers and the public. Manufacturers are required to report serious unexpected events.

The adverse events are coded using MedDRA, the Medical Dictionary for Regulatory Activities. There are about 3 million reports in AERS at the moment. A relatively small number of data elements, and there is lots of missing data, so if you have an AERS report, you probably have a list of drugs the person took, you have a bunch of events and no guarantee about the other stuff.

[Slide.]

Disproportionality analysis using Bill DuMouchel's MGPS method. The basic idea is that you calculate and observe an expected number of reports for a particular drug- event combination.

Here, the observed rate, number of reports for a particular event for the drug of interest divided by the number of reports for the drug. So you wind up with, say, 5 percent of that report for a particular drug or for headache.

You can, for headache, calculate the expected rate. This is basically the fraction of reports in the entire database and. from that, you can calculate this observed rate over expected rate, or the relative reporting ratio, which we will abbreviate as RR.

That number is then shrunk towards 1 and the shrunk or adjusted value is referred to as the EBGM score. The amount of shrinkage that is done is a function of the amount of information that AERS contains about the drug-event combination, and just expand a little bit on that.

[Slide.]

Expected counts are often very, very small, so that a single report can yield a huge RR.

So, for example, in AERS, acetaminophen has a report for Alice in Wonderland syndrome, which has 9 reports in all of AERS. The expected number of cases is 0.011, which gives you an RR of close to 90.

Well, that is a very implausible result, the EBGM shrinks that, taking into account the fact that it is a very rare event and acetaminophen has a large number of reports and shrinks it to a much smaller sensible number of 1.37.

The shrinking is really what gives you a handle on the false positive rate. If you just use RR, you get drowned in signals for things that you only observe 1 or 2 cases of.

[Slide.]

I should just say in some sense, we only did 3 analyses. We did an EBGM analysis on 3 different looks on AERS and that yielded millions and millions of EBGM values, so the first, I am not

going to present all 26 million or so EBGM values today. We had to winnow them down.

What we did is we looked at EBGM scores for 16 drugs that were selected by the reviewing division. We initially looked at all adverse events that were in the AERS database and then we selected the ones that had to have an EBGM of greater than or equal to 2, and it ended at least 2 for at least 1 of the cumulative time periods that we analyzed.

We also didn't look at adverse events that were probably related to the indication being treated, pneumonia, meningitis, et cetera, and we opted to look more at the serious adverse events rather than the lesser ones, so "hepatic failure" was considered instead of "aspartate aminotransferase increased," et cetera.

[Slide.]

So that winnowed things down to somewhat more manageable size but we still had about 170 adverse event terms, still had close to 3,000 EBGM values to present.

We couldn't present them all, so we went to another level of data reduction; that is, we grouped similar adverse event terms into the bins things that we thought were getting at the same adverse event. We only considered the maximum EBGM score over both the adverse events in that particular grouping and over a cumulative subset of time.

[Slide.]

So we still couldn't necessarily present all of those. But we are going to look at 11 of those today. There is a review in the briefing package that does describe the other events in greater detail.

[Slide.]

So, to condense them all down, we put them in this table. Now, the colors in the table represent the EBGM score, the actual EBGM values are also there. The columns represent drugs and rows represent adverse events. So 16 drugs are across the top.

The left column is for telithromycin. The

next 4 columns are for macrolides and then there are 5 cephalosporins, amoxicillin/clavulanate, 3 quinolones, nitrofurantoin and acetaminophen is there as both a positive and negative control for this case.

[Slide.]

You looked at these grouped adverse events, eye, myasthenia, syncope, hepatotoxic events, drug interaction, drug ineffective, clostridial infection, toxic skin and hypersensitivity and the key here at the bottom, people can't see the keys all that well, I guess.

Basically, the lightest color, well, start at the beginning. The cells that have nothing in them, that are completely white, those mean that an event was not observed for that drug. The slightly darker light color indicates that the EBGM score was between 1 and 1.5. Then the next level, the next gradation up from that is 1.5 to 2.

The next is 2 to 4, and the darkest orange-brown color indicated an EBGM greater than 4. So the darkest color, you are seeing something

that occurs at 4 times what you would expect it to occur in the AERS database.

[Slide.]

The first things to look at, the signals for eye and for myasthenia. The signal for eye events is clearly much larger than any of the others, it is over 100. It is a uniquely large signal. Similarly, the myasthenia signal is quite large, as is the signal for azithromycin.

Some of the others do have doublings and triplings EBGMs but the two that stand out really for myasthenia are telithromycin and azithromycin.

[Slide.]

Syncope, there is a high signal for syncope with telithromycin, not as high as the one that is observed for moxifloxacin.

[Slide.]

Hepatic failure and hepatitis. Hepatic failure, the strongest signals are with trovafloxacin and nitrofurantoin, still a fairly high signal for telithromycin. Telithromycin signal is similar to the amoxicillin/clavulanate

signal.

Hepatitis. Again, hepatitis looks a lot like amoxicillin/clavulanate and trovafloxacin and nitrofurantoin. Erythromycin is in the ballpark there.

[Slide.]

