FOOD AND DRUG ADMINISTRATION

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ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE

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62nd MEETING

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Wednesday, November 19

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The meeting was held in the Versailles Room 3 and 4 of the Holiday Inn, Bethesda, Maryland, at 8:00 a.m., William Craig, M.D., Chair, presiding.

PRESENT:

WILLIAM A. CRAIG, M.D., Chair

ERMONA McGOODWIN, Executive Secretary

MEMBERS:

PARVIN H. AZIMI, M.D.
MARIAN E. MELISH, M.D.
NANCY K. HENRY, M.D.
DONALD E. PARKER, Ph.D.
CARL W. NORDEN, M.D.
JULIE PARSONNET, M.D.
ROBERT L. DANNER, M.D.

CONSUMER REPRESENTATIVE:

KEITH A. RODVOID, Pharm.D.

GUESTS AND CONSULTANTS:

BARTH RELLER, M.D.
JON S. ABRAMSON, M.D.
IRENE BIDAULT, M.D.
JOHN S. BRADLEY, M.D.
SCOTT DOWELL, M.D., M.P.H.
JEROME O. KLEIN, M.D.
PAUL S. LIETMAN, M.D., Ph.D.

DAVID C. VAN SICKLE, D.V.M., Ph.D.

A-G-E-N-D-A

PRESENT - (Continued):

P-R-O-C-E-E-D-I-N-G-S

(8:14 a.m.)

CHAIR CRAIG: Could people please take their seats?

I'd like to welcome you to this meeting of the Anti-Infective Drug Advisory Committee. This is the 62nd meeting. They are going to be changing the board, so fairly soon everybody else will have their microphone, but I think they are picking it up on the documentation of the record for the meeting, so we can still go around and introduce each individual telling who they are and where they are from. And, I guess I'll go ahead and start.

I am William Craig. I am from the University of Wisconsin, and I'm the chair of the Advisory Committee.

So, if we could start here on my right. Use the microphone because it is still at least being picked up -- none of them are now? Say it loud.

DOCTOR VAN SICKLE: Doctor Dave Van Sickle from Perdue University, Department of Basic Medical Sciences.

DOCTOR LIETMAN: I'm Paul Lietman. I'm Director of the Division of Clinical Pharmacology at Johns Hopkins.

DOCTOR DOWELL: Scott Dowell from the Respiratory Diseases Branch at the Centers for Disease Control.

DOCTOR BRADLEY: John Bradley, Children's Hospital San Diego and the University of California San Diego.

DOCTOR ABRAMSON: Jon S. Abramson, Chairman of the Department of Pediatrics at Bauman Gray, and also representing the American Academy of Pediatrics.

DOCTOR KLEIN: Jerome O. Klein, Pediatric Infectious Disease, Boston University School of Medicine.

DOCTOR BIDAULT: Irene Bidault from the Agence du Medicamanet, the National -- and the Pharmacovigilance.

DOCTOR RELLER: Barth Reller, Committee for Infectious Diseases and Clinical Microbiology, Duke University.

CHAIR CRAIG: And, I guess I might inject here that these are all our consultants for this meeting, and now the members.

DOCTOR HENRY: Nancy Henry, Pediatric Infectious Diseases, Mayo Clinic, Rochester, Minnesota.

DOCTOR DANNER: Robert Danner, Critical Care Medicine Department, National Institutes of Health.

DOCTOR AZIMI: Parvin Azimi, Pediatric Infectious Diseases, Children's Hospital, Oakland, California.

MS. McGOODWIN: Ermona McGoodwin, FDA.

MR. RODVOLD: Keith Rodvold, University of Illinois, Consumer Representative on this committee.

DOCTOR NORDEN: Carl Norden, I'm the Head of Infectious Diseases at Cooper Hospital in Camden, New Jersey, at the University of New Jersey Medical School.

DOCTOR PARKER: Don Parker, Professor, Department of Biostatistics and Epidemiology at the University of Oklahoma.

DOCTOR MELISH: Marian Melish, Pediatric Infectious Disease, University of Hawaii School of Medicine.

DOCTOR PARSONNET: Julie Parsonnet, Infectious Diseases and Epidemiology at Stanford University.

DOCTOR GOLDBERGER: Mark Goldberger, Director of the Division of Special Pathogens Immunologic Drug Products, Safe for Drugs, FDA.

DOCTOR LEISSA: Brad Leissa, Medical Team Leader of the Division of Special Pathogens.

DOCTOR HOPKINS: Bob Hopkins, Acting Medical Team Leader of the Division of Special Pathogens.

DOCTOR ELLIS: Amy Ellis, Pharmacologist and Toxicologist of the Division of Anti-Infective Drug Products.

CHAIR CRAIG: Okay, thank you, and, again, I'd especially like to welcome all of our consultants for this meeting.

Ermona McGoodwin will now read the Conflict of Interest Statement.

MS. McGOODWIN: Thanks, Doctor Craig.

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

Based on the submitted agenda and information provided by the participants the Agency has determined that all reported interests in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest at this meeting with the following exceptions.

In according with Section 208(b)(3) full waivers have been granted to Doctors Craig, Norden, Parsonnet, Azimi, Danner and Rodvold. A copy of these waiver statements may be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A30 of the Parklawn Building.

With respect to FDA's invited guests, there are reported interests with respect to the firms that make fluoroquinolones that -- should be made public to allow the participants to objectively evaluate the comments. Doctor Jon Abramson would like to disclose for the record that he has received honorarium from Bayer and has consulted for Merck. Doctor Jerome Klein is a member of the Pediatric Anti-Infective Advisory Committee and Ortho Consultant to the Scientific Board. Doctor David Van Sickle owns a nominal amount of stock in Merck, he has been an investigator and co-investigator on studies funded by Eli Lily, Bayer and has been a consultant to Eli Lily. Lastly, Doctor John Bradley was a co-investigator on two studies sponsored by Pfizer.

In the event that the discussions involve any other products or firms not already on the agenda, for which an FDA participant has a financial interest, the participants are aware of the need to exclude

themselves from such involvement and their exclusion will be noted for the record.

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

Thank you.

CHAIR CRAIG: Thank you, Ermona.

Our next speaker is going to be Murray Lumpkin, who is the Office Director of ODE, that will have some opening remarks.

Murray?

DOCTOR LUMPKIN: Good morning, everybody.

My name is Murray Lumpkin, and what I'm here to say this morning is, first of all, welcome to all of you on behalf of the Center for Drug Evaluation and Research. To the guests we have in the audience today, our consultants, and to the members of the committee we are delighted to have all of you with us today.

I know you have your plates quite full, as you can see from the agenda, on several different diverse, and, I think, very interesting topics. One of the things, though, that I thought would take just a few minutes this morning and try to clarify,

particularly, for the committee, is some of the structural and personnel changes that have happened within the Office for Drug Evaluation since the last time you met.

Just to try to keep things from getting a little confusing, as you meet different people, and hear people's titles, I wanted to spend a few minutes to tell you about some of the changes that we've undergone. The first change is the fact that I am not really the Office Director for OED IV, as most of you know. I'm the Deputy Center Director at the Center for Drug Evaluation and Research, but about six weeks ago David Fiegal, who had led the Division of Antiviral Drug Products, and who was then the Office Director for OED IV, was promoted to Deputy Center Director at CBER, at the Center for Biologics. I think this was a great promotion for David. It was one that he truly deserved, and I think he will use his considerable talents in that particular area to look at some very concerning issues for the country, particularly, the safety of the blood supply and the development of vaccines and, particularly, vaccines for various viral diseases.

However, for us within the Center for Drugs it was quite a loss to lose David, and it began

a series of dominoes as we started looking for replacements for David, and also looking at how the Office of Drug Evaluation IV was structured.

As many of you know who have followed over the last five years as we have endeavored within the Center for Drugs to meet the performance goals that were established five years ago under the Prescription Drug User Fee Act, one of the management things that Janet and I undertook at that point in time, with the idea of creating more divisions who would be smaller in number and more focused in their work products, and both Janet and I believe that this has worked well over the last five years and has been one of the things that has helped us achieve and actually exceed the performance goals that Congress established for us five years ago.

This also has affected this particular office. For those of you who have been on the committee for a while, who remember the days when I was in the Division of Anti-Infective Drug Products, we had the Division of Anti-Infective Drug Products, and they had this advisory committee to help them, and we also had the Division of Antiviral Drug Products, and they have a committee that looks at their particular drug products.

We now have three divisions within the Office of Drug Evaluation IV that oversee the antimicrobial products. There is the Antiviral Division, there is the Anti-Infective Division, and there is a division now that we call the Division of Special Pathogens and Immunologic Drug Products, and this is the group that you are going to be hearing from first today. It's a group that primarily deals with anti-fungal drug products, anti-microbacterial drug products, various drug products for parasitic diseases, as the name implies, drugs for immunologic diseases, particularly, various immunomodulatory drugs, but also because of the work load implications in trying to spread the work out between the three divisions they also oversee the fluoroquinolones.

The individual who was chosen to be the Division Director for that division is Doctor Mark Goldberger, whom you will be hearing from in just a few minutes, and the person who is his Deputy is Doctor Renata Albrecht, whom you will, I'm sure, be meeting through the day.

The Division of Anti-Infective Drug Products is right now being capably led by an Acting Division Director whose name is Gary Chikami, and you will be hearing from him when you get to some of the

other drug products, and his Deputy is Lillian Gavrilovich, who many of you, she has had that position for many, many years. She was the Deputy when I was there, and she is still ably fulfilling that position.

Within the Division of Antiviral Drug Products, as you know also Donna Freeman, who was leading that division from the time that Doctor Fiegal left, she has also retired from government service and that division is now under the leadership of an Acting Director by the name of Deborah Bernkrant.

We have been, for the last several months, in a series of national searches to find a permanent director for the Anti-Infective Division, for the Antiviral Division and for OED IV. Those have been incredibly interesting. We have had a lot of interest expressed in these positions, both internally and externally. There has been a series of search committees for the three jobs. Many people have been brought in and interviewed, and I think we will have announcements for those permanent positions within the next several weeks.

But, at least for today, as you begin your work here on the committee and in the future, I just wanted to make you aware of some of these personnel

changes and some of these structural changes, because as our products go we will be bringing products from these three divisions to either of the advisory committees that seem to be the most appropriate advisory committee based on the issue and based on the drug product.

So, if you have any questions about this, you know, please feel free to see me. Please feel free to see any of the leadership individuals whom I've mentioned today, and, again, Bill, I appreciate the time to explain this, I appreciate all of you coming here today, and I wish you tremendous success in a very daunting agenda.

Thanks again.

CHAIR CRAIG: Thank you very much, Murray.

This is the last meeting for the year for the committee in its current grouping, and some individuals will actually be leaving the committee after this meeting, and to present their certificates Gary Chikami will now -- there you are, okay.

DOCTOR CHIKAMI: Thank you, Doctor Craig.

There are actually five members of the Anti-Infectives committee who will be rotating off after four years of very able service, and we certainly appreciate their scientific and clinical

input into our deliberations over the years.

I'd like to present them with a letter of appreciation from the Deputy Commissioner of the Food and Drug Administration and also a plaque from Doctor Woodcock, who is the Director of the Center for Drug Evaluation and Research.

Doctor Henry Francis?

CHAIR CRAIG: Not here.

DOCTOR CHIKAMI: Not here, okay.

Doctor Marian Melish.

Doctor Roselyn Rice.

CHAIR CRAIG: Also not here.

DOCTOR CHIKAMI: And, Doctor Parvin Azimi.

A fifth member is also rotating off, and that's Doctor Edwin Thorpe, who couldn't join us for this three-day meeting.

Thanks.

CHAIR CRAIG: Thank you, and, again, I'd also like to join in my appreciation to the members for their service on the committee.

And now, we are here for the issue, which is the development of fluoroquinolones for use in pediatric patients, and the individual that's going to give our introduction to the topic is the Director of the new division, as was just mentioned, the Division

of Special Pathogens and Immunologic Drug Products, and that's Mark Goldberger.

DOCTOR GOLDBERGER: Thank you, Doctor Craig.

I'd also like to extend a welcome to the committee. As Doctor Lumpkin indicated, there will not be a new advisory committee created especially for this division, so we anticipate bringing quite a number of products to the Division of Anti-Infective Drug Products, just as we will be to the Division of Antiviral Drug Products.

Doctor Craig indicated the topic that we will be discussing today, that is, the development of fluoroquinolones for pediatric indications. As all of you are probably aware, this is, I think, the third committee meeting that has occurred on this topic. One of the lead-off FDA presentations by Doctor Brad Leissa will, in fact, give a little history of some of the previous committee meetings.

We're interested, obviously, in getting some general advice from you about this question of further development of fluoroquinolones for pediatrics. Depending on the answer we get from that, as to whether this is appropriate, we would like to get from you first some advice on particular

indications, where there is currently the greatest amount of interest, and I think the one that is most obvious would be the development of fluoroquinolones for otitis in children, and I think it would be, if the committee feels that further development is something that is appropriate, that's a topic that we would like you to give your advice about.

Beyond that, more generally, we would like, if further development is recommended, or even not, a framework for how we could proceed in assessing specific indications and thinking about how one might proceed in the future.

Going along with the issues that relate, obviously, to activity of the fluoroquinolones in a number of situations, of course, the major indication and the major concern has been safety. We will be presenting at least a couple of pre-clinical presentations talking about the toxicity related to arthropathy in animals, as well as some clinical epidemiologic data that will be presented by a number of people during the morning to outline some of the concerns that exist, and also the amount of data that currently exists about the use of these products in children.

We would expect the discussions to focus

on the issue of arthropathy, but they do not necessarily need to be limited to that, and that is up to members of the committee in terms of other concerns about toxicity that you would like to bring up.

We are interested, obviously, in thinking qualitatively. Certainly, when we talk about the issue of arthropathy that potentially includes a number of things, ranging from simple effusion, for instance, of a knee joint, which might rapidly resolve after the conclusion of therapy, to a more permanent disability. We'd like to get a little bit of advice about putting together a hierarchy of these events, in terms of how you would value them in their importance, and going along with that some sense of how you would view them qualitatively, particularly, the issue, perhaps, of severe toxicity that might occur relatively uncommonly. And, again, beyond specific advice, we'd like to get a framework of your thinking about how we might approach safety over time, as different companies present different questions to us.

Before I close, I'd like to thank a number of people who participated in putting together the agenda for this meeting. Many of them, in fact, will be presenting, that would include Brad Leissa to my left, and also Bob Hopkins. I'd also particularly

like to thank Doctor Renata Albrecht, the Deputy Director of the Division, who helped with much of the presentation, and in particular also some of the reviewers in the pre-clinical area, most notably Teri Peters, a pharmacologist from the Division of Anti-Infective Drug Products, the supervisory pharmacologist in that division, Doctor Bob Osterberg, and Doctor Amy Ellis, also a pharmacologist in Anti-Infective who will be one of the presenters.

Perhaps, later on this afternoon when we actually get to discussion of the questions, we may want to talk a little more about some of these issues to ensure that, you know, we get the advice that we need on some points, but I think now I'll close in the interest of keeping us relatively on time.

Thank you.

CHAIR CRAIG: Thank you, Mark. In fact, we're even ten minutes ahead, gained a lot of time very quickly there.

Our next speaker then is Brad Leissa, who is going to give us the history of the previous advisory committee meetings on the question of the use of quinolones in pediatric populations.

Brad?

DOCTOR LEISSA: Good morning. I'm going

to try a very difficult task, which is to try to catch everyone up in the next 15 minutes with regards to history of this issue.

As Doctor Goldberger had mentioned, this has been brought up twice to the advisory committee back in 1989 in a closed session, as well as in 1993, the issue about what do we do about quinolones in pediatric populations.

History is interesting because, obviously, it's a continuum and issues that occur and how one responds depends on what are the various factors going on at the time. Last night, of interest when I got home and went through my mail, the most recent issue of Clinical Infectious Diseases, November, 1997, has an article called, "Quinolone Arthropathy in Animals Versus Children," with the authors Doctors Burkhardt, Walter Schiel, and Doctor Schaad, so it's still an issue which is being presented and discussed in the medical literature.

CHAIR CRAIG: Could I comment, Brad? For the committee members, there is a copy of his slides that were handed out to you if you want to follow along.

DOCTOR LEISSA: Okay.

In 1962, nalidixic acid, or NEGGRAM, was

approved for use in pediatric patients over three months of age. In 1972, arthropathy was first described in animals per Bailey. In 1973, a new formulation of nalidixic acid was produced, suspension, and it was approved.

In 1997, animal studies identifying histopathological joint changes were also described, and this brought us then into 1989 where during a closed session, and I can't mention specifically the drug, but I can share with you some of the issues that were discussed and some of the recommendations that came from the advisory committee relative to fluoroquinolones in pediatric populations, and I will go over that briefly.

In 1993, there was another advisory committee, and then, of course, we are in the third one today.

I did want to mention very briefly, but Doctor Hopkins will go over this in more detail, in 1994 the "Pediatric Rule" was finalized in the Federal Register, and just very briefly, what that allows is to extrapolate adult clinical data to pediatric data, as long as there is a pharmacokinetics extrapolation.

In 1995, the FDA sent a letter to the New England Journal of Medicine warning against

fluoroquinolone in tendon rupture, especially achilles tendon.

And then, just for your interest, in September of 1997 there is now a coprofloxacin suspension which is available, and although it continues to have the same warning statements about arthropathy in juvenile animals and the potential concern in pediatric populations, obviously, the issue of off label use will extend over to pediatric populations in this formulation.

To give you a taste of what the current labeling says, and this is representative of most of the fluoroquinolone labeling, it says, "Safety and effectiveness in children and adolescents less than 18 years of age have not been established. Quinolones can cause arthropathy and osteochondrosis in juvenile animals." So, this is the labeling that we currently see for most fluoroquinolones.

So, bringing you up to 1989, there is, again, there was a closed advisory committee, and there were questions that were posed to the advisory committee at the end, and I'm shortening the answers but to give you a sense of what was recommended to the company that came to that advisory committee.

The first question was, should clinical

trials of quinolones, in subjects under 18 years of age, be allowed, and the answer from the advisory committee was, "We feel it is reasonable to go ahead with clinical studies."

Question number two was, if so, what age group? And, again, the answer from the advisory committee was, "A six-year old cut off," so, essentially, six and above.

Question number three, what populations and for what infections? The answer came back, "The recommendation of the advisory committee members was cancer, cystic fibrosis, sickle cell anemia with salmonella infections, especially salmonella osteomyelitis," and that was of particular interest to one of the advisory committee members who deals with sickle cell patients.

And, the fourth question was, should each child's growth potential be evaluated before treatment as well as in the analysis of results, and the response back from the advisory committee was, "Plain x-rays, no MRI, and good growth charting, monitor over a two-year period." And, "Have an expert examiner monitor these patients with joint examinations."

So, there is a lag period to 1993 where there was, again, interest in pharmaceutical companies

developing quinolones in pediatric populations, and so this issue was brought up again to the advisory committee, which was, where do we go from here, how do we extend, or should extend the use.

At that time, the guests to the advisory committee were Doctor Urs Schaad, many of you presumably know of him and he's obviously published a lot about this issue, Doctor Jamshed Kanga from Lexington, Kentucky, who is at a cystic fibrosis treatment center and presented some of the data, and then there were two company presentations, one from Otsuka America, Doctor Bill Pitlick, and then Doctor Roger Echols, who was with Miles at the time, and who will be also presenting today from Bristol-Myers-Squibb.

Doctor Schaad offered a list of potential pediatric treatment indications for fluoroquinolones, and this is to get you thinking about from relative to our future questions to you about various indications that might be developed, but in 1993 indications that were offered out to the advisory committee included cystic fibrosis, complicated urinary tract infections, chronic suppurative otitis media, pseudomonal osteomyelitis, invasive enteritis due to multiple resistant pathogens, femoral neutropenia, and the

elimination of nasal pharyngal pneumococci.

So then the questions, the first question was, should the investigation of quinolones in children and adolescents be limited only to certain special disease entities, where the products potentially offer significant advantage over present therapies, for example, cystic fibrosis, gastrointestinal disease, due to multiply resistant organisms, and the response was unanimous from the advisory committee and it was a yes. And, I focus you on the issue as, "... to be limited only to certain special disease entities."

It's always interesting going to transcripts and finding what seems to be a very interesting comment that would have been made during that meeting, and I offer to you this from Doctor Russell Steele, who was a member of the advisory committee from New Orleans, during that meeting, and this goes over several slides.

"We do not know about the toxicity, so it still ends up being what was very nicely displayed as an analysis of risk benefit. With cystic fibrosis, I think there is feeling among pulmonologists, as we heard today, that there is significant benefit to be offered so we can assume those risks.

But, if the question whether there should be studies for otitis media encouraged, I think that they might be considered if, indeed, we reach that point in time where that might be the most logical class of antibiotics to use for resistant pneumococcus, but we are not there yet. I think we are a long way from there.

We are really seeing relative resistance but not that much absolute resistance. So, I do not think that there will be that much enthusiasm among pediatric investigators to pursue the more routine indications, particularly, otitis media or streptococcal tonsillitis/pharyngitis, pneumonia, sinusitis, et cetera."

The next question was, if the answer to question one is no, are there restrictions the committee would suggest at this time on the investigative use of these products, or does the committee recommend them for general investigative use in children and adolescents, and this was not applicable because they had obviously answered yes to question number one about still limiting its use.

Question three, are there any further recommendations to the committee, that the committee would like to make regarding the investigation of

quinolones in adolescents, and there were none at that time.

So, the question is, is from 1993 has anything changed, where are we today in this continuum of time. So, to help us address these, these are some of the questions, I think, that we're searching through collectively.

One, is bacterial resistance a greater concern today than it was in 1993, and to help us answer or to address this issue we have Doctor Dowell from the CDC who will be discussing this.

Do we know more about the clinical relevance of arthropathy seen in juvenile animals, and what about a mechanism? We'll have presentations from Doctor Amy Ellis and Doctor Van Sickle.

Have we globally accumulated additional pediatric safety experience since 1993? Doctor McCloskey of FDA will be presenting data from our Adverse Event Reporting System, as well as Doctor Bidault from the Pharmacovigilance in France.

Are pharmaceutical manufacturers interested in developing fluoroquinolones for pediatric populations, and we asked all the current approved -- pharmaceutical companies that have approved fluoroquinolones and who are developing them,

and invited them to present to the advisory committee and we had three that responded back that they would, and we have Doctors Church from Bayer, Doctor Hopkins from Pfizer and Doctor Echols from Bristol-Myers-Squibb.

And, lastly, is there an increased clinical demand on the part of pediatricians and infectious disease specialists for fluoroquinolones in 1997 or the near future, and we've invited several clinicians to come and speak to this issue. Doctor Abramson will be discussing and reading the position statement from the American Academy of Pediatrics relative to this issue, and other clinicians in the field dealing with these issues, Doctor Bradley, Doctor Klein, and Doctor Lietman.

Thank you.

CHAIR CRAIG: Thank you, Brad.

Are there any questions for Doctor Leissa? Okay, thank you. We'll move on to the next presentation, which will be by Robert Hopkins, another one of the Medical Officers, on the future role of fluoroquinolones in pediatric populations.

DOCTOR HOPKINS: Okay. I'm going to be discussing the future role of quinolones in the development of pediatric patients. What I'm going to

discuss is initially review factors which should be considered when addressing quinolone development in pediatric patients.

I'm going to next outline three possible approaches to the development of quinolones in pediatrics, and finally discuss some of the questions that will be raised for each approach.

As Doctor Leissa had suggested, there is increasing concern regarding the development of emerging bacterial resistance in pediatric patients. This has prompted many clinicians to ask the question whether there's a need for a new class of antimicrobials, specifically, quinolones.

These agents may be highly active against strains which are either highly resistant or multiply resistant to a variety of other classes of antimicrobial agents in these patients. And so, the factors to consider regarding resistance include the current and future resistance rates, as well as the clinical significance or variance of resistant strains as compared with susceptible strains.

In addition to the issues regarding resistance, quinolones may also offer additional advantages, such as convenient oral dosing, daily dosing, and possibly even increased tissue

penetration, depending on the specific indication.

Doctor Amy Ellis and Doctor Van Sickle will review some of the preclinical toxicology data and go over some of the data regarding arthropathy, as well as we will hear various speakers describe the pediatric clinical safety database, specifically, addressing issues of the incidence, severity and duration of adverse events, including arthropathy.

So, the essential question for the committee is whether current quinolone developmental restricts for pediatric populations should change in 1997.

Option number one would say that the restrictions should remain the same, such that we should no longer -- we should not allow clinical trials to proceed in indications other than cystic fibrosis and hematologic and oncologic malignancies.

Option number two, you would essentially be recommending that all indications should be developed regardless of the severity of indication, whereas, in option number three one would recommend an incremental development approach, otherwise as a stepwise development approach of indications based on factors such as severity of indication.

So, essentially, it's a risk benefit

analysis, and in option number one the risk outweighs the benefit, such that there is not a need for a new class of antimicrobials, such as quinolones. Whereas, in option number two the benefit outweighs the risk, and the recommendation would be, go ahead and develop quinolones in this pediatric population.

And finally, in option number three, where you would choose an incremental development of quinolones, the risk benefit analysis would essentially depend on the severity of the indication and also potentially the etiologic organism responsible for the indications, and possibly even specific age groups of pediatric patients.

I'm going to discuss option number three later on in my presentation in more detail, however, the immediate question that will come up when you talk about this option is which indication should be developed first. If you recommend option number one then the immediate question would be, what preclinical studies would be suggested in order to even consider the development of further quinolones in pediatrics, and regardless of which option you recommend we really need to clearly define what is an adequate safety database in pediatric populations.

As Doctor Leissa had mentioned, one thing

the advisory committee needs to be aware of is the "Pediatric Rule," which is currently in effect, which essentially states that sponsors may garner pediatric claims using the clinical data from adult studies, as long as pharmacokinetics bridging studies are conducted, and this is not to preclude the need for an adequate safety database in pediatric patients.

An important safety question is, what adverse events should be monitored, and Doctor Goldberger alluded to this earlier. This is some of the examples I present. One is permanent lameness, reversible lameness, joint effusion, joint pain, and even latent articular disease or damage that may occur months or years following drug exposure, and there may be others.

In addition, we would like to know how well we should be estimating rare, but potentially severe, adverse events. For example, if in a pediatric study you include 100 patients and you don't see any arthropathies, all you can really say is that you are 95 percent confident that the incidence of arthropathy in that population is less than three percent. If you include 1,000 patients and you don't see any arthropathies, then all you can say is that you are 95 confident that the incidence of arthropathy

is less than .3 percent.

Stated another way, to be 95 percent confident in detecting a one percent adverse event risk, you need a sample size of 300. So, this gives you an idea of how to think about estimating rare but potentially severe adverse events.

Getting back to option number three, where you would recommend an incremental developmental approach, I've listed on this slide some of the more common indications that are sought by sponsors, and these are broken into severe indications on this slide, and the next slide will be less severe indications.

Now, on the top of the list is bacterial meningitis, and certainly this is one that you may consider development initially if you use this approach, because the benefit of treating these patients may outweigh the risk. However, the potential pitfall here is that in some of these severe indications it may be difficult to get enough patients in order to define an adequate safety database in terms of numbers.

In addition, many severe indications, patients are treated in the hospital setting where they are not ambulatory, and so it is believed -- if

you believe the preclinical data, where arthropathy occurs in weight-bearing joints, this may preclude an adequate safety database.

Alternatively, this is the list of less severe indications. Often, these are treated in ambulatory patients, and the one I'll highlight here again, that Doctor Goldberger had mentioned earlier, is otitis media. Again, this is a very less severe infection, however, it is very common in pediatrics, and it will certainly be easy to accrue enough patients using this indication to define an adequate safety database. However, you need to balance that with the sheer numbers of patients that will be treated in the post-marketing studies.

This slide outlines the market share of antimicrobials in 1995 in adults, and as you can see, otitis makes up 6.2 percent of antimicrobial use in adults. In contrast, bronchitis makes up almost 20 percent of antimicrobial use. This is compared to the pediatric population, where otitis makes up 50 percent of the market share of antimicrobial use.

I tried to give you an outline as to how to think about developing quinolones in pediatric populations, and I'm going to next read the questions that will show up later on in the day.

The first question that we have, of the following three options, which approach does the advisory committee recommend for the development of quinolones in pediatric populations? Number one is continued restricted development only in patients with cystic fibrosis and hematologic and oncologic disorders. Number two is no restrictions on the type of indications for which quinolones may be developed, and number three, as an incremental development of indications.

If option three is recommended, which indications should be studied first? Finally, keeping in mind the approach recommended in question number one, does the committee believe the safety profile of quinolones for adults and children differ significantly for arthropathy or for other potential safety problems? If so, how does the committee recommend that the FDA address this concern, specific clinical testing, duration of exposure, size of the pediatric safety database.

Thank you.

CHAIR CRAIG: Questions for Doctor Hopkins?

Yes, Carl?

DOCTOR NORDEN: Could you just repeat the

"Pediatric Rule" for me? I wasn't quite clear I understood it.

DOCTOR HOPKINS: Well, the intent of the "Pediatric Rule" is to expedite the development of new drug products for pediatric populations, and so, essentially, it's not a question for you today, but you need to be aware that this rule is in existence, and, in essence, what it is trying to do is encourage the development of drugs in pediatrics so that you can use, in specific indications you can use the clinical trial data from adults and extrapolate that down to pediatrics, given that it's appropriate, as long as you do adequate pharmacokinetics bridging studies where you are defining the dose in pediatrics, depending on the metabolism of the drug.

DOCTOR NORDEN: Thank you.

CHAIR CRAIG: I guess I would ask, are there any of the fluoroquinolones that are approved for otitis media in adults?

DOCTOR LEISSA: No.

CHAIR CRAIG: Okay, thank you.

Any other questions? Okay.

We'll move on to your next speaker, which is Scott Dowell from the CDC, who is going to give a presentation on Streptococcus pneumoniae and

resistance. Scott?

DOCTOR DOWELL: Thank you.

I was asked to talk about this question, given that there is an increasing problem of pneumococcal resistance, does this mean that we should be looking to a new antimicrobial agent?

And, as you are aware, the pneumococcus is the latest in a long line of bacteria to become resistant to antimicrobial agents. Beginning back in the 1950s, soon after the widespread availability of penicillin with hospital-acquired infections first and then community-acquired infections later.

I think that pneumococcal resistance has generated a lot of concern among the medical community, as well as the public health community, because of the importance of pneumococci as pathogens, and actually now, meningitis, pneumococcus is the leading indication for meningitis in this country. Those are recent data from Ann Schuchat's paper, New England Journal, about a month ago, showed about 5,000 cases per year. It's also the leading cause for bacteremas, with about 50,000 cases per year, for pneumonia with an estimated 500,000 cases, and for otitis media with an estimated 7 million cases per year.

I think it's worth keeping these data in mind as you think about fluoroquinolone use for these indications, because there's a big difference, I think, in terms of driving pneumococcal resistance whether the indication is approved for 5,000 cases of meningitis versus 7 million cases of otitis media.

You are all aware of the recent dramatic rise in pneumococcal resistance. This is from a sentinel surveillance system that was maintained at CDC in the late 1980s, showing really no high level pneumococcal resistance, and the system was discontinued because it was felt to be superfluous. And then, of course, look what happened when the system was started up again in 1992, high level pneumococcal resistance rapidly increased and that increase has continued.

I won't say anything more about this sentinel surveillance system. Most of the data I'll be talking about is from a separate active surveillance system, but here's an example here where CDC seemed to have missed the boat.

We believe that emergence of pneumococcal resistance is closely linked to antibiotic exposure, and particularly widespread antimicrobial use, and I think we could look to a lot of different studies to

support that belief. Now there are more than a dozen studies that show that one of the biggest risk facts for carrying a resistant pneumococcus is preceding exposure to antibiotics, and preceding exposure to antibiotics is also a leading risk factor for having a resistant pneumococcal invasive disease.

This study illustrates the point I think nicely in a graphical way. This was a study of children who had recurrent otitis media, and needed to go on antibiotic prophylaxis, so they were giving a low dose of amoxicillin for a four to six-month period, and what the investigators did was, they did nasal swabs once each month and they plotted out in this figure the proportion of kids who had a resistant strain of pneumococcus, H flu or moraxella, and what you see nicely illustrated is that with a period of prophylaxis there's a steadily increasing proportion of kids carrying resistant strains, and I think the encouraging part for us was that when this driving force for resistance was released the proportion carrying resistant strains returned towards baseline.

And, this has led to our response to the problem of resistant pneumococci, which is to work on a national campaign to promote judicious antibiotic use. And, as we think about the response to resistant

pneumococci and think about whether new classes of antibiotics are indicated, I think it's also important to keep in mind that this is an important component of the response. The objectives of this campaign are to decrease unnecessary antibiotic use and to reduce the spread of resistance, and we are trying to do that by establishing a lot of partnerships, by developing educational materials, developing and implementing intervention programs, and assessing the impact on antibiotic use, but most importantly the impact on antimicrobial resistance.

And, this winter will be an exciting time for us because a lot of the intervention programs that we've put in place are going to begin to mature and we'll see if these intervention programs are effective at slowing or even reversing this trend towards resistant pneumococci.

I think I'll skip over this slide. I like Bob's slides better, where he split it into adult and pediatrics. This groups adults with pediatrics, but makes the point that he did, that when you look at out-patient antimicrobial therapy in the United States that otitis media is the leading indication, 23 million courses per year.

The next indication is non-specific URI,

or recombinant cold, bronchitis, pharyngitis and sinusitis fill out the list, and so three quarters of all out-patient antimicrobial use is for upper respiratory infections.

Let me turn now to pneumococcal resistance and the surveillance system that I'll be talking about. This is an active population based surveillance system that's been maintained at CDC for the last number of years, it's now in nine different geographic locations. The aggregate population is about 19 million people, and in each of these areas there's a well-defined population, all laboratories that would isolate pneumococci are periodically surveyed. Audits are done every two weeks to ensure that all sterile site pneumococcal isolates are obtained, so it should not be a biased group of pneumococcal isolates and should give a relatively unbiased overall picture of pneumococcal resistance.

Here's a first look at the geographic distribution of penicillin non-susceptibility among pneumococci in these areas, and you can see that there are some geographic variations from 18 percent up in Oregon, lower than ten percent in San Francisco, and something that we're not particularly proud of, the hot bed seems to be in the southeastern part of the

United States, with 33 and 34 percent in Atlanta and Tennessee, respectively. Those numbers are higher this year, this is from '95 and '96.

Also, as I think most of you are well aware, it's not a problem that's limited to penicillin resistance, but it's resistance to a number of different antimicrobials. In fact, leading the list of non-susceptibility is cote thermoxixal, with 25 percent of strains non-suspectable, penicillin with 20 percent, and then other agents also, merapenem shown here, erythromycin representing the macrolides class of antibiotics, cefotaxime, amoxicillin and on down.

In this surveillance system, oflaxacin has been the representative fluoroquinolone that's been monitored, and I'll also point out that vancomycin to date, no vancomycin resistance strains in pneumococci have been confirmed. That also, I think, is important to keep in mind.

I knew I was coming here last week, had a look at the surveillance system again with a specific question in mind, and that is, among almost 9,000 pneumococcal isolates what proportion were resistant to three different classes of antibiotics? And, the three classes picked, amoxicillin representing the beta-lantans, erythromycin representing the

macrolides, and trimethoprim sulfa representing the sulfa drugs, and as you saw from the previous slide trimethroprim sulfa resistance leads the list at about 25 percent non-susceptibility, and that's been relatively stable over the last four years.

Similarly, macrolide resistance, and erythromycin in the ten to 15 percent range maybe dropped a little bit and then came up a little bit in 1997. Amoxicillin resistance is a little bit different, in 1994 it looked like about five percent resistance, in 1997 it's closer to 15 percent resistance, with a sort of steady increase from '94, '95, '96 and '97.

But, I think what's most interesting here is these white bars, which represent strains which are resistant to all three classes of antibiotic. You can see in 1994 it was well less than one percent of strains which met those criteria, whereas, in '95 it was about two percent, about five percent in '96, and now in '97 a little over seven percent of these isolates are resistant to all three classes, and I think that's reason to pause and think about what the implication is a couple years down the line.

We also looked at oflaxacin resistance, and you can see in '94 about four percent of strains

had intermediate resistance, about three percent intermediate in '95, and now two percent fully resistant, but these percents don't seem to change, at least to my eye, in '96 and '97, still about three percent intermediate and .2 percent fully resistant, so I don't see that in this surveillance system oflaxacin resistance is increasing.

I want to turn now from the laboratory, so far we're looking at in vitro resistance among pneumococci to the clinical setting and say a little bit about the implications for in vitro resistance with respect to meningitis, pneumonia, and, finally, otitis media, and I think that the answer about the implications for pneumococcal resistance for meningitis is already in, the decision has been made. There's the report of the Academy of Pediatrics saying that reports of meningitis treatment failures necessitate a revision of the Academy recommendations. There were a number of anecdotal reports, but they were very persuasive anecdotes that treatment failures were seen with resistant pneumococci, and vancomycin plus cefotaxime with cefriaxone is now recommended for treatment of bacterial meningitis.

Pneumonia, I think the field is wide open. The question is still an open one. The early data on

whether there was a clinical impact of pneumococcal resistance for pneumonia treatment were no, there was no impact, and the most important study was a study by Pallares in Spain in 1993, where they showed that among patients with susceptible pneumococcal pneumonias compared with patients with intermediate pneumococcal pneumonias all treated with penicillin there was no difference in outcome once they adjusted for severity.

I think it's important to keep in mind that study, in Spain at the time, concentrated on intermediate resistant pneumococci. There were less than five, I think, fully resistant pneumococci in that study, and so I think the question about the clinical impact of fully resistant pneumococci, like we're seeing in the southeastern part of the United States, is a little bit of an open wound.

These data were presented by Dan Feiken at the IDSA meeting this year, and are a look at that active surveillance system, comparing patients with penicillin resistant isolates and pneumonia with penicillin susceptible isolates, and you can see that the odds of mortality for penicillin resistant infections was increased, and that was significant before adjusting for severity. So, let me emphasize

that these data are still being analyzed and that the final word isn't in, but I think if you think about the Pallares data showing no effect of intermediate resistance and see that that's true also here, but that there's a different answer for fully resistant isolates, I think that the answer about whether there's going to be a clinical impact of penicillin resistance on pneumonia is still a little bit open. For now, I think that probably the answer is still no.

For otitis media, it's becoming a little bit more clear. Like the story with meningitis, there were anecdotes early on of treatment failures. These were the first controlled data that looked at this question. This is from Ron Dagan's group in Israel, and this is a double tap study, so tympanocentesis at day zero, and then again at day three to five, and in this table are all the patients who had a pneumococcus isolated on the day zero tap.

He grouped the patients into those with penicillin susceptible taps on day zero, low intermediate on day zero, and high intermediate. In Israel, at the time, he didn't have any fully resistant pneumococci.

When treated with ceuroxime, bacteriological failure was shown on that three to

five day tap in nine percent if they were suspectable, eight percent if they were low intermediate, and 50 percent if they were high intermediate.

For cefaclor, which is a less active pneumococcal drug, the answer was a little bit different, low intermediate four percent, 43 percent bacteriological failures at, I'm sorry, low intermediate, four percent for susceptible, and 80 percent for high intermediate penicillin resistant strains. And so, indications for the first time that if you treat with a relatively less active pneumococcal agent that you will see bacteriologically confirmed treatment failures in otitis media, bacteriologically confirmed treatment failures correlate very well with clinical treatment failures, and I think these are the first sets of data that said that there was a clinical impact of pneumococcal resistance, or likely to be for otitis media. The magnitude of that impact is a little bit open.

I said that cefuroxime was a less active agent, and I think that it's important to keep these things in mind, too. This was a study, I believe, by Doctor Jacobs, of activity of oral beta-lactans antibiotics against pneumococci. Tabled here are the MIC_{90s} for penicillin susceptible strains in this

column, intermediate strains in this column, and resistant strains in this column, and the agents are ranked in order of activity, with amoxicillin being the most active, need to achieve about two -- per mil to get 90 percent of the penicillin resistant strains, penicillin G about a dilution less active, cefuroxime and cefpodoxime both relatively active pneumococcal drugs, and then these drugs at the bottom much less active against intermediate and resistant pneumococci.

This leads me to the last thing that I wanted to talk about, and that's the DRSP Therapeutic Working Group, that's the Drug Resistance Strep Pneumo Therapeutic Working Group, which is a group put together by CDC, and I think we still need to work on the name of the group, it's very difficult to say, but this was a group of about 30 or 40 experts in pneumococcal treatment and otitis media treatment, who met last spring to discuss changes in otitis media treatment in an era of pneumococcal resistance, and these data were considered at that meeting.

One of the results of the meeting was a letter to FDA suggesting that data like these would indicate that some of these agents are probably not very good otitis media drugs, and strongly emphasizing that bacteriological eradication should be part of the

evaluation. That's a little bit separate from what we want to talk about here.

What I wanted to communicate from that meeting was the sense of that group of experts on the current status of otitis media treatment in an era of pneumococcal resistance, and these are draft recommendations so please don't commit these to memory because I think they are likely to change as we continue to work through them, but I wanted to convey the sense of the group to this meeting.

First, the sense was that amoxicillin, despite the data that you saw, remains the first choice for otitis media treatment, and that increasing the dose is likely to help, at least in some patients.

Second, we asked the group to consider if amoxicillin failed, what were useful second-line agents, and in particular, what agents would be useful, not only against penicillin intermediate or possibly resistant pneumococci, but also beta-lactamate stable agents for the more moraxella and H flu, and there was no shortage of second-line agents that the group chose from, amoxicillin clavulanate, cefuroxime, cefprozil, cefpodoxime and -- ceftriaxone. They also emphasize strict diagnosis, tympanocentesis in some cases to guide therapy, going back to the

judicious antibiotic use that I talked about earlier.

So, I'll end the talk there and be happy to entertain any questions.

CHAIR CRAIG: Questions?

Yes, Doctor Azimi?

DOCTOR AZIMI: You made a reference to the existence of vancomycin resistant pneumococci, are those in an in vitro or an in vivo setting?

DOCTOR DOWELL: Thank you for the opportunity, let me reemphasize, there are no confirmed vancomycin resistant pneumococci, so vancomycin remains a drug that should effectively treat all pneumococci isolated to date.

CHAIR CRAIG: Yes, Doctor Lietman.

DOCTOR LIETMAN: Scott, did you -- the surveillance that shows the --

CHAIR CRAIG: Could you please speak in the microphone, so that we can record it?

DOCTOR LIETMAN: -- yes, sorry -- the surveillance that shows 33 percent in the southeast, and 16 percent or whatever it is, is that combining intermediate and fully resistant, or is that just fully resistant.

DOCTOR DOWELL: Thank you, yes, those numbers were both intermediate and fully resistant.

DOCTOR LIETMAN: Combined.

DOCTOR DOWELL: So, I should have -- if I said resistant, I should have said non-susceptible.

DOCTOR LIETMAN: Could you give us an indication of what the fully resistant incidence is?

DOCTOR DOWELL: Yes, and that has changed impressively over the last year or two. Early on, it was a minority of strains that were fully resistant, now, in essentially all of those surveillance areas, about half of the non-susceptible strains are fully resistant.

CHAIR CRAIG: Doctor Abramson?

DOCTOR ABRAMSON: Scott, as you know, in the effort that the CDC and the Academy are making to more judiciously -- or promote the more judicious use of antibiotics, it's not simply a matter of decreasing the antibiotics, but also using the most narrow antibiotic that you can for a particular disease.

I wonder if you would like to comment on that in relationship to the issue for today, which is the quinolones.

DOCTOR DOWELL: Thank you.

Yes, in the set of recommendations that are being put together by a group, including the -- Committee on the Academy of Pediatrics are coming out

in January, there are several recommendations in there that emphasize using narrow spectrum agents, such as penicillin G for Group A streptococcal pharyngitis for example. And, I think that's an important component.

I think when we have designed our field trials and we want to be sure that we have the best chance of decreasing pneumococcal resistance, we've concentrated on decreasing the overall numbers of antibiotic prescriptions, because we think that the data shown that that's the best chance for success, but I think using narrow spectrum agents is also an important piece of that pie.

CHAIR CRAIG: Sure.

Doctor Klein?

DOCTOR KLEIN: One of the initial initiatives of the Academy, and CDC and the American Society of Microbiology was the publication of a parent education brochure, and that seems to be a very worthwhile avenue in terms of educating the consumer about the appropriate usage of antimicrobial agents.

Academy members received that some time in the spring. There's been about six months of experience. Is there any feedback that you can identify in terms of the number of brochures distributed, how they were used by pediatricians,

accepted by parents, any post-marketing surveillance of the brochure?

DOCTOR DOWELL: Yes, thank you.

As you mentioned, that brochure came out in the spring and we were somewhat ambitious, I think, in printing a million copies of the brochure. We didn't have a clear distribution system in mind.

And, what I can tell you is they flew out of the warehouse. We ran out of the first million within a couple of months and we had to print another 500,000 almost immediately, and we're on the third printing. So, I think that this hit a cord someplace out there among pediatricians and, perhaps, parents as well, who were glad that somebody was addressing this issue of judicious antibiotic use and had some materials from respective bodies that could help them address that issue.

So, yes, and there are also a number of other materials now that build on that basic message in the pamphlet that communicate to the general public this concern about antibiotic resistance and antibiotic over-use.