A fairly low signal for cholestasis. The higher signals are with the macrolides and the amoxicillin/clavulanate.

[Slide.]

Drug Interaction. Again, the drug interaction scores are there with all of the macrolides, somewhat smaller for telithromycin and for three others. I guess I should mention that the erythromycin tends to have low signals because it has fairly low usage and I believe it is no longer on the market, so as a control.

Drug Ineffective Signal. There really isn't much of anything for telithromycin for drug ineffective, large signals for azithromycin and for cefditoren.

[Slide.]

Clostridial Infection. Nothing for telithromycin, lots of signals for the cephalosporins, amoxicillin/clavulanate.

[Slide.]

A weaker signal for toxic skin reactions. Most of the strong signals are with the cephalosporins, something for azithromycin.

[Slide.]

Again, hypersensitivity, much stronger reactions with the cephalosporins, quinolones, less so at the moment with telithromycin.

[Slide.]

So, to summarize that, there is a very large signal for the eye events with telithromycin. There is an unusually large signal for myasthenia with telithromycin and also a lesser signal with azithromycin but there is clearly one there.

There is a large signal for telithromycin and syncope and that is second only to the one observed for moxifloxacin.

[Slide.]

Hepatic failure and hepatitis both have

signals with telithromycin. Hepatic failure is less than that for trovafloxacin and nitrofurantoin, comparable to amoxicillin and clavulanate.

Hepatitis has a signal comparable to trovafloxacin, nitrofurantoin and amoxicillin and clavulanate.

Cholestasis only has a weak signal with telithromycin.

The majority of the antibiotics have a stronger signal for cholestasis.

[Slide.]

Drug interaction does have a high signal score with telithromycin but azithromycin, clarithromycin and erythromycin all have higher signal scores than does telithromycin.

Toxic skin and hypersensitivity reactions have weak signals for telithromycin compared to the majority of the other antibiotics.

Drug ineffective and clostridial infection do not have signals for telithromycin.

DR. EDWARDS: I actually have time for one

or two questions. Are there any questions?

Committee Questions

DR. WIEDERMANN: I don't think you can get us, or at least not get me, up to speed on the derivation of this algorithm but if I asked four statisticians about the validity of using this approach with this kind of data, would I get five different answers, or how solid is this?

DR. LEVINE: I think it is pretty solid. It is something that I think statisticians who aren't used to dealing with this type of data would have to think about for a while and they would also need to be comfortable with some of the Bayesian thinking.

I think what makes it most unusual is that it is an analysis of structure in AERS, so it is what is unusual in AERS. It is not saying this is unusual in the general population. AERS can't do that, AERS is not some wonderful sample from the general population. It is a collection of spontaneous reports.

So this says it's really unusual to get

this many reports of eye events for a drug in AERS and to make some kind of definitive statement about that is not something that a statistical method can do. It is only applicable to the AERS database ultimately.

But I add to that, though, I think it looks about right. I mean the adverse events that it does pick up and have seemed to match from what clinicians tell me, match up with clinical experience. I will let others argue the veracity of that.

DR. EDWARDS: I would like to ask a question. I have done something here that I am sure is statistically highly illegal but I want to ask this question anyway.

If I add the numbers up for hepatitis, cholestasis and hepatic failure, those boxes, for telithro and trova, I get a total of 11.4 as a sum of those numbers versus 15.3 for trova.

Hepatic failure, can you see that? Hepatitis and cholestasis. I am comparing that group of numbers to the similar group for trova

over here. This one, this one, and this one compared to this one, this one, and this one, and I get 11.4 for telithro and 15.3 for trova.

DR. LEVINE: Oh, adding them.

DR. EDWARDS: I want to know what the magnitude of that difference is. As I say, I realize this may be completely statistically illegal.

DR. LEVINE: Well, they are ratios.

DR. EDWARDS: Dr. Leggett, did you want to amplify?

DR. LEGGETT: Insignificantly, statistically, or just as poorly statistically. In the packet, we had EB-5 to EB-95, sort of like the equivalent of a confidence interval and I assume that it is not a sharp confidence interval that we use for non-inferiority.

DR. LEVINE: Right.

DR. LEGGETT: Can we tell if 5.8 is different than, say, 12, or we can't really tell?

DR. LEVINE: No, that's in the packet. I don't recall offhand.

DR. LEGGETT: I just had a hard time looking at the tables to see if trova was statistically significantly more than telithro, because all the 90 percent confidence intervals, so all we have to do is look at that and just look at that one number, correct?

DR. LEVINE: I am sorry?

DR. LEGGETT: In the data mining thing, there is the EB-5 and the EB-95. Then the numbers provided on the left only for telithro and then there is a table that just has the numbers.

So what I was wondering is if that confidence interval on the lefthand column for the telithro overlaps with one of the numbers in one of the cells.

DR. LEVINE: Right. That can be cautiously interpreted.

DR. LEGGETT: Okay, cautiously.

DR. LEVINE: Correct.

DR. LEGGETT: My other question is, is this data per year a person since AERS has started?

DR. LEVINE: This is the maximum value

over all of the cumulative years, so it might be all of it, it might just be through a particular year. We just looked at the worst case.