CHAIR CRAIG: Doctor Azimi?

DOCTOR AZIMI: Can you shed any light on why we are seeing so much resistance to penicillin

resistant pneumococci now at this time? Penicillin has been available like, what, 50 years or so, with the other antibiotics we generally see the development of resistance in a matter of ten, 15 years, but we have been able to use penicillin for pneumococci until very recently, at least in this country, and it's about really half a century since penicillin has been used and we are just seeing that.

Can you discuss some of the reasons possibly, other than just a lot of use of antibiotics, penicillin has been used for all of this time.

DOCTOR DOWELL: I can't really. I'd be interested if somebody else could. I think that there was some evidence early on of sort of an MIC-creep, that although the pneumococci remains susceptible to penicillin by the MIC cut-off that was used, that there was a sort of a creep up towards that cut-off, and so it may not have been as dramatic as it appears to be.

Also in other parts of the world, back in the 1960s and '70s, penicillin resistance was a problem, it's really in the '80s and '90s that we've seen it in this country, but why it took 40 years -- Doctor Abramson.

DOCTOR ABRAMSON: Well, I think that one

of the things that we've clearly seen is in the last five years the number of prescriptions written has remarkably increased, and some of that may be related to day care, but for whatever reason it's clear that the number of prescriptions given out for URI, for otitis media, for things that we're trying to decrease antibiotic usage in, is markedly increased.

And, I think part of that may -- or that may play a partial role in the sort of new -- it's not newly seen, it's newly -- it's more evident resistance that we are seeing.

CHAIR CRAIG: Yes, I might just comment also. I think there's evidence to suggest that they are picking up the genes from the -- streptococci, and I think if you look back with those there is evidence that there has been creep in the MIC with those organisms for some period of time.

Doctor Bradley?

DOCTOR BRADLEY: In the CDC data regarding resistance patterns, have you broken down the data into CSF, blood and respiratory tract isolates and further broken it down between patients who have primary isolates without previous therapy and isolates obtained from patients who have failed antibiotic therapy?

The reason I ask this question reflects the fact that we've been part of an eight pediatric center study since 1993, headed by Doctor Sheldon Kaplan at Baylor, and the differences in the resistance patterns are striking, depending on which group you are looking at, particularly, primary resistance versus resistance in children who failed antibiotic therapy.

And, I think the answers to these questions have direct impact on our advice to the committee.

DOCTOR DOWELL: Yes, I agree, and thank you for making that point.

The active surveillance system that I showed you is limited to sterile site isolates, so there aren't respiratory tract isolates in that surveillance system. But, as you observe in a number of different studies, when you compare isolates from sterile sites to isolates from respiratory tract, such as middle ear fluid isolates, you tend to see a higher proportion resistant among the middle ear fluid isolates.

Certainly, the biggest risk factor for isolating a resistant strain is previous exposure to antibiotics, and if you compare isolates from people

who have been recently exposed to antibiotics and isolates from people who have not, those recently exposed are much more likely in study after study to have a resistant pneumococcus.

CHAIR CRAIG: Okay.

Any other questions? Yes, we've time for one from the audience.

MR. ROSS: I'm David Ross, I'm a Medical Officer with the Division of Anti-Infectives. One issue I was wondering if you could comment on, there's some evidence that there can be transfer from one continent to another of resistant strains, and there's also the factor that antibiotic use in other countries may be subject to different restrictions or in some cases no restrictions, such as over-the-counter use. And, I'm just wondering if you could comment on what that means in terms of public health efforts to control pneumococcal resistance.

DOCTOR DOWELL: Okay, thank you.

Yes, there are a couple of very interesting small reports that show spread of a clonal resistant strain of pneumococcus from one area to another. A 23-F clone was called, I think it was a 23-F, called the Spanish clone for a while, but I think if you focus on those spreads of those resistant

clones you miss the big picture, which is that pneumococcal resistance has emerged across this country in all areas. I don't think it can be linked to immigrants. It can't be linked to importation of resistant pneumococcal strains from countries where there's more liberal use of antibiotics. In fact, if you look at the data I showed you 17 million quarts of antibiotics per year in this country for the common cold, there's certainly no shortage of unnecessary antibiotic use in this country, despite our best efforts.

So, I think that those are interesting case studies, but I don't think that gives the full picture of where pneumococcal resistance is coming from.

CHAIR CRAIG: I think we have time for one last question, Doctor Jacobs?

DOCTOR JACOBS: Michael Jacobs, Case Western Reserve University Cleveland.

Several points that have been brought up here are extremely important, and there aren't answers to a lot of them, and certainly the question of where resistant pneumococci came from I don't think is a question anyone can ever answer, but one point about that is that, now that you have strains resistant to

the three major classes of antimicrobials used in pediatrics any one of these will select for resistance to all three.

But, one point I wanted to make and a question I wanted to ask to Doctor Dowell is, all the surveillance that's going on does not tell us what's going on in otitis media, because, except for a few patients who have tympanotomy or get bacteremic, none of these isolates come from otitis media and very few of these isolates come from the otitis media age group under the age of 24 months.

So, my feeling is that the incidence of resistance in otitis media is probably even higher than the data we are seeing.

Do you have any idea of what the best approach would be to try and find this?

I also have a second question, and this is the last point you had up on the slides there, and that is the break points for otitis media pathogens when not designed for otitis media, and that's a major problem, and a lot of the data that's been presented this morning, and a lot of the data in the literature, uses break points that are not appropriate for otitis media.

DOCTOR DOWELL: Thank you.

Doctor Jacobs was the DRSP working group meeting and knows that those points were important considerations at that meeting, and I think that we in the public health community heard from Doctor Jacobs and others that surveillance for sterile site isolates is not the complete part of the picture and that we need to be looking at pneumococcal resistance among middle ear fluid isolates as well.

And, in just a minute we'll hear a little bit about that. I think there are data from nasopharyngeal swab surveys from around the country that confirm that if you look at nasal swabs and what kids carry, they tend to be higher rates of resistance than invasive disease isolates.

And, I think that the issue about MIC cut-offs with otitis media in mind, I agree is an important one, and maybe a little bit separate from what we are considering here.

CHAIR CRAIG: Do you have some data, Doctor Bradley?

DOCTOR BRADLEY: Yes. The otitis media isolates from our eight center study were actually presented, the resistance data were presented by Doctor Ellen Wald at the annual infectious disease meetings in an abstract, and they are currently being

written up, and, indeed, the resistance in middle ear isolates of children with otitis is greater than that seen in blood isolates, but I can't remember the exact numbers, but thank you.

CHAIR CRAIG: Okay. We thank you, Scott.

We need to move on to our next topic, which is quinolone-induced arthropathy in juvenile animals, preclinical data that will be presented by Amy Ellis.

DOCTOR ELLIS: Good morning.

I'm going to show you some data that has been submitted to the Agency on quinolone-induced arthropathy in juvenile animals.

Firstly, the arthropathy looks like blisters on the cartilage, and Doctor Van Sickle, who is going to speak to you after I'm finished, will discuss the lesions themselves in greater detail and show you some examples, and also discuss something about their histopathology.

Animal species that are known to be sensitive to quinolone-induced arthropathy include the dog, the rat, the rabbit, the marmoset, which is a small primate, and the guinea pig, and of these the dog is the most sensitive species. And, data submitted to the Agency, as well as data from the

scientific literature, indicate that these lesions don't appear to be reversible.

The arthropathy is most severe at weight-bearing joints, and there is a study demonstrating that when dogs were dosed with one of the quinolones the arthropathy was less severe if weight was kept off the joints of the animal.

To give you some perspective on the scope of human quinolone use, there are about nine quinolones that are approved in the U.S., and about eight more in development, and if you count some drugs that are no longer used for a variety of reasons, and some others that have never been approved in the U.S., there are about 24 quinolones that have been used in humans worldwide. All of these have been shown to cause arthropathy in animal models.

I will now present to you some data from some individual drugs that have been submitted to the Agency, and these data are representative for the quinolones.

Since this is a public meeting, I'm going to be identifying the quinolones by number and not by name, and for each drug I'll denote the species that was tested, the age of the animals in weeks, this is important because adult animals are much less

sensitive to quinolone-induced arthropathy than the juveniles, although you can see the arthropathy, especially in young adults at higher doses of drug.

And, in fact, veterinary labeling for the quinolones recommends that they not be used in dogs less than 18 months old, or in large or giant breeds of dogs that are less than 24 months old.

This column, the LOEL, is the lowest dose of drug tested in that particular study that will induce arthropathy and in the studies that may have been identified grossly or preferably had some histopathology, some microscopic data as well. It doesn't mean that the arthropathy was seen in every animal that was tested at that level, it just had to be one out of the number that were dosed.

Also in this column is the duration for dosing for this particular study, and that doesn't mean that the arthropathy might not have developed in a shorter period of time, it's just that that happened to have been the period of time that was studied, and we may not have data with animals that were studied for a shorter period of time.

And also as you can see indicated here and indicated in the subsequent slides, these studies were all from animals that were dosed with the drug by the

oral route.

This column here is the LOEL as a multiple of the highest recommended human dose and the comparisons were made based upon body surface area, and the big take home message from the multiple of the human dose that you'll see is that it's not necessary to give the animals really heroic doses of drug in order to see the arthropathy.

The last column on the slide is the NOEL, or the no observed effect level for arthropathy.

And, for the dog all of the studies here had histopathology data on the bone and cartilage of the joints to identify the NOEL, but histopathology data were not available for most of the rat studies so that was just identified grossly, and that also means that in some cases the no observed effect level for the rat might have been lower if histopathology data had been available for those studies, something might have been picked up there that wasn't something that one could observe grossly at the joint.

The quinolone-1, the lowest dose that induced arthropathy in the dog, was 25 milligram per kilo per day in a 30-day study, and this was about 2/10s of the maximum recommended human dose based on body surface area, and there was no no effect level

found in this study. Presumably, it's somewhere below 25 milligram per kilo, which was the lowest dose tested.

In the rabbit, 400 milligram per kilo in a 28-day study was the low observed effect level, and this is almost twice the highest recommended human dose based on body surface area. And, in this study there was a no effect dose identified, and it was 200 milligram per kilo per day.

In the rat, 250 milligram per kilo was the LOEL in a one-week study, and this was approximately equal to the highest recommended human dose, and, again, there was no NOEL determined in the study because the 250 milligram per kilo was the lowest dose tested.

For this drug in the dog, the low observed effect level was 30 milligram per kilo per day in a 28-day study. This was equal to about half of the highest recommended clinical dose based on body surface area, and, again, there was no no effect level for this study, since that was the lowest dose tested.

In the rat, which is somewhat less sensitive than the dog, the low observed effect level was 500 milligram per kilo in a ten-day study. This is about four times the maximum recommended human

dose, and the no observed effect level found in this study was 250 milligram per kilo per day, again, keeping in mind that there was no histopathology conducted on the rat. So, it's conceivable that that could be a little bit lower.

For the third quinolone, for the dog the low observed effect level was ten milligram per kilo per day in a one-week study, and, again, this was about half of the highest recommended clinical dose, and there was a NOEL that was identified in this study. It was five milligram per kilo per day, so half of the LOEL.

For the rat in a 90-day study, 90 milligram per kilo per day was the low observed effect level, and this was approximately 1-1/2 times the highest recommended clinical dose, and there was a LOEL identified in this study, 30 milligram per kilo, so one third of the low observed effect level, no effect was seen in the joints of these animals.

For this quinolone, again, the data are fairly similar to quinolone-3, for the dog, 4-1/2 milligram per kilo per day in a one-day study, approximately half of the highest recommended human dose was the low observed effect level, and since that was the lowest dose tested there was no NOEL

identified for the dog.

For the rat, in an 84-day study, 100 milligram per kilo was the low observed effect level, and this is approximately three times the highest recommended clinical dose of this drug, and there was a NOEL identified for the rat in this study and it was 30 milligram per kilo per day.

Quinolones-5 and 6 are intriguing to me, because the LOELs for these drugs in the dog, as you can see here, 50 milligram per kilo and 80 milligram per kilo per day, each in a one-month study, are a little bit higher than some of those that you just saw for the other drug products, and I think it's tempting to speculate that there might be some congeners that are less potent inducers of arthropathy.

The next slide -- oh, and before we leave this, though, I'll just indicate that there were NOELs identified for these, for this quinolone it was 15 milligram per kilo per day. I think it would have been interesting to have seen some study results for doses somewhere between these two, because it's a little difficult to know if that's really a true LOEL or if one might still have seen effect, say, at 30 or 40. For this drug, we did have a NOEL of 60 milligram per kilo per day.

And, again, the next slide summarizes all of the dog data for the drugs that I've discussed today, and I think that it demonstrates that it might be worthwhile to perform some head-to-head comparative studies on some of the quinolones to rank them according to arthropathogenic potency.

One thing that -- I think there are some important things to keep in mind when looking at these data, and I think that I should also let you know that I'm not sure that we really have all the data that we need in house right now to really compare these drugs with quite as much scientific confidence as we would want to do.

I think that it's important to consider that all these studies were performed in different laboratories, and they used animals of slightly different ages, although please let me emphasize that this is an appropriate age range here for testing the dog, so these animals were -- the oldest of these animals were six months old, and they are still growing rapidly at that time.

You'll start to see the animals getting somewhat less sensitive when they approach ten months old, a year old. As I said earlier, it doesn't mean that you can't induce the arthropathy, just that they

are going to become less sensitive to it.

And, the animals were also from a variety of sources and kept under different conditions, and as you can see here in this column they were also dosed for really different periods of time.

While these numbers here for the LOEL, and also are somewhat higher for quinolones-5 and 6, I also think that it would also be really helpful to have no observed effect levels for the drugs. As you can tell, it's unknown for three out of these six, and while this number here for quinolone-6 is somewhat higher than the other two that have been identified, and presumably when one considers the low doses that were tested, would also be higher for these three that are marked unknown. It would be nice to know whether this is real or whether this number be a little bit higher for this particular drug product.

The other thing that I think that we really need to have more confidence in doing this kind of ranking would be to have more toxicokinetic data in the animals. Not only serum concentrations of drug but levels in cartilage and in synovial fluid so we could be confident about the fact that any differences that we'd be seeing wouldn't just be based on distribution.

I think that it's probably unlikely for some of these drugs because actually most of them have fairly similar half lives in the dog and the quinolones are fairly well distributed throughout the tissues, but I think that it would be important to have those data to look at in order to really do valid kinds of comparative studies.

Before we leave the nonclinical data, I would like to show you on the next slide that it is possible to induce arthropathy in animals after only a single dose of drug although, as you'll note, higher concentrations were used in these studies. In this case for quinolone 2 a single dose of 100 milligram per kilo which is about twice the human dose caused induction of arthropathy in these animals. And in this case for quinolone 3, this is a much higher dose, a thousand milligram per kilo which is about 15 times the human dose, arthropathy was induced in four week old rats after a single dose of the drug.

And our next slide please. In closing, I'd like to leave you with the thought that it would be really helpful to learn more about why juvenile animals are more susceptible to quinolone-induced arthropathy than adults and why some species are more susceptible than others. Unless you have some

questions for me, Doctor Van Sickle is going to get into these issues a bit more when he discusses the difference between adult and immature cartilage and the relationship of immature cartilage to quinolone-induced arthropathies.

CHAIR CRAIG: Thank you, Doctor Ellis.

Are there questions for Doctor Ellis? Yes, Scott. Scott Dowell.

DOCTOR DOWELL: Yes. It's interesting data and I think you showed us data from dogs and rats and rabbits. I think also that we're going to hear later that there are not as persuasive data from humans. And my question is are there other animal species that have been tested? Are all animal species that have been exposed showing arthropathy in juvenile animals and are humans the only exception or are there other species that simply don't show that?

DOCTOR ELLIS: It's my understanding -- I mean these are really the kinds of things that we've gotten in the agency. I think most of the veterinary literature will show you that for most animal species you're going to see arthropathy if quinolones are dosed to them at a time in their lives when they're sensitive. I can't think of any animal species offhand that are completely insensitive to these kinds

of effects. There are some data indicating that primate species may tend to be a bit more resistant than the dog, for example. As you can see from the rat data, the rat was certainly more resistant.

The one caveat that I'll give you with the primate studies is there aren't very many, at least that we have in-house that were done and part of the reason why I didn't really present anything like that is most of them were done with really either small numbers of animals or it was very difficult to determine the real age of the animals. There were some questions about that. So I would not want to try to draw a lot of conclusions from those data.

CHAIR CRAIG: Any other questions for Doctor Ellis? Yes, Doctor Leitman.

DOCTOR LEITMAN: One other way of comparing intra-species is to look at the exposure rather than the dose.

DOCTOR ELLIS: Oh, no question. That's why I think toxicokinetic data would be extremely important.

DOCTOR LEITMAN: But we must have that kind of data already for some of these quinolones.

DOCTOR ELLIS: We have the data for some of them. We don't have it in cartilage.

DOCTOR LEITMAN: Okay, but in --

DOCTOR ELLIS: There are very few. There's one drug that I can think of actually where we have some cartilage data in the dog.

DOCTOR LEITMAN: Well, but we do have the data in blood.

DOCTOR ELLIS: Yes.

DOCTOR LEITMAN: And one could make a comparison. So let me ask directly. Is there any reason to suspect that the non-primate animals would have a greater exposure to the flouroquinolones? Do they have longer half lives?

DOCTOR ELLIS: No.

DOCTOR LEITMAN: Do they stay in those animals longer than in humans?

DOCTOR ELLIS: No. In the rat, for the most of the quinolones, the half life tends to be a couple of hours so that's less than humans. For most of the quinolones that you see there, the half life in the dog and the half life in humans is very similar. About seven to eight hours. There is one quinolone in particular that I showed you data from where the half life in humans is actually somewhat higher than half life in dog by about twice and there's one also there where the dog half life is about half of the human.

For the others, it's very similar.

DOCTOR LEITMAN: And I suppose there are no obvious metabolites that the animals make that humans don't.

DOCTOR ELLIS: No. No, nothing obvious.

CHAIR CRAIG: We have time. Go ahead and identify yourself.

MR. VON KEUTZ: My name is Eckhard von Keutz. I'm head of pharmatoxicology at -- I would like to make a comment. First of all, I appreciate your presentation making all these comparisons on these different quinolones and I think you made the right mentioning that it's especially important to compare the exposure data and to try to collate these exposure data with the other toxic potentials. And we have made some head to head toxicological trials and it appears that in young -- dogs there's a threshold for arthrotoxicity and this threshold is around four to five micro -- This holds true for a number of different quinolones.

Interestingly, in rats the threshold for the induction of the arthrotoxicity is much higher. It's around 20 micro -- for ML which explains that rats are really less sensitive compared to dogs. The reason for this is not clear, at least not to our

knowledge.

And one final comment because it was also mentioned that there is animal species known for which these lesions are not induced. I think there is one animal species. That's the mice. For mice, a lot of data are available, but mice are obviously completely insensitive to the quinolone arthrotoxicity. Thank you.

CHAIR CRAIG: Any comments, Doctor Ellis?

DOCTOR ELLIS: No. Actually, at least with the data that have been submitted to me, I haven't seen histopathology on the joints of the mice that were submitted to the agency, so I'm glad that he spoke to that issue because I did not have knowledge of the mouse.

CHAIR CRAIG: Okay. Any other questions?

Okay. We'll move on to our next speaker who's just getting his slides set up which is Doctor Van Sickle from Purdue University who's going to be talking on the relationship of immature articular cartilage to quinolone arthropathy.

DOCTOR VAN SICKLE: Good morning. This morning I'd like to hopefully -- of course I've hoped for 30 years and I haven't gotten the job done, but maybe we have a reason to do it today. And that is I

want to initially compare adult articular cartilage to immature articular cartilage because I think there's some units that take the adult articular cartilage and apply to the immature articular cartilage. And then secondly I'd like to show you some histopathology from a study that we did on cinoxicin for Lily.

The other one, too, please. I was afraid of that. Can you run the sets for me, please? Okay. We're behind on the left. Okay. Now the next set, please. Sorry. This doesn't seem to be operating. Okay. I wanted to show you first adult articular cartilage. It might be well, since I understand most of you are pharmacologists and microbiologists, to acquaint you again with this very thin covering that in man that is destined hopefully to last 70 years.

It's very thin, and you can see over here on the right it consists of a non-mineralized portion and a mineralized portion. And we sometimes forget about this mineralized portion, but it's very important because it allows the joint to remodel in response to changes of biomechanics.

But we'll principally talk about this portion right here, and we also see here that it is interlocked with the subchondral bone. However, the collagen fibrils from the articular cartilage here to

the calcified cartilage are interlocked, but the only interlocking here between the articular cartilage and the subchondral bone is through the interdigitation that you see there as well as a cement substance.

Next set, please. Here you see a ontage of scanning the M showing you the lacunae where the chondrocytes have popped out and over here we have a transmission electron micrograph pointing up the fact that in this matrix we don't have fibers. We have fibrils, and there is a connection between the fibrils and you see -- I hope you can see -- there's little electron dense areas associated with the fibrils, and that's the proteoglycams and that's the unit that is most liable in the articular cartilage.

We have several species of proteoglyc enzyme, one that turns over in half life of about 28, 14 - 28 days, and then another one that has a half life of almost a year. But there are no vessels, there are no lymphatics, and there are no nerves in adult articular cartilage. The pain comes from the synovial membrane, and so you can't get pain from articular cartilage.

Next set, please. Scanning in here of the chondrocyte in its lacunae. You can see the fibril network of the matrix. There is a totally different

set of enzymes and so forth here versus and we in the cartilage work talk about the pericellular matrix which is condensed over the surface of the chondrocyte, the territorial matrix and the inter-territorial matrix. And if you cut this in half, there you can see the chondrocyte. It's not very exciting. It's a general type of cell with organelles and you can see that it has a complement of glycogen as well.

Next set, please. Now I mentioned the fact that we have a subchondral bone relationship. You can see here that the fibers or fibrils form a connection with the calcified layer which is right here and the division between the calcified layer and the non-mineralized portion of the articular cartilage is called a tidemark and this tidemark is a dynamic ossification front. The changes in your joints occur during lifetime, slowly but they occur. And the remodeling occurs in this area right here and then you can see that the collagen, the type of collagen that we have here in the subchondral bone is certainly much different than what you see here in the calcified cartilage.

Next set, please. Synovial membrane relationship. This is the membrane that feeds the

articular cartilage. Since there's no blood vessels, there's no lymphatics, the blood vessels produce an ultrafiltrate of the plasma and add some components to it and then provide the synovial fluid which then takes care of the nutritional aspects and absorbs the metabolites from the chondrocytes. And the vessels in the synovial membrane are very, very close to the surface and the Swedish investigators have also said that they are ranged to skim the formed elements of the blood to provide a very large plasma front plus the fact that the capillaries in the synovial membrane are fenestrated for rapid exchange.