DR. LEGGETT: So, for instance, if erythromycin, you would have all the data from 30 years ago or whenever this thing had started.

DR. LEVINE: Right.

DR. LEGGETT: Whereas, for telithro, you would only have it the last three years.

DR. LEVINE: That is correct.

DR. LEGGETT: So there is inherent bias in both, because erythromycin 30 years ago, we didn't even know about myasthenia gravis, for instance.

DR. LEVINE: Right, yes.

DR. EDWARDS: Well, not quite that bad.

DR. LEGGETT: It was presumably defined differently for the AERS 30 years ago.

DR. LEVINE: Yes.

DR. LEGGETT: So that when we have a column that says a specific entity, it is even more confusing because what we call it now is not what we called it two years ago.

DR. LEVINE: Right, although I mean it's a little bit fuzzy because we did try--that's why we put multiple terms into each of these bins. But the myasthenia terms, I think we concluded are all fairly recent.

DR. EDWARDS: Dr. Bradley, did you have a question?

DR. BRADLEY: No, that was exactly my question, thank you very much.

DR. EDWARDS: Dr. Follmann.

DR. FOLLMANN: Thanks. I just wanted to make a couple comments on this. First, as we all know, this is based on the reporting data, which is sort of a shaky database. It is based on self-report by the physicians associated with giving the drug.

In the paper that describes this method--and so you can't really assess causation with this, The paper that describes this methodology has an interesting example where they listed side effects for polio vaccination and 7 of the 15 or so were associated with the injection

site but it was an oral polio vaccination and so it didn't really make sense.

What was happening was that they got that vaccination with some vaccination that involved injections. So I wouldn't place a lot of precise descriptions about this data and I am a little uncomfortable sort of in saying that these confidence intervals or whatever overlap.

I think it is encouraging and interesting that it really identifies the myasthenia gravis, which was identified in Europe, I guess, but not here, so that is an appealing thing about this. Also, the eye adverse events.

But one thing I was wondering about in the European report, they mentioned I think 33 percent of all adverse events were related to the eye. So I think what this would mean for this database, if we removed eye, some of the signals for hepatitis, et cetera, might be increased somewhat, because you are looking at a signal of statistical independence between adverse event and drug relative to the universe of adverse events you are including, this

will change a bit with what you decide to include in terms of adverse events.

So, since eye is so common for Ketek, if we eliminate this, it might make the other adverse events have stronger signals or larger ratios there.

I guess the bigger issue really is what I am really wrestling with in these two days is the hepatitis signal, the risk of hepatitis. I don't think this analysis can really give us a lot of new insight about that particular risk.

DR. LEVINE: I did at one point do an analysis removing the eyes, and my recollection is that it didn't make all that much impact. But we probably could rerun that analysis and see what happens.

DR. EDWARDS: Yes.

DR. PROSCHAN: I think that it is very difficult to take a huge data set like this and figure out exactly what is going on and I do think that this is a reasonable way to do it. I think a lot of statisticians would agree that this has as

lot of nice properties.

I also agree that it can only really give you rough signals and you can't get as precise as I think some of the members are trying to get. But it is interesting that it identifies the things that I think were the strongest, namely, the eye, when you look at all the evidence in the packet, it is pretty clear.

I think both sides agree really that there are eye problems with this drug, how serious they are there might be disagreement. But I think the strongest evidence was in terms of the eye, blurred vision, that kind of thing, and this is detecting that.

I think the fact that it makes sense from a statistical point of view, it handles a lot of different aspects, namely, the tradeoff between a relative risk that is very unstable. The other option which would be to look at a p-value instead of looking at a relative risk, which is too far the other way. It is not sensitive enough--you know, small data sets with kind of drastic things going

on, and this is sort of a compromise between them.

So I think both from a statistical point of view and from the fact that it seems to be matching at least my impression of what the strength of evidence was for the different components, I think bodes fairly well.

DR. EDWARDS: Thank you.

Mr. Marco, last quick question.

MR. MARCO: I was wondering if you could just walk us through. It's in the briefing document, the background materials, page 18, Table 6. That has the confidence intervals and maybe that will help with Dr. Edwards' question about are things either overlapping more or less.

Can you pull that up?

DR. LEVINE: Right.

MR. MARCO: That seems easiest to look at versus the other.

DR. LEVINE: Maybe the best thing, I can ask Dr. Szarfman.

DR. SZARFMAN: I think that here what you have, in our review, there are lots of more details

of how this was done. You have also a time course of the signals course and the number of reports across the whole database.

Here, what we are looking is we are comparing telithromycin for different event codes, that in the memorandum we have collapsed hepatic failure. We have used hepatic failure, liver transplant, liver reprocess, you have it exactly.

On hepatic failure event code is more associated with fatal outcome from the rest of the event codes except with one exception that we will know when we get to cholestasis.

But essentially, in red, you have the drugs that are higher, non-overlapping signals done with telithromycin telithromycin is always in green. In blue are the drugs that have confidence limits that overlap with the ones for telithromycin, and in black is when telithromycin has higher, non-overlapping signals.

Then, you see for hepatic failure, acetaminophen and trovafloxacin have higher and non-overlapping. Telithromycin overlaps the

signals with nitrofurantoin and amoxicillin and clavulanic acid.

There is no overlapping with clarithromycin. Clarithromycin is higher for telithromycin, larithromycin, azithromycin, gemifloxacin, and you have the total number of reports. We analyze 13,000, over 13,000 reports.

For hepatitis, essentially, you see that most are overlapping or telithromycin is higher. What you are seeing is that except for amoxicillin-clavulanic acid, that is higher and non-overlapping. The rest are either overlapping with claritho or the telithromycin is higher.

[Slide.]

If we go to the next here, cholestasis is different, because if we look at cholestasis across, essentially, with cholestasis, you have more drugs.

For cholestasis, these drugs have higher, are non-overlapping. But telithromycin overlaps with all of these.

If we go and look at the next page, for

fatal outcomes, the fatal outcomes you don't have reports of five events. I am answering your question, and it is not interfering.

Next page. These are fatal outcomes, they are all overlapping essentially.

Let's now go to the next one. Next page. For cholestasis, the fascinating thing is when you are looking at cholestasis and fatal outcome, essentially, the observer will expect there is one in the whole database. But for amoxicillin and clavulanate, they are higher and non-overlapping than the other ones.

It is not only cholestasis but it is essentially instead of having an observer expected of one, you have 13.86. This was a simultaneous analysis across the whole database. There is another problem that was really difficult to summarize everything that we have done. But, essentially, the problem of if this is a signal or is not a signal is really easy to ascertain because with one mouse click, you would do the report.

Essentially, we have other graphic

displays that are essentially they optimize visualizing where the action is with events. I have some other presentations, one at the Institute of Medicine that I can show you how this works, but, essentially, the Institute of Medicine report recommends the use of this methodology, some of the graphic displays that we use.

DR. EDWARDS: Thank you very much.

Dr. Dal Pan, did you have a quick comment?

DR. DAL PAN: I just want to make a quick comment to just explain to the members of the Committee how we use this in our work in postmarketing safety in the Office of Surveillance and Epidemiology.

Our database is very big, it has over 4 million records. One option is just to look at them one at a time. That is not very efficient. So tools like this help us by telling us what is more common with one drug versus what is less common with that drug.

It helps us to generate signals and generate hypotheses, which then require further

evaluation. So when Dr. Levine and Dr. Szarfman put up terms like hepatic failure, hepatitis, eye, whatever, these are coded bioinformatic terms that require further evaluation at the level of the individual case.

So, if you were to, say, be interested in telithromycin, you would look in the database, you would see this big signal for eye. You would then go to all those reports on eye and look at them to see what they are telling you.

So we use this as the first step to orient us in a very large complex database to help guide us. It is helpful, as Dr. Levine said, it looks up all these combinations without any a priori hypotheses. So things we might not have thought of might come up this way.

The basic message is in our work, in postmarketing safety, we really use this as a first step for further clinical evaluation and we will be presenting some of those results throughout the course of the meeting.

DR. EDWARDS: Thank you.

At this point, I need to turn the meeting over to Mark Moyer again from Sanofi-Aventis, who is going to introduce the next series of speakers.

Mark.

Sponsor Presentation

MR. MOYER: I am going to take the opportunity to introduce this as a series of five presentations that the sponsor has put together. Once the signal is identified of concern, such as hepatic events, as has already been suggested, it needs to be further evaluated.

So we will have a presentation on the safety overview of hepatic events by Dr. Barbara Rullo from our Pharmacovigilance group.

That will be followed by an expert review by Dr. James Lewis, who is a Professor of Medicine and Director of Hepatology at Georgetown University, who will provide his perspective on those individual events.

We will then go to another approach that further enhances our ability to evaluate these and that is two epidemiologic investigations. One is

through the PHARMetrics database, and Dr. Wanju Dai will present that. She is the head of our Epidemiology group over in our Pharmacovigilance and Epidemiology Department at Sanofi-Aventis.

We will then have Dr. Alex Walker, who is the head of I3 Drug Safety and an Adjunct Professor of Epidemiology at the Harvard School of Public Health, present his data from the Ingenix database.

A final review of the epidemiology by Dr. Judith Jones from the Degge Group, who is also an Adjunct Professor of Pharmacology at the Georgetown School of Medicine.

I would like to introduce Dr. Rullo at this time.

Adverse Events of Special Interest: Hepatic Safety Overview

Barbara Rullo, M.D.

DR. RULLO: Good afternoon.

[Slide.]

As I indicated this morning, I would now like to describe our hepatic safety experience with telithromycin since the drug was approved in April

2004.

[Slide.]

I am first going to briefly summarize our pre-approval hepatic safety experience and then we will examine our postapproval hepatic experience, and we will look at a couple of points in time.

In April of 2005, at the one year time point, we received three reports of liver failure from North Carolina. These were subsequently written up in the Annals of Internal Medicine in January of this year. So we are going to look at two points in time, we are going to look at the one-year time point when we received the cases, and then we are going to look at the two-year time point shortly after the Annals article appeared, and then conclusions.