Next set, please. Here you can see the injection of the blood vessels in the synovial membrane. You notice there is none here. And this is a villus and depending upon where there are regional differences of synovial membrane within a joint of its structure and you'll have one area that's like this that has a tremendous number of villi and then you'll have another area where there is nothing and then you'll have another area where there is folds.

Next slide, please. Within a joint -- and this is from articular cartilage from the same joint-- there is differences in proteoglycams and this is related to the biomechanics that this articular

cartilage sees and, for instance, from here to here, this is principally chondroitin sulfate whereas in another area of the joint that isn't utilized you see very little chondroitin sulfate. So the heterogeneity of the proteoglycam within the articular cartilage within a joint.

Next set of slides, please. Now we are also getting into regeneration of articular cartilage and some folks are beginning to have some fairly good results and you have to divide out what is healing and what is regeneration. Healing is where you just get a nidus of hyaline cartilage.

Next slide, please. Regeneration is where you have the usual zonal makeup of the adult articular cartilage. The two have different powers of durability. Next slide, please. And small lesions. This is just in zone one -- this is a lesion made in zone one of adult articular cartilage -- will heal in about 28 days but these do not -- and I emphasize -- if you extend much beyond this zone one, they will not heal. They're what we call vertical fibrillations. We also have initially horizontal or tangential fibrillations that precede these vertical. These were made by a graduate student of mine and then we followed their healing just to see if we could indeed

get healing of very subtle lesions.

Next set, please. Okay. Now in mature articular cartilage we've attempted to show the difference between adult articular cartilage and immature articular cartilage by calling it an articular epiphyseal cartilage complex and it is indeed a complex. It has a portion on the surface that is an articular cartilage anlagen and we have an underlying portion that will undergo endochondral ossification that is epiphyseal cartilage.

Okay. Next slide, please. Here you see the articular cartilage portion. We can stain it differently. If you look at it under a dissecting scope you can see the differences grossly. Unfortunately you can't see the top here but this area here is this area right here, this area right here that you see a little more density of the eosinophilic staining, represents this area right here. So this is the area that is going to become the adult articular cartilage. This area here will undergo endochondral ossification and become the subchondral bone. And if you notice, this does not appear to be too well calcified and that is indeed the truth and if you inject a dye into this secondary center of ossification right here, it will appear in the joint

cavity within five to 10 minutes. So it is not a -- barrier.

Okay. Next slide please. Another difference here. This is from Doctor Ralf Stahlmann in Berlin. And this is stained emulocellular chemistry for fibronectin. You can see that there is a considerable amount of fibronectin staining here in the epiphyseal portion but it doesn't hardly stain at all in the articular portion. So already we are seeing changes.

In the immature articular cartilage there are two zones of germinal chondrocytes and as the animal ages, you want to pay attention here to the -- here's the tidemark and here's the surface. You lose these areas of germinal chondrocytes. Okay.

Next slide, please. Also, this is lipid content in the articular chondrocyte. This is lipid content in the epiphyseal chondrocytes and we have isolated the articular cells and the epiphyseal cells. They have a different generation time in days and a different mitotic rate.

Okay. Next slide, please. So there are not only tangible differences but there are physiological differences as well. If you look at the embryo and this is a developing knee joint in a swine

embryo, this is the joint capsule here. This'll become the synovial membrane and here you can see the articular portion is different than the underlying epiphyseal portion. So even in the embryo there are differences.

Next set of slides, please. This gives you an idea of the vascularity in the epiphyseal cartilage at -- this was, I think, two days of age in a small puppy. But even at that time, you see there's no vessels that penetrate the articular cartilage anlagen. But this entire area here is riddled with cartilage canals and if you're acquainted with John Ogden's work, you also know that this is true in the human as well. At certain areas within these chondral epiphyseals there's endochondral ossification and this is how the secondary centers are developed. And those of you who recall your radiology and your anatomy know that they come in at a very timed period and I think probably these vessels provide the stimulus for the initiation of these on a time basis.

Next slide, please. Let me mention again that here you see the -- now this is the epiphyseal plate cartilage right here and this is epiphyseal cartilage and then there's articular cartilage up on top. Okay. Next set, please. And then once you get

the secondary center of ossification to form and what we're looking at here is from here to here, from here to here, you can see that indeed that there are no more blood vessels. The cartilage canals have been resolved and that this then becomes a very slow, very slow epiphyseal plate. It's about 35 times as slow as this epiphyseal plate here that provides the growth in length.

Okay. Next slide, please. As far as regeneration, you can have regeneration in immature articular cartilage. We created defects and put pieces of the cartilage and turned it upside down so that the articular portion is here and, if you notice, the articular portion is not being invaded by blood vessels. But the rest of the bone has grown around it and this has established articular cartilage again.

Okay. Next slide, please. Now into the quinolone arthropathy, and I'll recall some of the things I've mentioned. What we saw in the humerus, for instance, is the fact that the lesions started usually -- every time we looked at it -- right along this line right here and then secondarily along this synovial line right here. This synovial line right here is the type of synovial membrane that -- has indicated is responsible for the elaboration of

synovial fluid. The type of synovial membrane that you see with the villi is responsible for the absorption of the synovial fluid.

Okay. Next slide, please. Species affected. We've already seen these today. I would add one other thing. Doctor Stahlmann in a telephone conversation last Friday told me that mice are susceptible. So I don't know if it's his data or where it is but he has evidence, so I just threw away our last non-susceptible animal species.

Okay. Next slide, please. Age and site predilection. Here you've got two to three months are controls for all zero to two and we went up to 15 months and we gave 250 milligrams per kilogram per day and we had four out of four, three out of three, and then look at here A, zero to three, zero to three, zero to three. What's happened here is that the joint has matured to the point that the tidemark has been established. The adult articular cartilage has been established. Okay.

Next set of slides, please. Here you see our lesion summary. These are on small beagles, young beagles, T-1 we had 69 percent of the humoral heads and thermal heads affected grossly and we had 75 percent effective histopathologically. At T-2 we had

100 percent effective. So within 48 hours we had 100 percent affected and in the T-5 group here, since these had been so uniform, we allowed the T-5 group to go out for about 35 days before we sanitized them and looked at them histopathologically and by that time we had five distal femora and two distal humeri that were affected, the articular cartilage in those areas were affected by that time.

At no time did we see any change in the staining ability of the epiphyseal plate cartilage. It is my understanding in some chronic experiments that they are seeing some changes in the epiphyseal plate.

Next set of slides, please. We looked at biochemical measurements, we looked at collagen, hexosamines, alkaline phosphatase in all of these, and then we also checked the synovial fluid for sterility to make sure that we were picking up a residual bacterial infection.

Next slide, please. These are the beagles. This is what they looked like when they started. This is what they looked like in three days and by five days they were back on their feet again, the ones that were remaining. And so when Lily called me and told me that this is what happened, I figured that we were at the end of our study but then the

rascals got back up and you could not tell that there was anything clinically wrong with them by clinical examination. Okay. But I'll show you what their articular cartilage looked like when we looked at them histopathologically.

Next set, please. What we found, for instance, in the femoral head, had a very high predilection for the lesion right around the round ligament. The round ligament in the young animal is extremely vascular and, of course, is sheathed in synovial membrane and at the caudal aspect of the joint margin was another area where we had a predilective site for blister formation.

Next slide, please. In the humoral head it was interesting because I mentioned the fact that the blister started here and it started here and then it moved into this area here over a period of two to three days and then it stopped. And we have done an in vivo kinematic study with adult dogs and we have found that the scapula articulates in this area right here and so this is an indication of how far the biomechanics of the articular cartilage is active.

Next slide, please. Here, this is the round ligament. I mentioned the fact that it was quite vascular. Here you see the cleft formation and

this is the articular cartilage anlagen up here and this is what it looks like within about three additional days of treatment and you see that it's almost completely separated from the underlying epiphyseal cartilage. You also see that there is chondronecrosis in about a 65 micrometer rim around the lesion.

Next slide, please. Here you see the area. The cells are still present. They have not produced any more proteoglycam and it is about ready to detach and that's what we found is that the articular cartilage anlagen rolls up like Saran Wrap and you find it in the crevices in the synovial membrane. Now it's interesting to me that there seems to be questions about reversibility on this because there isn't any reversibility. There's no articular cartilage there to reverse.

And this represents the area that's going to undergo endochondral ossification and it calcifies but it has tremendous amount of clusters, chondrocytic clusters, that slows down the calcification and I think then what happens is that this breaks through and we get chronic osteochondric type of lesions. And this comes from another study that we've done just recently.

Next slide, please. So chronic effects. If it holds true, this is a seven year old humoral head from a dog that has an old osteochondritis lesion and you can see how the medullary tissue has proliferated through and then mineralized here and the size of the osteophyte that occurs here.

Next slide, please. So you end up with an old osteochondritis lesion with eburnated bone underneath it and osteoarthritic cartilage around it. Now the question is, how long does it take for this to develop? Who knows? And I'm standing here to tell you it took 40 years for me to develop osteoarthritis in the knee after I'd been in a cast for 16 weeks, then went out and started playing basketball. And I didn't give the chondrocytes a chance to wake up and so I lost my articular cartilage. But it's taken that long to develop.

So that's the story as I see it with the differences between the adult endoarticular cartilage and what effect this had then on the development of the quinolone arthropathy.

CHAIR CRAIG: Thank you very much.

Are there questions for Doctor Van Sickle? Yes, Doctor Abramson.

DOCTOR ABRAMSON: I'm wondering if you can

relate in age to us what age from the development of the human would you be concerned about to use the quinolones in from your data?

DOCTOR VAN SICKLE: I can't make that comparison. I'm sorry.

CHAIR CRAIG: Okay. Doctor Leitman.

DOCTOR LEITMAN: Doctor Van Sickle, I guess what I'm hearing or what I'm not hearing is that you haven't the faintest idea why this happens. That is, what do the quinolones or the flouroquinolones, but I think cinoxicin isn't a flouroquinolone, is it?

DOCTOR VAN SICKLE: No. I think it's a quinolone without the fluoride. So what do the quinolones do to cartilage that they don't do to other cells in the body? Why does this happen?

DOCTOR VAN SICKLE: There are several theories and while the cinoxicin may not be a flouroquinolone, it produces the cleft lesions and everything that's very similar to the flouroquinolone. One is the fact that you don't need the chondrocytes to produce the articular cartilage damage and this has been done by Bendelee and whereby she killed off all the chondrocytes and then looked at the development of the lesion.

Doctor Stahlmann in Berlin is working on

an idea that it may be an effect between the endocrines, the magnesium and the matrix and the quinolone. And that data is just coming out now. But as to the exact mechanism, I think you're right. I don't think we have a handle, as far as I know, on the exact mechanism. If there's anybody else that does, I'd sure like to hear it.

CHAIR CRAIG: Doctor Klein.

DOCTOR KLEIN: Relating your personal experience, I was wondering about the potential for a delayed effect that in fact one might have a patient who had some histologic changes that would not be manifest clinically for many years. Is that a potential?

DOCTOR VAN SICKLE: I think it is a potential.

DOCTOR KLEIN: So the clinical studies that are directed to an immediate period of time after the administration may not be sufficiently sensitive.

DOCTOR VAN SICKLE: I think you're right because we just completed a study where we know that there are osteochondrotic-like lesions and none of these dogs were clinically clean.

CHAIR CRAIG: Doctor Bradley.

DOCTOR BRADLEY: In trying to assess

toxicity with a very sensitive assay, obviously you've got tissue that you can look at in your animal models. There is some human data that were collected by Doctor Urs Schaad using MRI scanning in children and I'm wondering if you can correlate some of your histopathologic findings with MR in the animal model to give us an idea of how sensitive it would be sort of as a follow-up to Doctor Klein's question is the MR something that will be able to predict long-term outcomes, even if there are no clinical symptoms during therapy.

DOCTOR VAN SICKLE: That I don't know. I'll just be perfectly frank. I don't know. But on the slides I've seen from the animals from the chronic study, the repaired articular cartilage that is there is principally fibrocartilage yet it will provide the same joint margin and it has a calcified base and when we stain it with safrain O screen there's no proteoglycans there so it's going to make it an extremely chondromalaistic area and beyond the one year I can't tell you what the results will be.

The other thing that's interesting. You might say well, maybe we can do a synovial membrane biopsy and see if we've got a chronic condition there. I couldn't find anything in the synovial membrane that

I could pin to either.

CHAIR CRAIG: Other questions. Yes, Doctor Leissa.

DOCTOR LEISSA: To the issue that Doctor Bradley, you raised about MRI. I believe there are data that have looked at MRI in animals and have shown that prior to the development of frank arthropathy that you do see development of the fusion in the suprapatellar fossa and that that has been predictive but that has not been seen, I don't believe, in children that have been studied.

The other question I'd like to ask Doctor Van Sickle or anyone else is that in previous advisory committees and in the literature, one issue that has been raised about mechanism is whether or not there's an effect on the mytochondria, whether that's a pathogenesis to this and whether you could comment on that.

DOCTOR VAN SICKLE: Only what I've read and I believe that was mitochondria DNA and I think now there's evidence that that doesn't appear to work out as a possible path to the pathogenesis.

CHAIR CRAIG: Doctor Rodvold.

DOCTOR RODVOLD: Do you have any data or do you have any speculation of in the aspect of

repeating dosing? In other words, you give a dose, come off, get a dose, come off. Because the potential in clinical practice is people get multiple courses of therapy versus just one big long toxicological event of doses. Do you see any differences or is it any more insulting or less insulting to do that?

DOCTOR VAN SICKLE: I don't have any data on that. The other thing that I just happened to think about talking about the MRI and this is a study that was published I think in November of '97 in the -- I don't think of the journal's name. Anyway, it was by a group in Vienna where they looked at the articular cartilage of postmortem specimens of articular cartilage from kids with cystic fibrosis that had been on quinolones for a period of time and they found that there was damage in the chondrocytes. So I think that's important from the standpoint that we're looking at human articular chondrocyte under a therapeutic regime.

CHAIR CRAIG: Doctor Klein.

DOCTOR KLEIN: That is likely to be a very important study, the one that you cited about autopsy data in children with cystic fibrosis, but did they have an adequate number of controls to identify for these children who have an antigen burden?

DOCTOR VAN SICKLE: That I don't know. That's got to be there.

DOCTOR KLEIN: I'm still trouble by the question of a Trojan horse phenomenon. How do we overcome that?

DOCTOR VAN SICKLE: That's a good question. I don't know. I don't have any ready answer for that either. If I had, I wouldn't have the knee I got today.

CHAIR CRAIG: Doctor Lietman.

DOCTOR LEITMAN: But I think that does point out part of the problem, that is you're attributing your knee today to the fact that you played basketball but most of the thousands of people who have osteoarthritis didn't play basketball and still have it and so if you're looking for the contribution of a drug to osteoarthritis 40 years later, I suspect it'll be very difficult to tease out.

DOCTOR VAN SICKLE: That's true. If I had become interested in different research, I probably wouldn't have tied the knee to the problem that I had before because I wouldn't have known the literature but I also think that's one of the things that makes it very difficult for pediatricians and people in medical genetics when there's teratology. And then

you back and you ask the mother can you recall what drugs you were taking nine months ago? I can't remember what I took last week.

CHAIR CRAIG: Let me ask a question. One of the toxicities that's been questionably associated with the flourquoinolone is tendon ruptures. Would that have any similar potential in terms of pathogenesis from the arthropathy?

DOCTOR VAN SICKLE: Well, of course, the tendon is very vascular and has a number of -- cells and so forth that can add to the healing. I'm wondering -- this is just thinking out loud -- I'm wondering if these folks that have the tendon ruptures are in a certain phase of fibrous tissue remodeling. Fibrous tissue remodels just the same way as bone remodels. The bone goes through activation resorption formation and so if you hit this patient with a drug that potentiates the resorption, for instance, then you can possibly excite the rupture easier than if you hit the patient in a reformation phase. We have a certain amount of chondrogenic remodeling but it isn't quite as great as what we have in fibrous tissue and bone.

CHAIR CRAIG: Any other questions from anybody on the committee?

DOCTOR VAN SICKLE: John.

CHAIR CRAIG: We have time for one here in the audience.

DOCTOR BURKHARDT: I'm John Burkhardt, pathologist at Pfizer. This is to address the issue of the long-term effect on cartilage. I think we can agree that sufficient data is not really there to give us a lot of comfort around that issue but the data that is available that comes from the two year studies in rodents, these are particularly compound developed for food and animal or other use. There fails to be an increased incidence of joint lesions, osteoarthritis in these studies. So the point is this is some preliminary data that we could evaluate to monitor for this type of change and we're not seeing it so far.

DOCTOR KLEIN: I think one of the questions that you might be able to address from the animal data is when you do see some of the lesions that have occurred that the animal recovers clinically, is that identified with a subsequent exacerbation? In other words, there may be no clinical signs but they're systologic evidence and then at some point later that there would be evidence of clinical.

DOCTOR BURKHARDT: Right. That's a good question and unfortunately the design of our studies generally don't allow for that kind of determination. We do know, for example, that some animals can avoid the lameness and have microscopic lesions but the kind of temporal characteristics you're talking about, I'm not aware of anyone addressing that in particular.

CHAIR CRAIG: Okay. It's time on the schedule for a break and we'll restart again in 15 minutes.

(Off the record at 10:34 a.m. for a 22 minute break.)

CHAIR CRAIG: Our next speaker will be speaking on flouroquinolone use in pediatrics, epidemiology review of the FDA AERS and drug use data, and it will be presented by Carolyn McCloskey. Could I have silence, please.

DOCTOR McCLOSKEY: Thank you. Sorry to interrupt your break, but maybe we can move on and keep an advisory committee meeting on schedule.

Good morning. I'm Carolyn McCloskey from Epidemiology Branch and today I'm going to present first the drug use data, then the adverse report information on the flouroquinolones. The adverse event report information will include the U.S. FDA

adverse event reporting system or the AERS or MedWatch, as some of you might know it, data and the World Health Organization or WHO adverse event data.

As Brad told us this morning, the quinolones have been available since the 1960s in the form of nalidixic acid but the flouroquinolones first became available in 1986 with norfloxacin followed a year later by ciprofloxacin in 1987. The rest of the current U.S. flouroquinolones are ofloxacin approved in 1990, lomefloxacin approved in 1992 and levofloxacine and sparfloxacin both approved in 1996.

Next slide. The following flouroquinolone drug use data is from the National Prescription Audit Plus or what I'll call the NPA or NPA Plus computerized records of IMS America. Since 1992, NPA Plus collects data from 20,000 computerized retail pharmacies and 600 manual data pharmacies in the U.S. These are independent chain and food store pharmacies. The estimated total dispensed prescriptions including refills for oral flouroquinolones has tended to increase with ciprofloxacin and ofloxacin form 1992 to 1996, tended to fluctuate a little bit for enoxacin and decrease at least in the several years for norfloxacin and lomefloxacin.

Next slide. For those of you who have a

handout, just look at the bottom slide first on this page. I flipped the slide. This demographic data for the flouroquinolone drug use is from the National Disease and Therapeutic index or NDTI also of IMS America. This information is based on patient and treatment data collected from 980 randomly selected office-based physicians each month which includes new and refill prescribed or office-dispensed flouroquinolones.

This slide shows the drug use for ciprofloxacin from 1992 to 1996 and you can see that ciprofloxacin is being given throughout the childhood years and even to very young children although the numbers are very small. Now these are in thousands.

Next slide. The next slide shows the 1996 drug use information for the various oral flouroquinolones with ciprofloxacin being the predominant flouroquinolone prescribed for children. This is only 1996 data. These drug use numbers are so small for the pediatric age group that it is hard to definitely make a statement about their fluctuations from year to year. In reviewing the prior years of drug use data, only norfloxacin has a notable difference in gender use data with the female use more than twice the use in males.

Ciprofloxacin is the only flouroquinolone with reported drug use in the zero to one year old range. The most common indication for this age range zero to one years is a respiratory problem. This is from the NDTI data. With the exception of lomefloxacin, the most common indication for the older age range flouroquinolones is urinary tract infection. Lomefloxacin was prescribed for sinusitis and bronchitis in the preschool patients followed by lymphadenitis or tonsillitis in the school age patients and then urinary tract infections in adults. And this data was based on data prior to 1996 when they had lomefloxacin use in those age ranges.

Next slide. There are several limitations of voluntarily reported data and of the AERS system. These should be identified clearly before interpreting this data. Due to voluntary reporting of cases, there is no consistent quality of data. There may be duplicate reports and under-reporting of a particular adverse event. One case may have more than one COSTART term which is just a single term that's computerized to describe the event but one case can have up to four COSTART terms and, therefore, that case may be counted under more than one COSTART term when you search the system.

The drug use data presented as total prescriptions from MPA data is our best estimate of the number of persons exposed to the drug or who use the drug, but these are only estimates of the denominator. These COSTART counts and the AERS data and the drug use data can be used to calculate a reporting rate but incidence rates and estimates of drug risk can not be assessed based on this data alone due to duplicate reporting and under-reporting.

Next slide. It is not recommended to make comparisons of the numbers of reports between different drugs because of a number of factors: the length of time a drug is on the market, the type of drug use it has, the population in which it is being used, and the advertising. These factors affect the type of reports, the number of reports and the periodicity of reporting. Therefore, it is not recommended to compare reporting rates, the number of reports per year or other types of comparison. Once again, because voluntary reports do not reflect the actual numbers of an outcome, it is impossible to determine incidence rates.

Next slide. The U.S. FDA Adverse Event Reporting System, called AERS, contains reports that are voluntarily submitted from U.S. and from foreign

cases. Under-reporting of adverse drug events is well known and duplicate reporting of cases is not unusual. This slide lists the total number of reports for each flouroquinolone determined by a computerized count of the U.S. reports in the system and also the number of pediatric cases 18 years and younger. These are reports where the suspect drug for the adverse event was a flouroquinolone. I reviewed the pediatric cases so there are no duplicate reports in these numbers. However, these counts on this slide reflect all U.S. pediatric cases without regard to the route of administration.

There were no deaths reported in U.S. pediatric zero to 18 year old cases where a flouroquinolone was reported as the suspect drug. However, there are eight deaths in the whole cohort of suspect and concomitant flouroquinolone drug reports in the system. Five of these deaths reported ciprofloxacin as a concomitant drug and not the suspect drug. These five were U.S. cases with ages ranging from seven months to six years. The remaining three deaths were all foreign, all 18 year old patients with either ofloxacin or norfloxacin reported as the suspect drug.

For the five concomitant ciprofloxacin

cases the underlying medical conditions and reported adverse drug events were: 1) an unknown condition requiring hospitalization the child's entire seven months of her life in 1990. The adverse event was hemolytic anemia with procainamide as the suspect drug.

The second underlying condition was an unknown autoimmune deficiency in a 15 month old with low CD4+ T cells and a low absolute neutrophil count with subsequent disseminated Mycobacterium avium complex followed by Candida sepsis prior to her death in 1994. The adverse event was respiratory failure in the setting of profound neutropenia with Actimmune Interferon gama-1b as the suspect drug.

Third, an ependymoma in a two year old receiving chemotherapy in preparation for a bone marrow transplant developed liver and renal failure in 1993 with carboplatin as the suspect drug. The fourth underlying condition was a myelodyblastic syndrome in a two year old boy who was status post bone marrow transplant the year before his death in 1993. Cariogenic shock and renal failure were the adverse events with Biaxin as the suspect drug although a doctor notes in that report that the events were not related to Biaxin.

And the last underlying condition for these concomitant ciprofloxacin reports is the HIV positive status in a six year old with MAI and a Broviac for total parenteral nutrition who had a heart arrest and died in 1992 with DDI listed as the suspect drug.

The three foreign death reports are briefly an 18 year old female status posed hip fracture, meningitis secondary to spinal anesthesia with resulting hydrocephalus. Also status post respiratory failure and cardiac arrest following a ventricular peritoneal valve replacement. She was put on ofloxacin for a nosocomial pseudomonas pneumonia due to mechanical ventilation and steroids. Her cerebral death was attributed to an anoxic lesion.

The second case was an 18 year old male from India put on ofloxacin for a fever later confirmed to be typhoid who developed petechial hemorrhages which led to hemorrhagic bullikea and he died of respiratory failure after five days of ofloxacin. A third foreign death was an 18 year old female with a history of seizures who was admitted in ocularg yroc crisis with leg weakness. Norfloxacin was given for a urinary tract infection on the third hospital day but she went into status epilepticus

again, required intubation and eventually had heart failure, renal failure, and died.

So these deaths are the only reason I mention reports from the FDA AERS which are foreign or where the flouroquinolone is a concomitant drug. Otherwise, the data I present from now on from AERS today are only the U.S. reports where the flouroquinolone is the suspect drug.

Next slide. When only oral cases are considered, we've excluded the IV, the in utero exposure, the ophthalmic and the breast milk administration cases, there are 139 U.S. pediatric flouroquinolone cases in AERS with 54 percent reporting ciprofloxacin as the suspect drug. The other flouroquinolones with adverse event reports in AERS in the zero to 18 range are ofloxacin, norfloxacin and lomefloxacin. The asterisks down there at the bottom indicate an extra count for ofloxacin or lomefloxacin because one case received both of those flouroquinolones so the total is one count short of the actual addition.

Next slide. This slide shows the age and gender breakdown, at least where known, of each of the flouroquinolone cases. Adverse events are reported in both sexes although norfloxacin has a several fold

increase in the number of female reports compared with the number of male reports. Adverse events are reported in all the age groups and the number of reports for each group increases with the increasing age even though there are fewer years per age group as the age groups are sorted towards the older years.

The two children in the zero to one age group are both one year old, non-serious cases involving a boy on ciprofloxacin with a photosensitivity rash on his arms and a girl on ofloxacin for Lyme disease prophylaxis who developing vomiting and diarrhea.

There are seven other U.S. suspect flouroquinolone reports in the zero to one years in AERS which are not shown on this slide. Four are in utero flouroquinolone exposures reporting a clef lip, fractures ribs at birth, small for gestational age, and the fourth one was gallstones diagnosed at 10 months. The other three infant or zero to one year old reports are two reports of ophthalmic administration reporting conjunctivitis in a one year and blurry eyes in a one month old. The last is an exposure through breast milk reporting a generalized rash in a two month old.

Next slide. There are 14 reports of

arthropathy or arthralgia in the pediatric zero to 18 year old flouroquinolone reports. One report of a 14 year old girl had both ofloxacin and lomefloxacin as the suspect drug so there is an extra count because of the two flouroquinolones on this one report. This particular report indicates that a pediatric orthopedic surgeon diagnosed femoral anteversion as the cause for the girl's arthralgia, therefore you see it listed twice, and not the flouroquinolones. Most of the reports indicated that either an involved knee or elbow with or without other joints was involved. This comments column over here is just to give a little additional information about the adverse event such as dizziness was associated with two of the ciprofloxacin arthralgias.

The eight ciprofloxacin reports ranged in age from 10 to 18 years with a median of 16 years. The indications for the ciprofloxacin reports included two Pseudomonas infections, one in a cystic fibrosis patient and the other report simply reported Pseudomonas urinary tract infection in a 10 year old female. The other ciprofloxacin indications were a cellulitis of the toe, a sinus infection, a sore throat and an upper respiratory tract infection.

The ofloxacin arthralgia patients were 13

to 18 years old and the indications were only stated as pneumonia on one report. The two norfloxacin reports were both 18 year old females reporting arthralgias. One of these norfloxacin patients had a concomitant fever and had a prolonged hospitalization for a urinary tract infection in adverse event.

One interesting case which is not included on this slide for arthralgias was a 15 year old boy who received ofloxacin IV for an emergency appendectomy and had not grown more than his 70 inches in height over the last year. The 15th percentile for height for a 15 year old boy however is 66.5 inches and the expected growth rate is about two inches per year.

Next slide. Out of all the adverse events reported in the U.S. pediatric cases where a flouroquinolone was the suspect drug, those reporting rash or an allergy were the most frequent. I've already discussed the arthropathies on the previous slide. Of the CNS reports, the 14 CNS involvement reports, seven involved ciprofloxacin, six ofloxacin and one involved norfloxacin. Three of the ciprofloxacin patients age 14 to 16 years had a history of seizure disorder and their indication for urinary tract infection with epididymitis, septic hip

and bronchitis.

Three patients, two on cipro and one on ofloxacin, received their flouroquinolone for Pseudomonas infection on top of one of the following medical conditions: hepatocellular carcinoma, congenital myopathy with a tracheostomy, and cystic fibrosis. One patient on ofloxacin for otitis media had Hurler's syndrome with quadriparesis and another on ofloxacin for an unknown indication had cystic fibrosis with a seizure disorder and a previous exposure to quinolones. Three patients had their seizure after the first dose of flouroquinolone, one on ciprofloxacin and the other two on ofloxacin, one of which had received ofloxacin several months earlier.

The 15 hypersensitivity cases included 10 ciprofloxacin, four ofloxacin, and one norfloxacin reports ranging in age from 11 to 18 years. There are six anaphylaxis cases and four were on ciprofloxacin and hospitalized. The other two were on ofloxacin and not hospitalized. There were six angioedema cases and of those six, four were on ciprofloxacin and one each on ofloxacin and norfloxacin. None of them were hospitalized although three were reported as treated. The remaining three hypersensitivity cases were one

each of Stevens-Johnson syndrome on ofloxacin, serum sickness on ciprofloxacin and anti-platelet antibodies to all antibiotics on ciprofloxacin. All six of the anaphylaxis cases occurred after the first dose of either ciprofloxacin or ofloxacin and three of the angioedema cases occurred after the first dose of ciprofloxacin.

The 15 psychiatric reports are a loose grouping of reports which include events ranging from euphoria to psychosis. The ages range from five to 18 years with the median at 15 years. There were two suicide attempts, one on ofloxacin and the other on norfloxacin, three reports of hallucination, one each on ciprofloxacin, ofloxacin and norfloxacin, and one report of aggressive behavior with confusion in a patient who had a psychiatric history and was on norfloxacin. The seven cases of photosensitivity were reported with lomefloxacin with one case on ciprofloxacin and two cases on ofloxacin.

Next slide. This one year old down here with photosensitivity is the case I mentioned earlier with the rash on the arm. The two youngest CNS cases were the three and five year olds with congenital myopathy and Hurler's syndrome respectively and the five year old with Hurler's syndrome was also coded as

a psychiatric case because of his irritability, insomnia and agitation.

Next slide. The WHO adverse event data is simply a computerized line listing of reports in their system. The U.S. data was excluded from these WHO slides since I just presented them from the AERS where I could review the hard copy reports although I will mention that there were 152 U.S. cases aged zero to 18 years in the U.S. AERS system suspect flouroquinolones in the WHO line listing. The country with the most pediatric reports in the WHO foreign reports is the United Kingdom with 177 reports followed by Germany with 72 and France with 71. The rest of the countries had 20 or fewer reports.

Next slide. As with our U.S. reports, ciprofloxacin is the most commonly reported drug. This slide only shows those drugs marketed in the U.S. The other nine U.S. drugs had much fewer reports than these U.S.-marketed flouroquinolones.

Next slide. And this is similar to the other slide with the U.S. data. As you can see, the number of reports are similar for each flouroquinolone for gender although again norfloxacin tends to have almost twice the number of female reports and, as in the AERS data, the number of reports increased with

the increasing age group.

Next slide. The rash or allergy grouping has the most foreign WHO reports as it did in the U.S. data. And there are about 20 ciprofloxacin reports for each of the adverse event groupings of CNS involvement, anaphylaxis and photosensitivity, hypersensitivity and photosensitivity. There were 28 foreign ciprofloxacin arthropathy reports and ofloxacin is most common for the most reports but it tends to have proportionally fewer arthropathy reports and more psychiatric reports.

Next slide. The youngest group, zero to one year old, had more rash or allergy foreign WHO reports than for any other adverse event grouping. All of the adverse event groupings had more reports with increasing age.

So if we wanted to roughly calculate a reporting rate, which I've already said we probably shouldn't do, just for fun I went ahead and calculated the reporting rate for ciprofloxacin and ofloxacin arthropathies. This is not on some of your slides because I only presented the 1996 data for ofloxacin, but ciprofloxacin had eight arthralgia cases with three occurring in 1988 and three in 1992. Don't have the drug use data for 1988 so I used the 1992 data and

in order to determine the pediatric proportion of the prescription -- that's the NPA data from the first slide -- I calculated using the NDPI data where we have the age groups that about 1.5 percent of the office-prescribed flouroquinolones or ciprofloxacin were in our pediatric age range. This is the whole zero to 18 age range. Then applied it to the 1992 NPA data of about nine million prescriptions and the end result is about 136,000 prescriptions were filled in 1992 for ciprofloxacin in children between zero and 18 years of age.

The three reports of arthropathy in 1992 would give a reporting rate of about two cases of ciprofloxacin associated arthropathy in 100,000 filled pediatric prescriptions. Similarly, the ofloxacin pediatric proportion in 1992 was 3.6 percent and there were about three million ofloxacin filled prescriptions which gives about 115,000 filled ofloxacin prescriptions in the zero to 18 year olds in 1992. There were two reports of arthropathy associated with ofloxacin in 1992 so the reporting rate is about two cases of ofloxacin-associated arthropathy per 100,000 filled prescriptions.

Please remember that the limitations of voluntary reporting AERS database, there's under-

reporting of the events and most of the reports contain scanty information and the quality is inconsistent. The factors influencing reporting are how old the drug is, the type of drug use it has experienced, the type of population using the drug and the drug advertising. The numbers of reports and estimates of drug use are so small that calculating a reporting rate is only a rough estimate with wide confidence limits and that rate is certainly not a valid incidence rate.

In addition, the fluctuation in numbers of reports per year make it difficult to say anything about a drug's adverse event with any kind of certainty plus the drug use data or denominator data may fluctuate from year to year.

So in conclusion, we can not determine incidence rates for these events and these reports should not be used as a predictor of events, especially if there are different drug use circumstances. However, the numbers of defense pediatric prescriptions of ofloxacin, although low, are increasing, thus increasing the probability of more reports of serious adverse events.

However, the U.S. pediatric flouroquinolone adverse event reports did not have any

deaths and most of the hospitalizations were for the anaphylaxis cases. The arthropathy, CNS involvement, and the psychiatric cases either had scanty information or were confounded by the underlying disease or the other drugs that were given such that there was not a clear association with the flouroquinolones.

The hypersensitivity and photosensitivity cases are probably related to the drug, especially for the hypersensitivity adverse events which followed a single dose of flouroquinolone. The bottom line is that these issues raise a signal of a possible association with a flouroquinolone and warrant further investigation.

CHAIR CRAIG: Thank you very much, Carolyn.

Are there questions? We have time for a few. Doctor Leitman.

DOCTOR LEITMAN: Two questions. One, an association and causality are obviously different.

DOCTOR McCLOSKEY: You're right.

DOCTOR LEITMAN: what you may be showing, at least what you need to rule out is that these are arthropathies where because the child had a disease that was thought to be bacterial but maybe it was

viral and maybe it caused an arthropathy of some sort that was independent of the drug. Is it possible to chase back? Do you have the ability to look at those cases, the eight cases with ciprofloxacin, for example? Can you go back and find out who they were somehow and ask that question. And the second thing you might be able to do is then ask well, was this completely reversible or was it sometimes irreversible or did they have trouble later, five years later maybe?

DOCTOR McCLOSKEY: You bring up a very good point. I reviewed the hard copy reports which basically had arthralgias of left knee or something like that. Most of them do have the reporter's information and if they can remember, I can sometimes get follow-up, so I can work on that. But for the most part with the old reports, it's difficult to get physicians to either remember or follow up with it. But you're absolutely right. The reports did not indicate underlying disease. If they gave any kind of information, it was usually the Pseudomonas type of infection other than urinary tract, upper respiratory tract, whatever. So the information wasn't really in depth.

CHAIR CRAIG: Do you find reports of

arthropathies or did you receive reports of arthropathies with other classes of antibiotics?

DOCTOR McCLOSKEY: I did not look into it but I am sure they're there.

CHAIR CRAIG: Doctor Klein.

DOCTOR KLEIN: I think this is the only formal presentation on the adverse event database. Is that correct?

CHAIR CRAIG: As far as I understand.

DOCTOR KLEIN: I wonder if there are other ways that the problem can be approached and I was trying to think about looking at HMO data, Blue Cross-Blue Shield databases or even databases that would include unexpected arthropathies or tendon ruptures in a case controlled fashion or something that would give us a little more handle on whether it's a problem or not. By about the fourth slide, it suggests that 175,000 children have received an oral flouroquinolone and even among that group I wonder if there isn't a way of approaching the problem instead of the passive adverse event reporting system. It looks like there's a lot of ways to skin this cat and that we should be looking at a the huge databases.

I had lunch with the director of the Medicaid program in Massachusetts and she can identify

prescription and diagnosis in 180,000 children under 18 years of age. So I'm sure states that have similar databases that we ought to be able to look at across prescription, adverse events, diagnoses, unexpected occurrences in rheumatologists' databases, all the orthopedist databases. But we should be thinking about how we can develop new strategies for looking at the problem.

CHAIR CRAIG: Appreciate that. Doctor Dowell.

DOCTOR DOWELL: Thanks. I just wanted to agree. I think having a look at databases like that for arthropathies reported with other antimicrobials would be very interesting. I would hesitate a little bit or at least bring in the caveat that I would suspect that quinolone-associated arthropathies would be preferentially reported. They would be more likely to be reported than arthropathies that happen after other antimicrobials and so there would have to be built in some sort of active look at arthropathies after these.

I guess the other question that comes to mind is thinking back about the animal data again. We have at least an order of magnitude of reporting two cases of arthropathy per 100,000 kids who got

flouroquinolones. How many of those beagles would have been lying down, clinically obvious arthropathies after flouroquinolone dosing at levels that were seen in kids? One hundred percent?

CHAIR CRAIG: Doctor Leitman.

DOCTOR LEITMAN: I don't think you answered my second question. Do you have the legal ability to identify those eight people who were reported to you as having arthropathy and chasing them down or not ?

DOCTOR McCLOSKEY: If it's on the report, I have that. Yes, sir.

DOCTOR LEITMAN: You do, so you could actually contact the doctor and find out a follow-up.

DOCTOR McCLOSKEY: Yes, sir.

CHAIR CRAIG: Doctor Leissa.

DOCTOR LEISSA: One of the more perplexing issues is always trying to understand and relate the tendon rupture issue that we accept appears to happen in adults and then arthropathy. In your reports, Doctor McCloskey, do you have any information about tendon rupture, whether it occurred in pediatric populations?

DOCTOR McCLOSKEY: There were no reports of tendon rupture or tendon disease in anybody in any

reports in the flouroquinolones listed as suspect under 20 years of age. So all of the suspect flouroquinolone costarted as tendon rupture or tendon disease were 20 years old and older.

CHAIR CRAIG: How many total do you have?

DOCTOR McCLOSKEY: Is there an overhead? Let me just read this off. I have ciprofloxacin tendon rupture 24 reports aged 20 to 86, tendon disease 37 for cipro. Ofloxacin, tendon rupture 13, tendon disease 18 and then it goes down from there. Levofloxacin four and four, norfloxacin one tendon disease and enoxacin --

CHAIR CRAIG: A total somewhere close to 50 then maybe of tendon rupture.

DOCTOR McCLOSKEY: Right.

CHAIR CRAIG: Okay. Any other questions? Okay. Thank you very much. We'll move on to our series of presentations by people from the industry. First one is going to be by Deborah Church who's the Director of Medical Research at Bayer Corporation and it's entitled Pediatric Indications for Quinolones, the Ciprofloxacin Experience.

DOCTOR CHURCH: Can I ask if everybody can hear me just to make sure. Okay. My name is Deborah Church and I'm a Deputy Director at Bayer Corporation

and I actually have been personally involved in the research of the treatment of pediatric patients with ciprofloxacin since I joined the company six years ago. I'd like to review with you today our experience with ciprofloxacin and pediatric medicine.

May I have the next slide. I'd like to share with you today a historical perspective as well as describe with you just very briefly because you've already heard this the animal toxicology and discuss with you the selection of appropriate pediatric indications for development. I'd also like to share with you our clinical experience in pediatrics and finally end with a summary and conclusion.

Even less than 10 years ago when developing an uncomplicated gonorrhea study with a single dose of ciprofloxacin given at 250 milligrams, 16 and 17 year old women were actually excluded. Over the years, Bayer has been approached by medical communities both in the United States as well as abroad from CF centers as well as cancer institutes to look at the use of ciprofloxacin in pediatrics. It was reassuring to know prior to doing any of these clinical trials that actually Bayer internationally before and after the approval of ciprofloxacin had developed a compassionate use database of over 2,000

courses of ciprofloxacin in pediatric patients. They were from neonates to adolescents and, to the best of our knowledge, there has been no joint toxicity that's been discovered.

Based on the previous recommendations that you've heard by previous advisory committee meetings, Bayer had initiated prospective clinical trials in pediatric patients from the ages of five to 17. These were done in three indications. The empiric therapy for febrile neutropenia, acute pulmonary exacerbations for cystic fibrosis patients, and prophylaxis for bone marrow transplant patients, patients who actually developed neutropenia secondary to their chemotherapy.

What is it then that distinguishes the quinolones from any other antibiotics? Well, one of the distinguishing features is actually the concern secondary to the development of quinolone induced articular lesions. As we heard today, this is very species specific. It evolves within days. It is both dose and treatment duration dependent. It is associated with a joint affusion which is noninflammatory in nature with pain and lameness. All marketed quinolones exhibited these arthropathic effects but the variability has been seen among quinolones such as the effects of nalidixic acid when

compared with ciprofloxacin.

Despite the extensive efforts to investigate the efforts of quinolone on cartilage, there is still no definite explanation for the age-related differences in susceptibility to quinolone chondotoxicity. It is reassuring to know that nalidixic acid which has been approved in children from three months and older and has actually been on the market for over 30 years has not been associated with the type of articular lesions seen in juvenile animals.

Throughout the years, a large amount of data has been recovered regarding the efficacy and safety of ciprofloxacin in pediatric patients that have been treated for serious illnesses as well as multi-drug resistance. It is from this clinical data that it appears that humans are less sensitive to developing quinolone induced arthropathy than experimental juvenile animals.

Early justification for utilizing a quinolone in some pediatric infections has actually been the compassionate decision in the eye of an uncontrolled infection, life threatening infections, multi-drug resistant infections and even at times when there's a lack of an IV access and/or improvement of

quality of life actually becomes an issue.

Physicians who requested ciprofloxacin on compassionate use basis for patients less than 18 years of age were asked to document, among other parameters, the safety of the drug with special emphasis on joint evaluation. The compassionate use program consisted of 2,030 courses of ciprofloxacin. This correlates to 1,795 patients. The majority of these patients, actually over 60 percent of these patients, were cystic fibrosis patients. The majority of these patients also had a single course of ciprofloxacin that was given in oral formulation. The median age of these patients was 15 and less than five years of age we had three percent of the patients in the pool.

With regards to the median dose and milligrams per kilo per day, in the IV formulation that was eight. In patients who received oral therapy it was 25. With regards to the mean duration, in the IV portion it was seven days with patients being treated up to 72 days. For those patients that were given oral therapy, they were treated anywhere from one to 303 days with a median duration of 14 days.

Compassionate use database shows that 1.5 percent of these patients actually had arthralgia.

The majority of these patients had cystic fibrosis as an underlying disease. The median dose given to these patients was anywhere from 1,000 milligrams to 1,500 milligrams per day. The median duration of these patients was actually 23 days. It's important to recall thought that arthralgias, whether they're occurring episodically or sometimes even associated with a pulmonary exacerbation, can occur in up to eight percent of cystic fibrosis patients irrespective of the antimicrobial therapy given to these patients.

The next question is how should one approach the selection of pediatric indications for quinolone development. First, you need a clinical safety database which is well documented in adult populations. Then you can go on to initiate pediatric studies in patients with the greatest medical need. The specific indications that were considered for ciprofloxacin development include the following. Cystic fibrosis, diarrheal diseases including drug resistant shigellosis, febrile neutropenia, grand negative osteomyelitis, and complicated urinary tract infections.

In our efforts to perform these controlled trials to answer the safety questions regarding quinolones in pediatric patients, we actually faced a

number of inherent difficulties. As you all know, the pediatric populations with cystic fibrosis and cancer are quite limited, not only in their absolute numbers but also in their availability to participate in clinical trials. We also found that there was little inducement for enrollment from these patients because ciprofloxacin was already readily prescribed by their own cystic fibrosis physicians as well as oncologists.

Despite these limitations, our largest study with ciprofloxacin in children was actually in cystic fibrosis where ciprofloxacin was given IV to oral with anti-pseudomonal activity for their acute pulmonary exacerbations. The Bayer experience has included two comparative clinical trials that were conducted from 1991 to 1995 in cystic fibrosis, one conducted in the United States and the other in South Africa, Europe and Israel in patients all ages from five to 17. I also want to remind you that these two trials were actually the largest antibiotic prospective clinical trials done in cystic fibrosis during this time frame.

What I'd like to do now is discuss with you these two prospective trials and start out with the first one that was actually performed in the United States. It's a double blinded comparative

multi-center trial. It looked at ciprofloxacin initially intravenously at 10 milligrams per kilo given three times a day and on day seven the patients were given oral therapy at 20 milligrams twice a day. This was versus a combination parenteral therapy of a third generation cephalosporin and aminoglycoside that was administered three times a day. The treatment duration was 10 to 21 days.