[Slide.]

Prior to U.S. approval, we performed two in vitro studies to assess potential hepatic effects of telithromycin. The first study examined covalent binding to human liver microsomal proteins, and the other, inhibition of

mitochondrial beta-oxidation.

In both cases, telithromycin behaved similar to clarithromycin and azithromycin.

We also examined preclinical effects. We studied the preclinical effects in the rat, the dog and the monkey, and the hepatic effects were again comparable to macrolides.

[Slide.]

Based on the macrolide-like preclinical hepatic effects, we used some standard definitions for hepatic events during our clinical program and monitored these closely.

During our controlled Phase III studies, we found no difference in clinical hepatic events or hepatic enzyme changes between telithromycin and comparators. Those comparators were amoxicillin, amoxicillin-clavulanic acid, clarithromycin and cefuroxime.

During the controlled clinical studies, we had two serious events in patients receiving telithromycin and one for a patient receiving clarithromycin.

We also did a study in patients that had hepatic impairment and we found that no dose adjustment was needed in this population.

We had a vast amount of postmarketing experience that we had submitted at this time. There was one patient that had a hepatitis A Q fever, acute liver failure but no drug-related severe hepatotoxicity was identified.

[Slide.]

As a result of the data that we had reviewed, there was in our label at the time of approval a precautions regarding hepatic dysfunction including increased liver enzymes and hepatitis with or without jaundice.

Also, a note to use with caution in patients that had developed hepatitis with previous Ketek use.

[Slide.]

So what happened in our postapproval experience?

Well, as I mentioned, at the one-year time point, in April 2005, we received 3 reports of

acute liver failure from the same hospital in North Carolina. This hospital was a regional transplant center and a referral center, and these are the three patients that subsequently appeared in the Annals of Internal Medicine.

Now, prior to this, we had 4 reports of acute liver failure worldwide, and this is after an exposure of 17 million courses of treatment.

The first was the patient that we knew about prior to U.S. approval, the patient with the hepatitis A and Q fever. Then the other three patients occurred in 2004 and early 2005 and they were patients with septic shock and ischemic injury, and they had compelling alternative explanations for their liver failure.

Now, Dr. James Lewis is going to speak to his causality assessment for each of these cases very shortly but, at this time we did a qualitative and quantitative review of our data.

Qualitatively, we reviewed all hepatic reports that we had received up to that point in time. The data showed that the information was

consistent with what we had seen during our clinical program and what was in our product label.

I told you earlier today that we had a standardized questionnaire that we used to capture a comprehensive amount of information, so we also did an analysis looking at risk factors.

We looked at age, gender, duration of treatment, indications, concomitant medications, medical history, and we could not identify any risk factors.

[Slide.]

We did a quantitative analysis. We did a comparative reporting rate analysis using FDA Freedom of Information extracted data to identify spontaneously reported hepatic events that occurred within one year after launch for each of the products that we evaluated.

We used two definitions, broadly defined hepatic terms and critically defined hepatic terms. Broadly defined hepatic events were high level and preferred terms from the hepatobiliary, the investigation in the neurologic system organ class.

Critical hepatic events included hepatic coma, hepatic encephalopathy, hepatic necrosis, fulminant hepatitis, acute liver failure and transplant.

For telithromycin, since we were just at the one-year time point. We wanted to be as complete and current as possible, we used our own internal data in this analysis, because there is a lag time in obtaining FDA FOI data.

As you can see from the results, telithromycin for both broadly defined and critically defined hepatic events was within the range of other marketed antibiotics. Based on the preponderance of evidence, our qualitative and quantitative review of the data, a new risk beyond what was already identified in our product information was not identified, and we continued to monitor closely.

[Slide.]

As I indicated when I began, the article about these three patients from North Carolina appeared in the January Annals article. You can

see the dramatic increase in the number of cases that we received once the Annals article was published.

Reporting rates will change over time. As we talked about this morning, reporting rates are a measure of reporting intensity. They are affected by many things. One of them is press coverage that results in stimulated reporting and this is a classic picture of stimulated reporting.

Now, with stimulated reporting, as the number of cases, the quantity of cases increases, the quality of those cases decreases. Therefore, we had to find some measure to assess the cases that were being reported to us.

[Slide.]

So, in concert with our external hepatic experts, we adapted definitions and those definitions included, for acute severe liver injury, an ALT greater than 3 times the upper limit of normal, a direct bili greater than 3 in the absence of an elevated alkaline phosphatase.

Now, since the quality of the reports is

not good in situations like this, they are often incomplete, lacking details and unconfirmed, we decided to be as conservative as possible, so we also included any patient that had a serious hepatic event that was associated with a hospitalization.

We also have included them as a case of acute severe liver injury. For acute liver failure, we defined it as an acute onset of severe liver injury associated with either encephalopathy or coagulopathy in the absence of an underlying liver disease.

[Slide.]

So, throughout the year, we have done several re-analyses. This particular re-analysis is from September of this year. Now, the global hepatic reporting rate in May of 2005, when we looked at this, was 15 cases per million for all hepatic events. You can see that in September of this year, the global hepatic rate is still about 15 per million after the Annals article.