Out of 130 patients that were enrolled in this trial, 67 of these patients were given ciprofloxacin. The safety monitoring regarding the joint function was performed by clinical joint assessments that were done by treatment blinded examiners. The review of this trial on an ongoing basis, the results were looked at by an independent blinded safety committee which included among its members a rheumatologist which was actually a pediatric rheumatologist and a physical therapist.

With regards to the results overall, the safety and tolerability of ciprofloxacin were comparable to the control drug. And with regards to muscular-skeletal events, 21 percent of the patients had an event in ciprofloxacin versus 22 percent in the control arm. But you have to keep in mind when reviewing these results that the focus of the trial

was the monitoring of the joint finding by extensive serial clinical evaluations and that actually cystic fibrosis patients themselves have significant background prevalence for arthralgias as well as arthritis.

The second trial which was performed in Europe, South Africa and Israel was actually an open trial that was multi-centered that looked at ciprofloxacin orally at 15 milligrams PQO twice a day and that was versus the same control that we used in the United States which was the combination of third generation cephalosporin aminoglycoside. The treatment duration for this program was 14 days.

Out of 108 patients that were enrolled in this study, 55 were randomized to the ciprofloxacin arm. Once again, just like in the U.S. trial, the clinical joint assessments were done by a treatment blinded examiner. In addition though, every patient had a knee and hip ultrasound. In selected centers where MRIs could be done, MR imaging was done and actually 29 of the patients had this performed. Overall, once again, the safety and tolerability of ciprofloxacin was comparable to the control arm and the muscular-skeletal events were similar at seven percent in the ciprofloxacin arm versus 11 percent in

our control. Ultrasounds and MRIs did not show any joint pathology.

One could summarize then that the incidents of arthropathy in ciprofloxacin-treated pediatric patients from randomized clinical trials was similar to patients who received control drugs.

And what I've tried to do on this slide is summarize for you the number of ciprofloxacin-treated patients in completed pediatric studies. I just told you about 122 patients and I've added another 28 patients that came from smaller cystic fibrosis trials including even a pharmacokinetic trial to give us a total of 250 patients. There were 25 cipro-treated patients in our neutropenia program, 263 patients from diarrheal diseases and in order to make this complete, I've actually added the meningococcal carriage which was actually a prophylactic study that used a single dose of ciprofloxacin.

If we add those numbers, there are a total of 1,007 patients treated with ciprofloxacin in prospective clinical trials. If we add upon that our compassionate use data which is 1,795 patients, that would give us a total of 2,802 patients.

Expensive clinical experience with ciprofloxacin has defined a safety profile in adults

and children. We performed over 800 clinical trials. Within those trials, over 150,000 patients have been adults, 1,174 patients are pediatric. I've also told you about the compassionate use program which has 1,795 pediatric patients. With respect to the worldwide marketing experience, there's been 156.5 million adult treatment courses given worldwide. One hundred fifty million of those treatment courses have been in North America. There have been 4.3 million pediatric treatment courses worldwide and, of those, 1.5 have been in North America.

These data provide a wealth of clinical information upon which to base decisions regarding ciprofloxacin. Although I have focused mostly today on the muscular-skeletal system, based on this experience the probability profiles to ciprofloxacin in children does not seem to be significantly different from that seen in adults. Based on this global experience, ciprofloxacin can be used safely in children with infectious diseases where there is a clinical need.

In addition, quinolones are a heterogeneous class of drugs. The quinolones vary in pre-clinical to clinical characteristics including arthropathic potential, type and incidence of

toxicities, drug to drug interactions, and adverse events. We've heard today that articular lesions in animals do not correlate well with the clinical experience as an example of nalidixic acid. We have also shared with you today over a decade of clinical experience with ciprofloxacin.

Bayer has attempted in a meaningful stepwise approach to assess the risk versus benefit to pediatric patients by evaluating data worldwide from compassionate use to prospective clinical trials to 10 years of marketing experience. This experience should not be extrapolated to any other quinolone. We believe that the risk assessment should be quinolone specific when making clinical decisions considering the treatment of pediatric patients with a difficult to treat infection.

Thank you.

CHAIR CRAIG: We have time for questions specific. Doctor Norden.

DOCTOR NORDEN: Thank you. That was a very clear presentation.

DOCTOR CHURCH: Thank you.

DOCTOR NORDEN: I'm concerned though about your conclusion.

(Laughter)

DOCTOR NORDEN: I think that you have -- if I quickly calculated, of your compassionate use patients, three percent which is about 50 are under the age of five and I don't think that's an adequate safety base at all to make the conclusion you have. You may be correct and it might be fine but I'd be very concerned about going from the 97 percent who are above the age of five and extrapolating that down since we know the experimental data is clearly age related.

DOCTOR CHURCH: You're right. The majority of patients, as I said, was 15 years of age but as you also know probably that neonates or patients even under the age of five it's quite hard to give them oral therapy through the tablet and that probably was part of the consideration of what you see within the pool.

DOCTOR NORDEN: No. I'm not questioning why you didn't have the patients. I understand that. But I just think you can't make a conclusion if you don't have the basis to do it.

CHAIR CRAIG: Doctor Abramson.

DOCTOR ABRAMSON: I wanted to extend that comment and ask you your opinion about the use of it for otitis media since that is a disease that mainly

occurs in children less than equal to two years of age.

DOCTOR CHURCH: I'm sorry. I couldn't hear the question.

DOCTOR ABRAMSON: Otitis media is a disease that occurs and one of the things we're going to discuss today is the use of quinolones in otitis media. That's a disease that occurs mainly in children less than two years of age.

CHAIR CRAIG: Could I save that question for later on because I think in order to keep on time I'd like questions specifically now on the data that was presented and we'll bring those questions up later. Any other questions specifically on the data presented? Yes.

MR. ALEXANDER: My name is John Alexander. I'm one of the medical officers at the FDA.

DOCTOR CHURCH: How are you?

MR. ALEXANDER: Hi. I just wanted to make a clarification. You said in your international trial that they had ultrasounds and MRIs done and you said that there was no evidence of any toxicity at all.

DOCTOR CHURCH: There's no evidence in joint abnormality. Joints.

MR. ALEXANDER: Joint.

DOCTOR CHURCH: Joint pathology.

CHAIR CRAIG: Yes. Doctor Azimi.

DOCTOR AZIMI: On the indication for meningococcal prophylaxis, the ages were? How old were they? That's just a single dose.

DOCTOR CHURCH: That is a single dose.

DOCTOR AZIMI: That's not in children though, is it?

DOCTOR CHURCH: It included children. Yes.

DOCTOR AZIMI: Included children.

DOCTOR CHURCH: Yes.

DOCTOR AZIMI: Is it appropriate to include those in your database when you're looking for side effects when you're using only one dose?

DOCTOR CHURCH: As I stated, I wanted to put that in for completeness but I certainly understand that that's a single dose. All other therapies that I showed you were longer than one dose, of course.

CHAIR CRAIG: Thank you, Doctor Church.

DOCTOR CHURCH: Thank you.

CHAIR CRAIG: Our next speaker will be Scott Hopkins, Doctor Hopkins from Pfizer, a Group Director in Clinical Development, and he's going to

talk about duration of follow-up in clinical trials.

DOCTOR HOPKINS: My title got I guess a little mangled or maybe it was exchanged with Roger Echols' title in the communications, but the theme of my remarks is basically shown here in the title of my first slide. Where do we want to be in five years in the next millennium with our understanding of how to use or whether to use quinolones in various pediatric indications and, as a corollary to this question, we might also ask do we want to be at another advisory committee in five years asking the same questions that we're asking now and which we asked five years, four years ago and eight years ago? And I would submit that we don't.

Now from Pfizer's standpoint and my standpoint, where would we like to be in a few years? I think we all agree we would like to have better information on the toleration and adverse event profile and particularly focusing on the joint tolerability profile of quinolones. We'd like to have a better picture of the appropriate role for quinolones in pediatric practice based upon the tolerability profile and the prevailing resistance and use practices.

We would like an environment that

encourages increased appropriate clinical trial work rather than an environment which is at the least neutral or discourages investigation in clinical trials and we think as part of that approval for relevant indications where there is a clear medical need and the appropriate data exists will be beneficial, not only for patients but for the clinical research environment.

Quinolones, even if they were to be given broad approval in pediatric use, are unlikely, in our view, to make major inroads in the pediatric antibiotic practice. The most common pediatric infectious diseases right now are currently very well served, I think we all agree, by the beta-lactans and the macrolides for the things that occur day in and day out in the office and in the hospital setting. And in addition, I think pediatricians have gotten the message over the years very well that quinolones are to be used very cautiously in children and I think that's the recurring message of that last few advisory committees and pediatricians understand that.

In particular, they've very well gotten the message that there is the potential for joint toxicity in children and, in addition, there is no large motivation in the pharmaceutical industry, as

far as we're concerned, to extensively develop quinolones in children. In other words, there isn't a $1 billion market out there or a $2 billion market that the pharmaceutical companies are chasing after in this.

So why should investigate quinolones in children? I think you'll find different answers to that question depending upon who in the pediatric or infectious disease world or who in industry you ask, but we've seen many of these particular indications listed before and I think this is just my list and I think others of us could put a different lists, but I think we would all agree that there are many different specific and well-delineated situations where quinolones may very well have a very useful role and that we would all like to have better information on how effective they are and how safe they are.

And we need to keep in mind that the circumstances of today may not be the circumstances of five years from now and the things that we think need to be studied right now with great urgency may be less important than some things five years from now and if we want to have the information five years from now to be able to rationally use quinolones in children, we should keep in mind that the world is a changing place

and that we have to anticipate to some extent what the world may be like in a few years. For instance, the picture with respect to PRSP may be very different and maybe a lot scarier a few years from now than it is right now.

So how can we get to a situation where we have better information and a better understanding of where quinolones fit in? It's our view that the best way to develop a coherent, sizable and detailed database, rather than the rather squishy database that we have right now for both the FDA's use and the medical community's use, is for industry-sponsored studies to take place. Clinical research. And to do this, we need an environment that is conducive to such studies.

These should be planned with both the current problem areas and also in anticipation of potential future problems or things which are right on the horizon right now and those ought to be in at least the back of our minds if not the front of our minds in planning this clinical research. Unnecessary burdens and road blocks should not be created and, in particular, monitoring requirements should not seriously discourage clinical trials. And it is possible for road blocks and disincentives to clinical

research to be erected which will have the effect of preventing the information from being developed in rational clinical research studies.

In particular, extensive long-term follow-up for all patients who receive short-term therapy in clinical trials is not practical in our view -- again, I say all patients -- and in fact probably doesn't make a whole lot of sense given the relatively squishy database that we have right now which is providing at least some measure of comfort. In particular, we would with great hesitation pursue studies were required invasive diagnostic work-ups that were not otherwise called for by the child's particular medical condition. In other words, we would be very hesitant to stick needles in the knee of a child if that circumstance in and of itself didn't also require that sort of invasive procedure to be done. For a child who has minor arthralgias, for instance, we would not suggest that child to extensive and difficult investigations.

So those are my brief comments. I'll be happy to answer any questions that the committee may have.

CHAIR CRAIG: Any questions for Doctor Hopkins? Yes, Doctor Henry.

DOCTOR HENRY: Nancy Henry. I have a question or maybe it's better labeled as a comment. I guess I'm a little bit bothered by your comment that you don't think that there would be widespread usage. I'm afraid that if drugs are out there, it's at a physician's discretion to use them and I'm curious. I don't have hard information on this, but I would be really interested in knowing the prescribing patterns for pediatricians versus family practitioners because family practitioners are becoming the first line of patient/physician interaction and personally I've been chagrined by some of the prescribing patterns.

Family practitioners are less likely to get infectious disease consultations and when they see adults and kids, there may be some carryover so that I guess I'm a little bit suspect when you say there wouldn't be widespread usage. You put them out there and say that you can use them in a certain setting. I'm afraid that they will be over-used. It's just again no hard data but I'd be interested in knowing prescribing practices among the two big groups that see kids.

DOCTOR HOPKINS: Well, to contemplate that I think you have to contemplate a series of things that happen. For instance, first of all, that the FDA

would give approvals that permitted the kind of ad lib use of these and I don't think any of us in this room contemplate that. What we are contemplating or hope for is that in relatively narrow and well-defined situations there will be approvals and it's my contention that given the last 20 years of pediatric training regarding the use of quinolones in children that these sources narrowly prescribed indications probably would not lead to widespread use. But that's obviously an opinion.

CHAIR CRAIG: Any other questions? Okay. Thank you very much, Doctor Hopkins.

Our next speaker is Doctor Roger Echols. He's Vice President, Infectious Disease Research and Development at Bristol-Myers Squibb. What they've got listed here, Roger, is Rationale for Studying Quinolones in Children. Are you doing the follow-up in clinical trials or what?

DOCTOR ECHOLS: I'm not sure what the title should be. It wasn't one that I remember suggesting, but I think rationale sort of covers a lot of ground there. I'm pleased to have this opportunity today to discuss the subject of quinolone use in pediatric patients. As Brad Leissa kindly acknowledged, this is actually the third presentation

I have made before the Advisory Committee on this same subject. Although I'm currently employed by Bristol-Myers Squibb, the viewpoint I will present to you is significantly influenced by my previous association with ciprofloxacin clinical development.

At the onset, I would like to suggest that the focus of today's meeting should include not only the specific benefits and risks of quinolone use in the treatment of bacterial infections in pediatric patients but should also include discussion regarding the filing and labeling of clinical trials involving pediatric subjects. This larger issue of drug labeling for pediatric patients has been addressed in general by the FDA in recent years with the previously mentioned pediatric rule. Yet, aside from a change in the general warning and precaution section and despite extensive clinical research and post-marketing experience, no currently marketed quinolone contains any pediatric usage or pharmacokinetic information.

The sole reason for this singular cautionary approach remains the pre-clinical juvenile animal model which consistently demonstrates a dose-related and species specific articular cartilage toxicity. Yet has this animal model ever been validated as a predictor of drug-related toxicity in

humans? I believe that a close examination of the model coupled with the extensive experience of quinolones including nalidixic acid in children should lead one to the conclusion that flouroquinolones can be safely used in children.

Furthermore, recent trends in antimicrobial susceptibility patterns make it imperative that these remarkably effective agents not remain drugs of last resort. In November 1989 the FDA convened Anti-Effective Drug Advisory Committee to discuss the same subject we have before us today. The meeting was precipitated not by a pharmaceutical company new drug application but by the concerted influence of physicians treating pediatric cancer patients and cystic fibrosis patients.

Although the FDA concurred with the Committee's recommendations that clinical trials could be conducted in patients five years of age or older in these specific patient populations, it took another year of negotiations with the agency before they would agree that properly conducted trials would be accepted for review for possible changes in a product information document. Simply stated, the pharmaceutical sponsor of these clinical research trials was unwilling to invest the necessary resources

without assurances that the clinical trial data could in fact be filed. The Committee should be clear that its recommendations to conduct clinical trials in pediatric patients by itself is inadequate, that these trials are not incorporated into the package labeling.

From 1991 to 1993 a committee of the International Chemotherapy Society reviewed worldwide clinical trials involving flouroquinolones and presented their recommendations at the International Chemotherapy Conference in Stockholm in 1993. These same recommendations were presented by Doctor Urs Schaad at a second Anti-Infective Drug Advisory Committee Meeting discussing the pediatric use of flouroquinolones.

At that meeting, independent investigations in Bayer presented their cumulative safety and efficacy data including the extensive experience in cystic fibrosis patients where high doses of ciprofloxacin had been administered for extended periods of time. There were no cases reported of the irreversible arthropathy so well described in pre-clinical animal studies. Also discussed at that meeting were the difficulties involved in conducting prospective double blind randomized studies in children, especially with a

product already marketed and thus available to physicians for their patients.

No substantive recommendations were made to change the perception that for children the flouroquinolones should be restricted to specific clinical research trials where the benefits clearly outweigh the risks of joint toxicity. The reality, however, is that off label use of flouroquinolones have taken place without appropriate labeling guidelines. Marketing estimates available in 1993 identified over a million prescriptions of marketed flouroquinolones in the United States utilized in the pediatric age range.

Ironically at this time, clinical research was being impeded by the continued conservative assessment of benefit risk. A clinical trial proposed by a respected U.S. investigator for the treatment of life-threatening, drug-resistant shigella dysentery in young Bangladesh children had the approval of the New England Medical Center Review Committee, the World Health Organization and the local Bangladesh authorities. Nevertheless, despite the strong support by the clinical development group at Bayer, the company's board of directors blocked the study because they were concerned about the possible negative media

publicity regarding the conduct of pediatric studies in developing countries when no such trials were being conducted in Europe. Fortunately, this and other trials have been successfully completed in recent years.

1993 was an important year for another watershed event, the approval of norfloxacin for pediatric use in Japan. Kyorin Pharmaceutical Company, the original discoverer of norfloxacin, had conducted a variety of prospective clinical trials and were granted approval for the treatment of selected upper and lower respiratory tract infections, urinary tract infections, skin infections, and bacterial dysentery and enteritis. The drug was especially formulated in a 50 milligram size suitable for pediatric administration. These tablets that you see here are coated and have a dimension of 5.6 X 2.8 millimeters. They're very small.

Since the approval of norfloxacin in Japan in 1993, over a million prescriptions in the pediatric age group including nearly 100,000 in children four years of age or less have been administered. In addition, post-marketing safety surveillance of over 3,000 adverse events reported in children receiving norfloxacin have failed to identify any case of joint

pain consistent with the arthropathy demonstrated in juvenile animals.

Now in 1997, the medical need to assess the benefit risk of flouroquinolones is no longer just focused on special populations but rather the general pediatric population due to the rapid increase in penicillin resistant streptococcus pneumoniae. Both the intermediate and high level penicillin resistance is expressed across several classes of antibiotics including cephalosporins and macrolytes. Fortunately, the newer quinolones have enhanced activity against streptococcus pneumoniae and to date no cross resistance among penicillin resistant streptococcus pneumoniae has been identified.

The potential benefit of the newer quinolones for pediatric respiratory tract infections, especially otitis media, is a factor of both their activity against most all respiratory tract pathogens as well as their excellent bioavailability in pharmacodynamics including their ability to eradicate mucosal carriage of common bacterial pathogens. The flouroquinolones probably represent the best class of antimicrobial agents for the treatment of upper and lower respiratory tract infections involving pathogenic bacteria.

I will conclude by saying that in my opinion the quinolones are safe when used in appropriate doses in children. The clinical experience in pediatric patients with nalidixic acid and ciprofloxacin in the U.S. and Europe and norfloxacin in Japan is overwhelming. The pre-clinical model demonstrating articular cartilage damage in juvenile animals simply has not been validated as a predictor of human toxicity. We are faced with a changing benefit risk equation where respiratory tract infections involving streptococcus pneumoniae including otitis media need well-conducted clinical trials using the newer quinolones with demonstrated activity against this pathogen.

The Advisory Committee is being asked to choose between three options, yet these three options do not address the issue at hand and that is are the flouroquinolones toxic to children? To focus only on meningitis as a treatment indication will prove unsatisfactory in the long run even though I do not doubt the effectiveness of certain quinolones for this life-threatening infection. To choose option #3 which focuses on immediate life-threatening infection such as meningitis will only place us back where we were in 1989.

The safety data derived from meningitis studies will not provide the information we seek. The numbers of patients will be small, randomization and blinding will be problematic and the outcome measures will be complicated by the variable clinical and adjunctive treatment measures undertaken. Regrettably, choice #2 is phrased in such a way as to suggest uncontrolled use. This does not have to be the case. We, the medical community and the pharmaceutical sponsors, can and should design and conduct appropriate clinical trials in pediatric patients with complicated otitis media and other pediatric infections with significant morbidity. If given the opportunity, prospective clinical trials with appropriate outcome measures may establish a new standard of care.

Thank you for your attention.

CHAIR CRAIG: Questions? Roger, in the data base from Japan on norfloxacin in kids, especially those four and under, was there much CNS toxicity? I mean I think many of us -- I think this is being focused by many more on arthralgia and I think many of us are wondering whether there are some other toxicities that might occur in the very young that we just don't know about.

DOCTOR ECHOLS: I have to admit that my information that was given to me by Kyorin which is a partner we're involved with now in the development of another quinolone was relatively superficial. I just was asking them questions on joint toxicity and I didn't really get into all the other aspects of adverse events.

CHAIR CRAIG: Doctor Leissa.

DOCTOR LEISSA: Yes. I just wanted to make one comment relative to the Japanese experience which is I had seen Doctor Echols' slide in advance about the prescription use of norfloxacin. In this country, norfloxacin is marketed by Merk so I asked the people at Merk if they knew of any adverse event data that had been submitted to them relative specifically to arthropathy and essentially confirm what you say which they have not received any reports from Japan in relationship to the arthropathy issue.

CHAIR CRAIG: No information about others?

DOCTOR LEISSA: Not at this time. No.

CHAIR CRAIG: Doctor Rodvold.

DOCTOR RODVOLD: You might not know this, Roger, but in regards to the product of norfloxacin in Japan, is it pharmacokinetically similar to the product in the states, particular bioavailability and

systemic exposure?

DOCTOR ECHOLS: The dosage they recommend in the package labeling is approximately five milligrams per kilogram which gives pretty low serum concentrations. I would like to respond, however, to the issues of the toxicokinetics that was raised earlier and Kyorin really had done and published some very sophisticated data on the animal models correlating not only serum concentrations and AUCs but also tissue concentrations in joint with the incidence of the joint toxicity that's been so well described.

And in the monkey species which they have studied, even at doses which are a magnitude higher than that seen in humans, there was zero toxicity in the monkey species and those monkeys were in the age range of 10 to 13 months. All that data is published and actually available in the package insert for norfloxacin in Japan which I have an English translation for anyone who's interested.

CHAIR CRAIG: Doctor Klein.

DOCTOR KLEIN: Roger, one of the issues that might be a very potent one in terms of respiratory infections in children, particularly otitis media, would be the ability of any class of antibiotics to eradicate colonization. We know that

ciprofloxacin has been used for meningococcal eradication. Do we know about pneumococcal colonization or other elements of the respiratory flora? Are there data?

DOCTOR ECHOLS: I would say that there's an absence of data because we've not to date been permitted to study respiratory tract infections. So the meningococcal data was derived from the early 1990s, late '80s when we were pursuing that as an indication. In terms of pneumococcal, I wouldn't look at, say, some of the older quinolones to evaluate that. I'd want to be looking at a newer quinolone with better activity.

CHAIR CRAIG: Doctor Bradley.

DOCTOR BRADLEY: Since Doctor Echols raised a question regarding the three different options that are before the committee, one of the questions actually had occurred to me when I first got the list in trying to formulate some recommendations for the committee and that is option two which says, quote, "No restrictions on the types of indications for which quinolones may be developed." And obviously for a summary one likes to have things as short and concise as possible but my question is is choice #2 actually a choice and if you open it up to respiratory

tract infections, you can't say it needs to be used when there's failure with primary therapy and if you study it and you have to approve it.

CHAIR CRAIG: Well, I think we can discuss that later on. Right now I think just before the break I'd like any more questions specifically of Doctor Echols' presentation. Doctor Reller.

DOCTOR RELLER: Doctor Echols, you emphasized the safety data from Japan. What about the efficacy database for the approval of 50 milligrams of norfloxacin orally in children? Were there clinical trials demonstrating efficacy and, if so, what were the comparers and what specific respiratory tract infections, otitis media, sinusitis, and did microbiological database demonstrate efficacy if in fact that was done?

DOCTOR ECHOLS: I'm going to have to refer you actually to a symposium that was put on by the International Chemotherapy Society which reviewed these data for the NDA in Japan. What I can tell you is around 400 patients. I believe a lot of it was uncontrolled data. They do list in the package insert eradication rates which range in the 80 - 90 percent range and they do include pharyngitis, tonsillitis, bronchitis, as indications for which they had clinical

data. They do not have approval specifically for otitis media. I don't know whether that was studied or not.

CHAIR CRAIG: Okay. Anything else right now? Okay. Thank you very much, Doctor Echols. We will now take our lunch break. We're running just about 15 minutes behind, so if you could all be back here at 1:15 I think we can make up some of the time later on this afternoon. Thank you.

(Whereupon, the meeting was recessed at 12:15 p.m. to reconvene at 1:15 p.m. this same day.)

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

(1:20 p.m.)

CHAIR CRAIG: If people could take their seats again, we will get started with the rest of the program. The next portion of the program is going to give our various consultants a chance to give the Committee their views on the topic.

Our first one is going to be John Abramson, an FDA consultant representing AAP.

DOCTOR ABRAMSON: Thank you. First of all, I would like to state for the record that what I am about to read is the position statement from the Committee on Infectious Diseases for the American Academy of Pediatrics. Once I have finished reading that statement, I will then give you some personal opinions that are not necessarily the positions of the Committee on Infectious diseases.

The first paragraph that I am going to read is the current statement that is in the Red Book -- combined from two different places within the Red Book. The current American Academy of Pediatric's policy on the use of fluoroquinolones in children is contained in the 1997 report of the Committee on Infectious Diseases 24 Edition of the Red Book. The policy states that the use of the fluoroquinolones is

generally contraindicated according to FDA approved product labeling in children and adolescents younger than 18 years of age because they can cause cartilage damage in immature animals.

The available data, however, indicate that these drugs are well-tolerated, do not cause arthropathy in humans, and are effective in pediatric patients. Accordingly, in special circumstances in which alternative drugs are either not available or less effective, and after careful assessment of the risks and benefits for the individual patient and discussion regarding those risks and benefits with the individual patient and parent, use of a fluoroquinolone can be justified.

Circumstances in which fluoroquinolones may be useful include those in which no oral agent is available necessitating an alternative drug given parenterally and infections caused by multi-resistant gram-negative organisms and other pathogens such as certain pseudomonas and mycobacterium strains.

The policy further states that possible infection for which the fluoroquinolones might be used include urinary tract infections, chronic suppurative otitis media, chronic osteomyelitis, exacerbations of cystic fibrosis, neisseria gonorrhea infections,

mycobacterium tuberculosis and atypical infections, and in immuno-compromised hosts in which prolonged therapy is desired for gram-negative bacterial infections.

Recently, we have had reason due to the FDA meeting to consider a position further in regard to the questions raised by the FDA for this meeting. The Council on Infectious Disease has considered the issues raised, and although there are some reassuring data regarding the risk for arthropathy, concerns about the safety in children remain, including their potential to cause Achilles tendon rupture and central nervous system side effects. These issues can only be resolved by carefully done studies involving large numbers of patients.

The Council on Infectious Disease favors an incremental developmental approach for use of the fluoroquinolones in children. Further, clinical studies should first be done in diseases where the fluoroquinolones are used to treat serious infections such as meningitis due to resistant bacteria or in serious infections where alternative drugs are either not available, less effective, or more difficult to administer, for example, where there are no oral agents available.

Further consideration regarding whether the FDA should allow the clinical development for fluoroquinolones for a wider range of treatment indications should be based on the results from these studies and other considerations such as whether other more narrow spectrum antimicrobial agents are effective for treating a particular disease.

That is the statement from the American Academy of Pediatrics. Now for some personal views. I remain concerned that most of the clinical data that we have are in children greater than 5 years of age, and it is impossible for me from reading the literature and from asking various experts, including those here, to tell what is the age in pediatrics where we need to be concerned about arthropathy. Is it in children less than 5? Is it in children less than 2, et cetera?

And given that otitis media is essentially a disease that occurs in children 2 years and younger -- it can occur in older children obviously and it can occur in adults, but the vast majority of disease occurs in children less than 2 years of age, I remain personally concerned about its use where we are talking about 23 million prescriptions given out per year.

I will also point out that in upper respiratory tract infections, the CDC and the American Academy of Pediatrics estimate that if we would judiciously use antibiotics that we would save 50 million prescriptions per year by not treating things that we are currently treating. Given that we are so heavily over-using antibiotics for respiratory tract infections, one has to remain concerned that if we use the fluoroquinolones in that circumstance that resistance will develop.

I am told by company representatives and from data that I have seen that to date the incidence of resistance for strep pneumoniae has remained fairly stable. However, I will point out, as I am sure that all of you are aware, that as we keep pounding on various bacteria, for instance vancomycin usage, we are now seeing things that we never have seen before -- relatively resistant staph aureus to vancomycin, resistant enterococcus to vancomycin. One has to be very concerned that we are going to abuse a drug, the fluoroquinolones, for which they have a great potential for treating more serious diseases and ruin that class of drugs. Thank you.

CHAIR CRAIG: Thank you. Any specific questions on the data that he said? We will just move

on -- yes, Dr. Leissa?

DOCTOR LEISSA: I'll just mention for the audience, on the front chair there is a copy -- there are probably 30 copies or so of the position statement if anyone wants to pick that up.

CHAIR CRAIG: Thank you very much, Dr. Abramson. The next presentation will be by Dr. John Bradley from -- San Diego now still? San Diego still. Okay. And another one of the FDA consultants.

DOCTOR BRADLEY: Thank you very much, Dr. Craig. It is a real privilege to be here this afternoon to represent the clinicians' point of view, at least one clinician's point of view. Following my training, I have actually ended up spending half the time on the wards and clinics taking care of these children and half the time trying to study new antivirals and antibacterials to improve therapy. So for these children who end up having these multiple antibiotic resistant organism infections failing standard therapy, either I get called or one of the people in our division, and I am sure it is the same way for you.

Before I give my statement, though, what I would like to do is to read into the record the statement of an esteemed colleague of mine, Dr. George

McCracken, who is a Professor of Pediatrics at the University of Texas Southwestern Medical School. Dr. McCracken actually got the original invitation to sit as a consultant to the Committee, a well-deserved invitation, but because of his clinical responsibilities was unable to make it, so I am here in his stead.

Dr. McCracken's statement, which is actually in the black workbook that everyone received, goes as follows. "I strongly support an incremental developmental approach to the study of fluoroquinolones in pediatric populations. In addition to ongoing assessments of these agents in pediatric patients with cystic fibrosis or hematologic/oncologic disorders, including transplant recipients, I believe it is prudent to initiate studies immediately in infants and children with bacterial meningitis, and in those in the intensive care unit with nosocomial infections, i.e., sepsis, pneumonia, skin and skin structure infections.

Because resistant bacteria are a critical factor in initial management decisions in these patients, fluoroquinolones are logical agents to be investigated since they are extraordinarily active against multiple drug-resistant pneumococci and

extended spectrum beta-lactamase producing enterobacteriaceae, common pathogens in these settings.

Dependent on the results of these studies, the fluoroquinolones could then be evaluated in hospitalized pediatric patients with community or hospital-acquired pneumonia and possible middle ear or sinus infection caused by resistant pathogens, e.g, Pen resistant pneumococci in acute or persistent otitis media and pseudomonas or proteus infection in chronic disease. The incremental approach is favored because I believe we have much to learn about these agents, especially the new generation fluoroquinolones, which only experience in adequate numbers of patients will provide.

The rather extensive ciprofloxacin experience in pediatric patients with cystic fibrosis provides reassurance that synovial histopathologic changes observed in puppies is unlikely to occur in children. On the other hand, we know very little about the CNS effects -- drowsiness, insomnia, attention deficit -- and photosensitivity of these agents in children. Additionally, it is possible that the unbridled use of these drugs could rapidly lead to resistance, especially if used routinely for treatment

of otitis media in infants and children who attend daycare.

I believe there is a very favorable benefit/risk ratio to the incremental development program but not for open clinical development at this time. So Dr. McCracken gives his regards to the Committee.

My statement, which was written without the benefit of having seen Dr. McCracken's statement is very similar, which probably underlies why he gave the Committee my name. So I would like to show how we are together on a number of issues, but perhaps I am pushing for a little bit more prospectively collected safety data in pediatrics, especially given the information that has been presented this morning.

Quinolone class antibiotics have not been widely prescribed in children due to concerns regarding potential toxicity to weight-bearing cartilage as demonstrated in a number of animal models -- and actually all the animal models now. With respect to antibiotic therapy for neonates, infants, and children, considerations of safety have always taken precedence over considerations of convenience or cost.

Two infection situations currently exist,

however, in which oral quinolone therapy may be of significant benefit in pediatrics -- treatment of infections caused by pseudomonas aeruginosa and treatment of infections caused by antibiotic-resistant streptococcus pneumoniae. And of increasing importance is the therapy of infections caused by cephalosporin-resistant and trimethoprim sulfamethoxasol-resistant enteric gram-negative organisms such as enterobacter species.

Populations of children who are candidates for quinolone therapy include those hospitalized with serious infections who probably represent the group most in need of these drugs, those children with infections who reside in nursing homes -- these children generally do not ambulate and have a shortened life expectancy, yet frequently are infected with antibiotic-resistant organisms -- and finally, normal children. The risk/benefit ratio is different for each of these populations.

Although infections with pseudomonas aeruginosa may occasionally develop in immuno-competent children, they are most prevalent in children with cystic fibrosis and most serious in immune compromised children. Parenteral therapy has been and continues to be available for treatment of

pseudomonas aeruginosa infections in children. However, for all children, oral therapy has distinct advantages over parenteral therapy. Parenteral therapy, either administered in the hospital or in the home carries a small but definable morbidity. Just ask any child when the IV is being restarted. It is important to be able to prospectively assess the morbidity associated with quinolone therapy so that the risks of the two treatment modalities may be compared.

Streptococcus pneumoniae is the most prominent bacterial pathogen to cause blood stream infections and respiratory tract infections in children. Many strains of strep pneumo have become increasingly resistant to antibiotics over the past five to ten years, both in the United States and worldwide as we have learned this morning.

Vancomycin is now used routinely in combination with a cephalosporin for empiric therapy of suspected pneumococcal meningitis. However, if resistance should develop to vancomycin, it is crucial that we have well-studied, effective, safe antibiotic therapy available to treat these children.

Other serious but not usually life-threatening infections caused by strep pneumoniae

include pneumonia, otitis media, sinusitis, and bacteremia. At the present time, the great majority of these infections will respond to currently available antibiotics. And as was mentioned this morning, pneumonia as one particular focus of infection, virtually always responds to even high-dose penicillin.

However, there are several children who I have ended up treating, primarily with respiratory tract infections, who have had multiple drug resistant pneumococci, where none of the beta-lactam agents -- trimethoprim/sulfa or clindamycin have been active. Children with otitis media, mastoiditis, or pleural empyemas, where parenteral therapy, either with vancomycin or ceftriaxone was required. However, if the quinolones were found to be safe, oral therapy would clearly be preferable to parenteral therapy in these children.

Unfortunately, if resistance to beta-lactam antibiotics continues to increase, as we have seen previously, quinolone antibiotics active against -- well, as it continues to increase, therapy with beta-lactam antibiotics may no longer be effective for us. Quinolone antibiotics active against strep pneumo may be required to treat these infections in the

future.

Data on the safety of quinolones in children are important to collect prospectively. Clinicians will prescribe quinolone antibiotics for children based on efficacy data in adults if needed to treat antibiotic-resistant organisms even without adequate knowledge of the safety of this class of antibiotics in children. This morning, Dr. McCloskey presented information which supports this contention with 175,000 prescriptions for oral quinolones, ciprofloxacin, in children less than 18 years of age, and 12,000 prescriptions alone in children zero to one year of age just in 1996. Use of these agents is currently underway.

I believe it is important to collect prospective data on safety and efficacy of the quinolones in children who have failed conventional antibiotic therapy. I believe a reasonable balanced approach to investigation of quinolones in children is needed considering the unknown risks of cartilage toxicity and the need for effective therapy. I fully support studies in serious community infections, most importantly meningitis, as well as in nosocomial infections caused by antibiotic-resistant organisms. At the same time, I believe it is important to collect

data prospectively on the safety of oral quinolones in children without endorsing the uncontrolled use of quinolones or suggesting that this class of antibiotics be used as first line therapy for respiratory tract infections in children. Only by means of careful prospective evaluation will we understand the role of this class of antibiotics in children.

To address the questions posed by the FDA to the Committee, I support development in an area that is somewhere between option 3, investigation only in serious infections, and option 2, unrestricted development and unrestricted labeling. The oral quinolones are being used in children, and I believe it is our obligation to study the safety of these compounds. Our biggest fear is the development of arthropathy if the antibiotics have uncontrolled use. I suggest that drug use is increasing anyway, and I personally would prefer to know the risks from prospective data collection rather than by analyzing risk from retrospective data collection as was done primarily this morning.

The retrospective data collected thus far, however, in over 7,000 children -- the paper that Dr. Craig referenced this morning that is just being

published this month in Clinical Infectious Diseases, demonstrates no clear toxicity of the quinolones. This is one of Dr. Schaad's most recent reviews. But this is just retrospective data, and I have concerns that it does not accurately reflect toxicity. We need prospectively collected data in children receiving doses of quinolones that would be given in the treatment of otitis osteomyelitis and gastroenteritis.

Will I still recommend Amoxicillin even if quinolones demonstrate safety? Of course. We have actually been recommending high dose Amoxicillin since 1993, when we first collected our data on increasing resistance in San Diego.

How many children need to be followed for toxicity? Given data presented this morning, quite a significant number. Perhaps somewhere between 500 to 1,000 in order to accurately assess safety.

How should testing be performed? MRI appears to be the most sensitive technique for following articular inflammation. A single study perhaps at the end of a 10 to 14-day treatment course should be able to assess toxicity without any invasive procedures based on the kinetics of inflammation presented today. Assessing toxicity in toddlers, who would require anesthesia for an MRI however, is a much

more difficult matter. I would also hope that a serologic marker of joint inflammation could be developed based on the animal model. Perhaps a serum concentration of one of the constituents of cartilage could predict arthropathy. We have very sensitive markers of liver and kidney inflammation. It would be very helpful to be able to develop one for joint inflammation and it would be much more cost effective compared to an MRI.

In summary, I believe studies on efficacy and safety proceed quickly in the IV therapy of serious infections and studies on safety proceed quickly with oral therapy. Thank you very much.

CHAIR CRAIG: Thank you, Dr. Bradley. Any specific questions for him right now? Okay. We will move on then to the next presentation, which will be by Jerome Klein, obviously a well-known expert in otitis media. I have bought your book, Jerry. And he is going to be talking about -- giving us his views on the subject as well.

DOCTOR KLEIN: I have another book I would like you to buy. I have five items I wanted to address, and I hope it will not be redundant over the comments made by my predecessors. First, I think the time has come for this Committee and the Food and Drug

Administration to approve use of fluoroquinolones in children for selected uses in which it is uniquely effective, and we have heard much discussion about what those uses might be. But I think they should be based on analysis of the data that focuses on those areas that are not adequately represented by other antimicrobial agents. And, the list presented in 1993 by Dr. Schaad I think is a good start.

Second, I think we need more data about clinical pharmacokinetics in infants and young children and those should be begun now. Diffusion into different body cavities, the different pharmacokinetics that may be applicable to children at different ages. I think we need to continue surveillance data for including the fluoroquinolones in our battery of antimicrobial agents that are being surveyed, particularly for the concern for resistant pneumococcus.

I think some of the studies should look to some of the points that have been made this morning. Dr. Echols mentioned eradication. I think if we could identify in a study that the fluoroquinolones or selected fluoroquinolones were uniquely effective in eradicating colonization with pneumococci, that would be a very persuasive result suggesting value in upper

respiratory tract infections. So I think there is groundwork to be laid before we proceed to specific clinical trials in defined areas.

I think we should insist, as a community of pediatricians, of post-marketing surveillance. So that we can pick up not for the obvious arthroscopies or tendon problems, but for perhaps more subtle CNS issues which may turn out to be more troublesome or perhaps even other effects that would be unique to infants and young children. I think insomnia is distressing, though not as dramatic an effect as the arthropathies, and but certainly would be a concern and a side effect that would be unhappy for both the patient and the parent. So the post-marketing survey was third.

Fourth, I think we can do better in terms of identifying possible adverse effects. I think we have data bases from health maintenance organizations and from Medicaid groups that can identify large groups of patients who have received an antimicrobial agent, know the use of the agent, that is, the diagnosis, and be able to cross-tab with adverse effects. It may be that we have to incorporate our rheumatologic and orthopedic colleagues in a survey of new and unexpected cases of arthropathies or Achilles

tendon injuries that have arisen and do a case control study of those cases.

Finally, I think new approvals by the Food and Drug Administration should be accompanied by a plan from the industry that identifies an educational program for parents and physicians. Dr. Dowell mentioned this morning the important initiative of the Academy of Pediatrics, the CDC, and the ASM to educate parents about uses of antimicrobial agents that are not warranted, that is, disease conditions for which the antibiotic is not indicated. I think industry should be a partner or an initiator of such events, and I think new approvals should be accompanied by a question about how marketing will deal with addressing appropriate usage of the approved antimicrobial agent. Thank you.

CHAIR CRAIG: Thank you, Jerry. The next speaker is Dr. Paul Lietman from Johns Hopkins, who has actually got a title. His is going to be "Quinolones in Pediatrics: Viewpoint of a Clinical Pharmacologist." Obviously a professor since he has slides.

DOCTOR LIETMAN: Should I stand back here so I can change them also?

CHAIR CRAIG: No, I think we can get

someone to do that for you, Paul.

DOCTOR LIETMAN: Well, this is the prospective of a clinical pharmacologist. I should also have said in my introduction that I used to be a pediatrician, although my colleagues may not accept me anymore as a pediatrician.

My thesis is going to be -- in this brief presentation -- that it almost appears to me that there has been a conspiracy against children. I believe that the fluoroquinolones are clearly of value in children. May I have the first slide? And I believe that the FDA, this Committee, and the industry, and perhaps academia as well -- it almost appears as if they conspired to keep fluoroquinolones, valuable drugs I believe, from children.

Now in thinking about this, two years ago I was asked to speak at a conference in Berlin and I thought my thought then and to my chagrin very little has changed since then. I believe you need to think about interactions of drugs with microbes, mechanism of action, resistance, time dependent pharmacodynamics, and interaction of drugs with humans.

The first question I think we need to ask and it has been asked is is a fluoroquinolone

important for children. If yes, then there is a moral imperative I believe to study the fluoroquinolones in children. The process must be ethical and feasible for the pharmaceutical industry, pediatric investigators, regulatory agencies, and the children and their parents. I believe and we have heard today that there are numerous august organizations and well-renowned people who believe there is a place for fluoroquinolones in children and I believe they must be studied. I don't believe we can wait for a crisis. I don't believe we can wait until the pneumococcus has become completely resistant to penicillin. I think we need to study them now so that they are available when a crisis occurs.

I don't believe that irrational use is a reason to fail to study or approve drugs in children. We can cope with the rationality of the use after we know something about it.

I believe that overuse and subsequent resistance is not a reason to fail to study or approve new drugs in children. It isn't fair to children to limit the use of fluoroquinolones to adults to avoid the emergence of resistance overall.

Is a fluoroquinolone important for children? The decision should be a consensus with all

those representatives involved.

Fluoroquinolone interactions with microbes, I contend, are similar in children or adults. I don't think the bug knows whether it is in a child or an adult. So the mechanism of action, the inhibition of the topoisomerase in this case, and the mechanism of resistance is going to be the same in children and adults. And the time dependent pharmacodynamics, that is, the effect of the drug over time in bacteria is going to be the same in children as adults.

Fluoroquinolone interactions with humans, however, clearly may not be similar in adults and in children, and this involves both pharmacokinetics and toxicity as well. I believe that we need to determine the pharmacokinetics of the fluoroquinolones in children. Single dose pharmacokinetics need to be derived I believe in all those groups. Neonates are a question in my mind, and they are physiologically -- from my standpoint as a pharmacologist -- so different from the infant and the older child that I would categorize them in an entirely separate category. But I believe once you are out of the neonatal period, there is a continuum through the rest of childhood into adult life -- the physiologic variables that

effect drugs that is.

In infected children, I believe these studies should be concomitant at first with another drug. In other words, add the fluoroquinolone to a regimen that you already know works because ethically we aren't allowed to study and we shouldn't study drugs in children who are uninfected.

The micro -- I believe that the important thing to standardize between children and adults is the exposure, and I believe we should find a pharmacokinetic regimen that exposes the child to the same concentration over time as has been proven usually to be effective in adults, and certainly with the fluoroquinolones in lots of studies in adults by now. So I would choose the AUC as the starting point.

These are just a few of the data that have been collected about fluoroquinolones in children. But there is in fact precious little data about pharmacokinetics in children. Nevertheless, there is enough to get started, and we should be enthusiastically encouraging people to derive this kind of data. These are just studies of the pharmacokinetics in children.

I believe then that we need to formulate a dosing regimen that mimics the adult exposure. I

believe we need to study multiple dose pharmacokinetics and toxicity in a small number of children with simple infections that are almost sure to respond. I believe we can't assume that the toxicity in children will be either quantitatively or qualitatively similar to that seen in adults. Therefore, we do need to collect the data assiduously and carefully as we use the drug in children. But I do believe we need to focus on the unique toxicity seen in the mature animals, and in this case it is not CNS and it is not the phototoxicity and it is not other toxicities. It is the cartilaginous change that I believe we need to focus on.

The preclinical toxicology in animals should be related to humans with exposure and not dose as the common factor. I brought that up this morning. The toxicities of each new fluoroquinolone should be considered as if they were an entire new chemical entity, which of course each is. I don't believe we can extrapolate from ciprofloxacin to any other fluoroquinolone with regard to the toxicities. The antibacterial effects need not reflect the toxicologic effects.