However, in the United States, whereas,

the hepatic reporting rate again for all events was about 15 per million at the one-year time point when we received the cases originally, you can see now that it has more than doubled.

I want to draw your attention to the 12 cases of acute liver failure that we have received. Three of the 12 cases were received between April 2004 and January 2006, after an exposure of 4.6 million.

The remaining 9 cases were reported to us after the Annals article with an exposure of 1.3 million. This reflects the stimulated reporting.

[Slide.]

The United Network for Organ Sharing maintains a database, a tracking system for patients that have undergone a liver transplant. These data are drug-related liver transplants that occurred between 2004 and 2006.

You can see that acetaminophen accounts for the most common cause for drug-related liver transplant. Antibiotics, as a class, are an uncommon cause for liver transplant. The one

telithromycin patient that appears here was a patient from North Carolina that had been reported to us in April 2005.

If a patient had had a severe liver injury as a result of taking telithromycin. This resulted in a liver transplant, we would have been advised of it because we are monitoring the system.

[Slide.]

At the two-year time point, we did another comparative reporting rate analysis. The first one I showed you was the one-year time point. This is now the two-year time point. Again, the same definitions, broadly defined, and critical hepatic events were used.

Now, the reporting rate again can change drastically over the life cycle of a product being affected by many things including stimulated reporting. What you see here is for telithromycin for broadly defined and critically defined hepatic events. The reporting rate is higher than the other antibiotics but there are several factors to consider.

One, this reflects stimulated reporting. The second, we had augmented pharmacovigilance initiatives that were undertaken, which I described to you this morning, and that, coupled with the expedited reporting of all serious hepatic events--that is, whether the event was listed or not, whether it was a U.S. case or a foreign case, we expedited it.

It is difficult to assess the impact this would have had on the reporting rate.

Finally, it is important to emphasize that Augmentin was approved in 1984, clarithromycin in 1991, azithromycin in '92, moxifloxacin in 1999, and levofloxacin and trovafloxacin in 1997, however, the reporting practices have changed dramatically over the past 20 years, in fact, there has been a doubling of adverse event reporting from 2000 to 2005 alone.

This makes the assessment particularly difficult. There are so many confounders in here that is hard to assess this reporting rate, comparative reporting rate analysis. So you might

ask why did I even present it. Really, just to emphasize that it is practically impossible to interpret this data because of all the confounders and as we discussed this morning, reporting rates are a tool, an exploratory tool.

They help us to understand the significance of an event and to decide whether or not further evaluation is needed. What this tells us is that further evaluation is needed. This is why we had to go to other data sources in order to assess comparative risk of hepatic events. This is the reason we conducted two pharmacoepidemiologic studies to assess comparative risk.

[Slide.]

In conclusion, hepatic events have been well characterized through our intensive pharmacovigilance initiatives and further investigated through our two pharmacoepidemiologic studies.

Our conclusion based on our own internal assessment and in coordination with our experts, is that telithromycin may be associated with a

reversible hepatocellular or mixed injury comparable to other antibiotics and rarely reports of severe hepatic events or liver failure have been seen.

Dr. Lewis shortly is going to discuss the signature of telithromycin with respect to hepatic events and to discuss these more severe cases and his causality assessment.

[Slide.]

Finally, we made a labeling change in June of this year and that was communicated to physicians through a Dear Doctor letter and specifically, the change included a warning about acute hepatic liver failure including fulminant hepatitis and hepatic necrosis leading to liver transplant and that this could occur in some cases shortly after treatment.

Also, recommendation to physicians to monitor for signs and symptoms of hepatitis and if signs and symptoms develop, to discontinue treatment.

I would now like to introduce Dr. James

Lewis from Georgetown University Medical Center, who is going to discuss the signature of telithromycin and its potential effects on the liver.

Thank you.

Expert Review

James H. Lewis, M.D., FACP, FACG

DR. LEWIS: Thank you, Barbara, and good afternoon to everybody. I am going to continue our discussion about the liver hepatic events this afternoon. My interest in this goes back almost 28 years now working with Dr. Hyman Zimmerman, who is familiar to many of the people in the room. I think many of us graduated from Hy Zimmerman University either as a full-time student or certainly we audited the course work and much that we know about the liver and liver toxicity is due to Dr. Zimmerman.

I have also been working, as you heard before, with a team of people from Sanofi-Aventis, which included Willis Madri, Paul Watkins, Dr. Emanual Rubin, who is here with us, for the past

several years, as well as the Pharmacovigilance group at Sanofi.

We have been looking at these cases for quite a long time and what we have done is analyzed all of the cases that have been serious, and others as well, and I am going to offer you our perspective on that.

[Slide.]

You have heard of the clinical development program. I am going to just give a brief overview of what you are going to hear again. I have a feeling from Dr. Lee and Dr. Seeff relative to drug-induced liver disease in the United States, because it is not unique to telithromycin or the antibiotics, as you have heard.

What I am going to do is develop our analysis of some of the cases that we feel are likely to be telithromycin and what that looks like as a signature of the drug. I will have a few comments on the Annals cases and some new information that we have about those.

As you probably know, anytime there is a

serious case submitted to the company, all efforts are made to get as much information as we can about that, because the spontaneous reports are often lacking.

[Slide.]

Nearly all antibiotics, as you have seen from all of the different data, can cause hepatic effects and telithromycin is no different. There was a signal with telithromycin in the preclinical studies, and so the focus has been intent on what is happening with the liver throughout its development.

I am not going to dwell on these cases or the Phase III information, you have already seen it. It is very comparable to the comparator drugs that were used in the studies. The rest of my remarks are really going to be on the postmarketing information.

[Slide.]

Now, drug-induced liver disease is very common, it is up to about 9 percent of all drug-related adverse events can affect the liver.

You will hear about Hy's Law mentioned later and it involves hepatocellular jaundice carrying a case fatality rate or the need for transplant in about 10 percent or more patients.

It has been proven over time and recent studies in Europe have validated that. Lesser values just biochemically have not been as well validated, however.

You will hear that drugs cause acute liver failure about half the time. Of all the cases that occur in the United States, that's the estimate and we have Dr. Lee's Acute Liver Failure Study Group to look to for that kind of information. You have already seen that acetaminophen accounts for a vast majority of the cases of liver transplant from acute liver failure.

[Slide.]

The Liver Failure Study Group of Dr. Lee suggests that acetaminophen is somewhere around half of the cases and I was interested to see that acetaminophen was listed in the AERS database and, even though it's a very widely used drug, the

absolute number of cases is quite high, and, in fact, is half of all the acute liver failure and that includes viral hepatitis and all the other causes that we have.

All other non-acetaminophen drugs, including some herbals, represent between 12 and 15 percent of all liver failure.

[Slide.]

You have also heard from the tracking of the UNOS database for liver transplantation that drugs account for 15 percent of all liver transplants that are done as emergencies for liver failure. Fully half of those again are due to acetaminophen. All other drugs are the other half but that is every other drug that we have.

[Slide.]

The updated database, in fact, included the one telithromycin case from North Carolina, which did receive a transplant. These are liver enzyme values and some other interesting things that I have taken from Dr. Lee's Acute Liver Failure Study Group. I would like to point out

that the majority of people who develop injury are female.

The mean ALT and AST values I think are important to look at. If you have acetaminophen or some direct toxin to the liver, the enzymes are often in the thousands, much higher than we see for viral hepatitis and, as it turns out, about 10 times as high as we see for very severe injury from other drugs.

As I go through the analysis, I will show you that I think that the telithromycin cases fit well with this definition of how high the enzymes actually can go.

[Slide.]

There is an elephant in the room that we have already alluded to, which I think you cannot ignore, and no matter how prevalent acetaminophen use is, and how low the prevalence of liver failure, it is far and away the most common cause of liver failure and liver transplant in the United States and in much of the world.

So any risk of any other drug causing

liver failure, I think we always have to compare it to what is the risk of acetaminophen that is with us all the time in our transplant centers.

[Slide.]

Antimicrobial agents as a group top the list of drugs causing liver injury that are non-acetaminophen. The series here, the first one is a U.S. study, 44 percent were due to antibiotics, 27 percent, 32 percent, this comes from the Swedish report and the Spanish report recently validating Hy's Law showing how commonly the antimicrobials, as a group, show up.

You have seen this in the AERS database and take your pick of antibiotics, they are all associated with liver injury.

I think it is reassuring that we saw from the European data this morning by Dr. Mortimer that telithromycin was really on par with other antimicrobials as far as reporting rates were seen. The AERS database I think also suggests that it is fairly similar to others, as well.

[Slide.]

Now, there has been a very large postapproval safety database for us to look at. You have already heard these numbers before, 28 million global exposures, about 6 million in the United States.

You are going to hear shortly about the large epidemiologic studies that offer I think additional reassurance about the safety of telithromycin. Again, it is a drug with a signal of hepatic injury but we always have to put it into perspective.

[Slide.]

The number of adverse events that were recorded since approval in the United States are about 200, you can see them here, 45 acute serious liver injury events, and 12 acute liver failure cases, and then among those liver failure cases was the one transplant case.

This did lead to revised labeling as you have already heard, in June, to acknowledge this degree of hepatic injury.

[Slide.]

Assigning causality, as you will hear from Dr. Seeff as well, is difficult whenever we are dealing with drug injury, whether it's the patient in the hospital where we have some information, often more than we get with the spontaneous reports, because those often are heavily confounded, missing information.

We rarely have histopathology to look at, whether an adequate workup to exclude other causes has been done may or may not be there and the reporting term is really left up to the person who files the report.

Somebody who has a high enzyme or maybe jaundice, they might say that is acute liver failure, when, in fact, it may not meet the critical definition that we would use in the transplant center.

I envy people who work in Infectious Disease, because you can plate things out and know exactly what you are dealing with. I can't plate the liver out on a Petri dish, it won't tell me what the cause of the liver injury was, so we have

to use a number of different mechanisms to do that. You will hear about some of those methods that are in use.

[Slide.]

The causality assessment that we gave to the acute liver failure cases is presented here. This is the same information we provided in June to the Review Division. It represents our best estimate and opinion, the hepatologists who worked with me and the Pharmacovigilance group at Sanofi-Aventis, about what may have caused these acute liver failure cases.

We accepted two of them where we could not exclude the drug. The others we found more plausible explanations and I think, if you read through any of these cases, they are very difficult to interpret.

While possibly means possibly is, possibly isn't, we tried to say if the patient was in front of us, what would we really think the cause of the injury was or what did we think was going on.

There was one case, in fact, that was

retracted. The physician who reported it notified the company that instead of liver failure, he actually meant to say renal failure, so one of those acute liver failure cases isn't even real.

[Slide.]

These are the Annals cases. I think it is worth just a short review to say what they included.

The first one was a 46-year-old man treated for otitis and sinusitis and he had a reversible hepatocellular injury. He recovered normal enzymes 8 weeks later. That case is probably related.

Case No. 2 is the liver transplant patient, a 51-year-old woman who developed--we are not sure she developed acute liver failure. But she certainly presented with a subfulminant course and a month or five weeks later ended up with a liver transplant.

She is accepted as a possible case even though there was a confounding smooth muscle antibody that was present, suggesting that she

might have had autoimmune disease, but we may never know. But, fortunately, she is doing well after her transplant.

Case No. 3 as it was presented was a 26-year-old man treated again for sinusitis and bronchitis. He had high enzymes, as you can see. He had a very low platelet count. He was in renal failure on presentation and what the report said is he died after endoscopy of multisystem failure.

The preliminary autopsy report, which is provided in the Annals case report, said he had massive hepatic necrosis likely immune-mediated, possibly a hypersensitivity reaction.

Sometimes case reports are not a whole lot better than spontaneous reports even though they are published.

[Slide.]

This is the liver biopsy, the liver tissue from the autopsy that was limited to the chest and the abdomen. Dr. Rubin and I have looked at this.

We can't say a whole lot from a picture in a publication--and we have requested the actual

slides--but it is filled with lymphocytes and the information that was not contained in the report I have listed here.

[Slide.]

This is information that has been shared with the agency, it is new information that has come in. This young man complained of weakness, nosebleeds, nausea, hematemesis, right-sided belly pain for 2 months prior to going to the emergency room, which would have been about 6 weeks before he ever took telithromycin.

He had a cardiopulmonary arrest during endoscopy right after he was admitted. On the autopsy there was fluid and blood in the lungs. The final autopsy report said there was an absence of eosinophils but there was a major lymphocytic infiltrate in the liver which made a hypersensitivity reaction, in fact, less likely, and he had a massively enlarged liver and spleen.

His liver was twice normal size, his spleen was 3 times normal. He had very large, prominent mediastinal lymph nodes and the final

pathology report says he had a viral myocarditis, which is not listed in the Annals report.

Dr. Rubin and I and the other hepatologists have discussed this and why this might not be lymphoma or some other lymphoproliferative disease where he presented with acute liver problems as part of the lymphoma is certainly I think to be taken into consideration.

It certainly shows you how difficult interpreting even case reports that are published might be.

[Slide.]

Now, we have tried to look at the cases that we consider possibly or probably related in the database and here is what we have come up with.

Again, it's a female predominant injury, which is very similar to what we have seen with many other drugs. It's hepatocellular in three-quarters of the cases. I was particularly interested in the AERS data that suggested that cholestasis was really not part of telithromycin and I would agree with that.

I found that it was mixed injury meaning hepatocellular, or had some cholestasis, which is defined by an elevated alkaline phosphatase, not necessarily jaundice. But that was present in about a quarter of the cases, jaundice was present in about a quarter of the cases.

The mean ALT, the mean AST, you can see the values here, very similar to the non-acetaminophen serious problems that Dr. Lee's papers have alluded to. Again, these are not anywhere close to the range of what we see typically as the mean for acetaminophen or shock liver.

[Slide.]

The latency is a little bit harder to determine. People had a reaction after just a single dose of telithromycin, all the way up to 2 and maybe even 3 months after the drug.

The mean that we were able to calculate after dosing was about a week. So it is happening fairly quickly after but not always while they are taking the medication. There were some

hypersensitivity features, rash, and eosinophilia in some of the patients. It is difficult when you are treating patients with a febrile illness to know a fever means some form of immuno-allergy.

The majority of these cases, as you have heard, as in Europe, were self-limited reactions, the acute liver failures, subfulminant liver failure appeared to be quite unusual and, in terms of host factors that might predispose one to telithromycin injury, I am not sure.

Female gender appears to stand out a little bit. Whether underlying liver disease will do it is a possibility and, of course, it should not be used in liver disease. Prior exposure is another possibility. There were several cases where there was repeat exposure to telithromycin and liver injury occurred the second time.

[Slide.]

Delayed injury is not unique to telithromycin among other antibiotics but it is a fairly unique latency I think for most acute drug injury. Most drugs, if you get an injury from it,