I believe then we should create -- and I believe it is time to do that now for some of them --

a mechanism for limited and careful use of the fluoroquinolones in selected academic centers which have a special interest in situations in which the data can be recovered and where forms will be filled out and submitted to either the drug company or the FDA, and with selected investigators, choosing people who I believe are capable and interested in doing this sort of thing.

I believe we need to finally demand -- the FDA needs to demand that the industry create a mechanism for real time monitoring of adverse drug events reported, both by industry -- it could be by industry, and I believe that would be the best. It could be by a designated academic center or investigator under contract, or it could be by the regulatory agency itself.

So I believe that these are important drugs for children and that we have a moral imperative to study them and that we should create a climate in which they are eagerly studied, not a climate that delays their study for years and years and years. I believe there will be similar microbial interactions in children and adults. Microbial exposure I believe is what will be important. I believe we need pharmacokinetics and we need to dose and to mimic

adult exposure. We need multiple dose pharmacokinetics and toxicity in a few carefully studied children. We need limited and careful initial clinical use, and we need real time monitoring for adverse effects.

Finally, I believe as Gordon Millichap said in his introduction to his chapter in Goodman and Gilman, "those drugs thou hast and their adoption tried, grapple them to thy soul with hoops of steel. But do not dull thy palm with entertainment of each new hatched unfledged remedy." We must figure out how to do it without being on one side or the other. Thanks.

CHAIR CRAIG: Thank you, Paul. Any specific comments by anybody? Okay. Our last speaker among the session here of FDA consultants is Irene Bidault from France, who is going to give us some experience from Europe.

DOCTOR BIDAULT: Well first I want to thank you for giving me the opportunity to attend this meeting and to present to you some data we have collected several years ago in France on adverse drug reactions notified with fluoroquinolone in pediatric populations up to 19 years old in order to cover the growing period. This work was performed by the

Pharmaco-Vision Center. It is located in Paris in a pediatric hospital.

This work is a part of the global retrospective safety analysis which was first initiated in order to focus particularly on tendinitis. Then we noticed that six persons of all spontaneous reports during this period involved pediatric patients. Half of these pediatric reports are joint and muscle disorders, when the percentage is 11 persons in the adult population. If we look at all joint and muscle reactions, 22 persons are for pediatric patients.

I have forgotten to mention to you that in France fluoroquinolones are contraindicated in patients up to their growing period. So all these patients were prescribed off-labeling.

The drugs that were available were pefloxacin in 1985, then norfloxacin in 1986, orfloxacin in 1987, and ciprofloxacin in 1988. 150 patients experienced 159 adverse effects and the majority of them was treated with pefloxacin. These analyzed cases were reported to the national authority by the Pharmaco Vision Centers and by the companies too and the duplicate reports were eliminated.

In order to continue to compare this

pediatric data with other data, we can see here that pefloxacin pediatric reports represent 7 percent of all pefloxacin reports and it is the same percentage for ciprofloxacin.

We have focused our analysis on joint disorders and pefloxacin. 79 cases were reported and consist mainly of arthralgia. I don't know the pronunciation of hydrarthrosis -- 49 persons. It involved the knee in 52 cases, the wrist in 20 cases, the elbow in 20 cases, the shoulder in 6 cases, the ankle in 5 cases, and the hip once. It is associated with a functional discomfort in all cases, and when the duration of this discomfort is known, it can persist more than one month in 61 percent of these cases. But the outcome was favorable in 58 cases without discontinuation in two cases.

About follow-up, we can say that in only two cases we had a follow-up superior to 6 months, which confirmed the good evolution. There have been sequelae in three cases with knee effusions persisting one year later in one case with discomfort following 8 months later in the second case. The third case is articular. It is a 17-year-old patient who experienced arthropathy and the drug was not suspected and the treatment was continued two following months.

It leads to destructive arthropathy of the knees and the hip and prothesis was performed three years later. He was treated for a cerebral abscess. The outcome was unknown in 18 cases. In 9 cases, there was no follow-up. In the 9 last cases, we had a follow-up three months later and patients were not -- were still with disabilities and after we have no evolution.

70 percent of the patients were aged between 13 and 16 years old, but we are unable to conclude if it is according to a greater use for this age or a greater fragility -- I don't know if this word is correct -- of the joints at this period of the growth. 63 percent of these patients are boys.

The indications of the treatment were known for 94 percent of the reports and consisted of severe infections in 64 persons. The current medical history is known for 83 persons and it was for 12 persons only cystic fibrosis or hematological and oncological disorders in 4 persons. No medical history is noted in 41 percent.

As I have told you, all of these cases were reported with pefloxacin except three reports with ciprofloxacin. These three reports with ciprofloxacin are quite minor with arthralgia with fibralgia outcome within the following week, with two

reports with intravenous use.

For pefloxacin, there are 76 reports prescribed with adult dosage, which means 800 mg, and it is 90 percent. But when weight was known, we have calculated the dosage in mg/kilo, and we noticed that 65 persons received more than 15 mg/kilo.

For most of the reports, it was an oral route of administration and the treatment was prescribed in a hospital in 64 persons. The time to onset is 11 days -- from 3 days to 35 days. Treatment was not discontinued in only 2 cases. It was discontinued after one or two days after occurring of the symptoms in 37 cases, and treatment was continued more than 2 days in 20 cases.

We have been particularly aware with these data of probable misuse with patients with no severe infection, no medical history, and quite a lot of outpatients -- not in a hospital.

The other effects are distributed as follows. With 70 percent of cutaneous reactions, 11 percent of hematological reaction, 7 percent for neurological, 5 percent for digestive, allergy 4 percent, kidney 3. There are only 3 tendinitis. Two are associated with arthralgia and one is ulcerated. The three cases are also with pefloxacin.

Just to see that these effects are close to what we know in the adult population with photosensibilization, urticaria, and digestive and allergic and renal disorders. No real issue was raised with these effects.

So following this, the measures taken were we have also studied adult data at the same time. So we have restricted pefloxacin to only hospital use. We have revised the FPC in order to mention all adverse effect reactions we had and to focus on tendinitis. And for pediatric data, as the previous labeling was that the indications were limited in adults, this was not changed. But under the section for contraindications, it was initially mentioned that the contraindication was for children during growth period because of animal articular elasticity, and we changed it to that for children during the growth period because of the possible occurrence of joint disorders in children and adolescents as severe arthroplasties involving essentially articulations acute. In order to make aware of the physicians that it is not only theoretical data.

At the moment, we are also having the same issue raised in France. Firstly, we are -- well, it is in progress at the moment. But before data will be

available more accurately on pediatric benefit/risk, we should probably modify the labeling of the contraindication in order to permit the physician that need really fluoroquinolones in some indications to prescribe it, not out of labeling. And to mention that it is inadvisable for children during growth periods because of these toxicities except for -- and the except for is under discretion. It is not finished at the moment. We have also next month a Pharmaco Visions advisory meeting in order to evaluate again the overall global safety evaluation of fluoroquinolones including pediatric data. But it is only the 11th of December, so it is too early now to present you this data. So that is what I wanted to present to you today and I thank you for your attention.

CHAIR CRAIG: Thank you very much. I guess I would have one question. The three patients that had the more prolonged problems with their joints, did those all three receive pefloxacin?

DOCTOR BIDAULT: Yes.

CHAIR CRAIG: Thank you. Yes, Dr. Henry?

DOCTOR HENRY: I just have one clarification. Perhaps I missed this. You showed that there was a disproportionate number of the joint

problems in males over females.

DOCTOR BIDAULT: Yes.

DOCTOR HENRY: In looking at all the data was there that same distribution of males and females who were included in adverse drug reactions? When you look a the data by gender, was it skewed in terms of the total numbers?

DOCTOR BIDAULT: For the other effects you mean? I don't understand.

DOCTOR HENRY: Just overall. If you looked at all adverse drug reactions in children, were there roughly equal numbers of males and females?

DOCTOR BIDAULT: There are 50 boys and 29 girls.

DOCTOR HENRY: For the joint problems?

DOCTOR BIDAULT: Yes.

DOCTOR HENRY: But for overall looking at-- DOCTOR BIDAULT: I have not the -- I can't count them. I have not the information there. Because it was isolated cases, so we didn't pull them. I don't know if we can conclude about that.

CHAIR CRAIG: Okay. Dr. Lietman?

DOCTOR LIETMAN: I think that pefloxacin has never been marketed in the States. It is a drug that is owned by Rhone-Poulenc or Rhone-Poulenc Rorer.

I guess it is widely used in France. Am I correct, there was a very well-done study in France comparing the arthrotoxicity or arthropathy of pefloxacin to one of the other fluoroquinolones? And what it showed was that pefloxacin was indeed more toxic in humans than was the comparatory. Am I correct? Do you know that study?

DOCTOR BIDAULT: I don't know what you mean.

DOCTOR LIETMAN: You don't know.

DOCTOR BIDAULT: You mean a clinical study?

DOCTOR LIETMAN: Yes, a clinical study.

CHAIR CRAIG: Yes, Dr. Parsonnet?

DOCTOR PARSONNET: It is my understanding that one of the children had a joint replacement, is that correct?

DOCTOR BIDAULT: Pardon me?

DOCTOR PARSONNET: One of the children with the complications had an artificial joint replacement?

DOCTOR BIDAULT: Yes.

DOCTOR PARSONNET: Did they look at the pathology of the cartilage in that child and was it consistent with what is described for the quinolones?

Did they get a look at the pathology of the cartilage in that child?

DOCTOR BIDAULT: It was a cerebral abscess.

DOCTOR PARSONNET: No, but in the joint. The child had a joint replacement, yes?

DOCTOR BIDAULT: Yes.

DOCTOR PARSONNET: Did they look at the cartilage from that child?

DOCTOR BIDAULT: It is a retrospective analysis and I have not the information for that.

CHAIR CRAIG: Dr. Leissa?

DOCTOR LEISSA: Dr. Bidault, as was stated, pefloxacin is not in use in this country. Can you give us a sense about how widely used pefloxacin is used in France?

DOCTOR BIDAULT: Well, since it has been restricted only for hospital use, its use has really decreased.

DOCTOR LEISSA: So even for adults, you are saying pefloxacin is limited to use in the hospitalized patient?

DOCTOR BIDAULT: Yes.

DOCTOR LEISSA: I see.

DOCTOR LIETMAN: But wasn't it the most

widely used fluoroquinolone for a long time in France?

DOCTOR BIDAULT: Yes -- well, if you look, it was the first marketed. So, yes, for this reason. But not yet now. Because these data are dated 2/93.

CHAIR CRAIG: Okay. Thank you very much. Next we have the open public hearing and I understand Dr. Leissa is going to read at least one letter -- instead of two now, since Dr. McCracken's was already entered by Dr. Bradley.

DOCTOR LEISSA: Dr. Schaad had been invited to come as a consultant to the Committee, and he had other obligations. And because he could not make it here today, he did send in a position statement which is in the packet for members of the Advisory Committee as well as for consultants. I will read it for the record.

The title is "Use of the Quinolones in Pediatrics." "Fluoroquinolones are now an established class of new antimicrobials. They have a suitable antimicrobial spectrum and advantageous pharmacokinetic properties. Fluoroquinolones have been shown to be effective and safe in the treatment and prevention of a variety of bacterial infections in adults.

The use of fluoroquinolones in children

has been limited because of their potential to induce arthropathy in juvenile animals. This extraordinary form of age-related drug toxicity, chondrotoxicity, has been demonstrated with all quinolones tested thus far and has led to important restrictions. However, an increasing body of data is available to conclude that the quinolone antibiotics do not cause arthropathy in humans. The clinical observations temporally related to quinolone use are reversible episodes of arthralgia with and without joint effusions that do not lead to long-term sequelae when treatment with the quinolones is discontinued. There was never an unequivocal histopathologic documentation of quinolone-induced arthropathy in humans.

On the basis of personal experience and comprehensive review of published data, I come to the conclusion that it is ethically justifiable and scientifically indicated to use selected quinolone agents in pediatric patients suffering from specific infections. At present, I recommend to approve ciprofloxacin for antipseudomonal treatment in pediatric patients with cystic fibrosis.

Further prospective controlled studies of ciprofloxacin in children should be performed for the following potential indications: complicated urinary

tract infections, enteric infections in areas with increasing multi-drug resistance, e.g., developing countries, eradication of nasopharyngeal carriage of neisseria meningitis. Other indications to be studied may include chronic suppurative otitis media, complicated skeletal infections, and neutropenia. Some of the latest quinolone compounds, for example trivofloxacin, have increased activity against gram-positive cocci, including drug-resistant streptococcus pneumoniae and a good CSF penetration. With these agents, prospective controlled studies should be approved in the pediatric age group for CNS infections, for example pneumococcal meningitis, and selected complicated ear, nose, and throat infections such as non-responding otitis media caused by multi-drug-resistant streptococcus pneumoniae.

Let me conclude my position statement with the urgent appeal that the quinolones should never be used in conditions for which other antimicrobials with established safety and efficacy are available. This is especially true for pediatric patients where in addition to development of drug resistance, there is a minimal remaining concern regarding potential chondrotoxicity as described in juvenile animals. Whenever feasible, quinolone studies in children

should include monitoring for short and/or long-term effects on the bones and joints."

CHAIR CRAIG: Thank you very much. We had no other speakers for the open public hearing. What I am going to do is take the break a little bit earlier. But what I want to do first is to see if there are any questions that anybody has on the Committee or even of our consultants of any of the speakers that have spoken before. I know Dr. Van Sickle is going to need to leave. So specifically any questions that you need to direct at him, you need to do that now so that he will be here to answer. Dr. Parsonnet?

DOCTOR PARSONNET: I'm curious about cartilage growth during serious illness. A lot of the studies in ciprofloxacin have been done on children who are quite ill, and we have not seen cartilaginous effects in those children. But my impression has been when children are that ill, they may have growth arrest and their cartilage may not actually be functioning normally. So I was just curious about what really does happen in seriously ill children and whether that might explain some of the discrepancy we see in human and animal studies where the animal studies are done in healthy animals.

DOCTOR VAN SICKLE: I am afraid I can't tell you one way or the other because we haven't done long-term toxicity studies or the animals have been ill before. So I don't know what effect that would have. And I assume you are speaking principally on growth and length here for one thing. The only thing I can say is that in our experience, we haven't seen that kind of effect on the epiphyseal plates that would inhibit their growth in length.

CHAIR CRAIG: Yes, Dr. Klein?

DOCTOR KLEIN: My question is addressed to Dr. McCloskey.

DOCTOR MCCLOSKEY: Yes, sir.

DOCTOR KLEIN: It has to do with the time limit, if there was any, for identification of an adverse effect. Was it any time in days, weeks, or years?

DOCTOR MCCLOSKEY: Carolyn McCloskey, FDA. This is a voluntary reporting data base. So whenever they want to report, they can. For the most part, my experience has been that physicians and consumers who do report tend to report it fairly soon. But if it gets to the manufacturer, they have requirements that once they receive the information, they need to report it within a certain time frame.

DOCTOR KLEIN: The other comment I have was picking up on Dr. Parsonnet's comment. I think we have to be open to the possibility that this is a multiple or multi-variable event and that it may be it is a drug reaction occurring in a compromised joint or in a joint that is prepared in some way. I wondered if there were any data that would suggest that prior viral infection or we know of the infections that are likely to localize in joints such as rubella, enteroviruses, even meningococcal infections -- whether there is any reason to think of this as more than drug localization and that there may be -- we may or may not be able to pick this up from the adverse event registry. My assumption is that you are not going to get that kind of data.

CHAIR CRAIG: I would think -- I mean, what you have to get is enough cases so you could do sort of a case control study so you might be able to see if you could identify any other risk factors. But the numbers so far described sound relatively small. Dr. Lietman?

DOCTOR LIETMAN: Well, Jerry, isn't the problem exactly the opposite? That is, they have seen it in animals and all the animals are normal animals. They aren't animals with viral diseases or with other

dread diseases. And we haven't seen it, if at all or hardly at all, in children who are sick as all get out sometimes. So it seems to me that rather than think it was a combination of a virus plus a drug, I would have thought just the opposite. In the animals, it is pretty clearly just the drug.

DOCTOR KLEIN: Or in the adverse events that are identified, that in fact it is the rubella or perhaps other --

DOCTOR LIETMAN: Oh, yes.

DOCTOR KLEIN: -- other event that is now associated with the administration of the drug.

CHAIR CRAIG: Dr. Danner?

DOCTOR DANNER: I keep thinking about Dr. Van Sickle's own injury when he was playing basketball. Some of the indications that are being discussed that fluoroquinolones might be evaluated in are where you have ambulatory children who are going to be playing basketball or playing Peewee football, and is there any indication that activity or joint trauma might increase or lower the threshold for joint toxicity? Is there any way to evaluate -- if there is no data, is there a way of evaluating that in the animal models?

DOCTOR VAN SICKLE: Well, let me come in

the back door. I had a thought -- what was your initial question? I was thinking about the back door.

DOCTOR DANNER: You know, just that some of the indications are going to be in ambulatory children as opposed to a child in an ICU, and will running around and playing basketball -- would it potentially aggravate toxicity?

DOCTOR VAN SICKLE: The only thing I can give you a one-to-one on is that the biomechanics of the joint, once the lesion is started, will spread the lesion. That is one thing. The other thing is we know like for instance with adult articular cartilage that with exercise we can improve the proteoglycans in the cartilage by as much as 25 percent. In other words, rather than having keratin sulfate, which makes the articular cartilage stiffer, we wake up the chondrocytes and they produce chondroitin sulfate, which bind more water and consequently give you more resiliency in the cartilage. So I would guess with active kids that that would be the same thing or very similar.

DOCTOR ELLIS: I would also like to reiterate that there is some nonclinical data in the dog suggesting that if you keep the weight off the joints when you are administering the drug that the

arthropathy was not as severe.

CHAIR CRAIG: That was Dr. Ellis. Dr. Azimi?

DOCTOR AZIMI: I had a question not related to arthropathy. But if we were to use the quinolones in pediatric or in anyone, as a single agent, let's say for pseudomonas infection -- this happens in our hospital often. The child comes in and has stepped on a nail and has a puncture wound with pseudomonas infection and osteomyelitis. Can it be used as a single agent without the fear of development of resistance? Maybe the consultants or Dr. Craig can answer that.

CHAIR CRAIG: There are cases described with single drug therapy, even when you've got a relatively small number of organisms with the emergence of resistance with single therapy. But clearly it is much more a problem the larger the population mass. So that is why in pneumonia and infections like that where you have got a large number of organisms, the risk of emergence of resistance with monotherapy with a quinolone is greater.

DOCTOR NORDEN: Can I just add to that?

CHAIR CRAIG: Yes.

DOCTOR NORDEN: In our animal model with

pseudomonas osteo, which is not a puncture model but it is still pseudomonas osteo, the quinolones were highly effective and there was essentially no resistance developed. I think as Bill said, it is a very low inoculant disease usually. I wouldn't like to do it -- I think with pneumonia, the risk is significantly greater that resistance would develop, as has been developed.

CHAIR CRAIG: I guess I would ask another question. Getting back to the French data with pefloxacin. Are there studies that have been done with pefloxacin in the animals that show that you can produce these effects at a much lower dose than with other fluoroquinolones? The effects in the animals -- the blisters and the pathological effects with pefloxacin as compared to the others? Does anybody in the audience have any information on such?

DOCTOR ELLIS: We don't have any of that data in house at the moment since pefloxacin wasn't approved here. But I think that there are some studies in the literature and hopefully maybe this gentleman would be able to speak to it, suggesting that it is one of the more potent -- that it is one of the more potent quinolones in animals too. Because as I hope you took away from my presentation earlier --

CHAIR CRAIG: Yes, that there are differences.

DOCTOR ELLIS: There are differences between the drugs.

CHAIR CRAIG: Yes.

DOCTOR VON KEUTZ: Eckhard von Keutz from Bio-Toxicology. I have one additional information related to pefloxacin. I think pefloxacin is one of the very few quinolones which has induced these other toxic events, not only in juvenile dogs but also in adult dogs. There is a paper in the literature indicating that a dose of 140 mg/kg in adult dogs older than 12 months induced the typical other toxic events. So I think that is a clear difference to other quinolones which are only inducing these events in juvenile animals.

CHAIR CRAIG: Okay. Thank you. Any other questions or comments? Dr. Reller?

DOCTOR RELLER: This is actually a request before the discussion this afternoon for Dr. Hopkins or Dr. Leissa. Presented this morning were data in support that there may be differences in safety of the quinolones. There are data, both in vitro and perhaps clinical, suggesting differences in activity. We also saw that the vast majority of antimicrobial usage,

appropriate or not, is for respiratory tract infections. So my specific request is when we focus the discussion, given that there has been a suggestion or even a statement that quinolones may have been, because of past policies, denied to children, is which of the quinolones in the United States is currently approved for use in which respiratory tract infections, specifically in accord with FDA/IDSA guidelines in adults as of today?

CHAIR CRAIG: I think he is referring to what might come under the pediatric rule.

DOCTOR RELLER: Exactly. I mean, if -- where do we actually stand? I mean, there has been the implication that there are -- there is a great deal of demonstrated efficacy out there that may, if the studies were done, be shown to be present for children. And I am frankly -- you know, there has been a lot of discussion of safety and toxicity. But I think we need also to consider what the data are for efficacy and what the possible need for studies demonstrating that in children may or may not be.

DOCTOR LEISSA: We will try to handle this by our accumulated memories here. I am sure package inserts will fly out of the audience here if we mispeak about whoever has what. But for

ciprofloxacin, it is approved for, as I understand it, all of the lower respiratory tract indications, including nosocomial pneumonia, but that may have not been based on what you are referring to as the IDSA guidelines in terms of what evaluability might have been set up. Because obviously ciprofloxacin was approved initially back in 1987. Levofloxacin is approved for lower respiratory tract infections, bronchitis, pneumonia, and sinusitis. And then sparfloxacin is approved for lower respiratory tract infections. And then agrefloxacin araxar, which was approved about one to two weeks ago, was also approved for community-acquired pneumonia and acute exacerbations of chronic bronchitis.

CHAIR CRAIG: And Levo?

DOCTOR LEISSA: Levofloxacin.

DOCTOR LIETMAN: Oflaxacin?

DOCTOR LEISSA: Yes, oflaxacin.

DOCTOR RELLER: Any approved for sinusitis or for streptococcus -- implicit in the question as well is for those sites of infection for pneumococci, and do any carry the designation for penicillin-resistant pneumococci?

DOCTOR LEISSA: None of them have that designation for the penicillin-resistant.

Ciprofloxacin is approved for sinusitis. And what else did someone say? And levofloxacin.

CHAIR CRAIG: Okay. Anything else? We will take our break and we will meet back here at 3:15 and start precisely at that time.

(Whereupon, at 2:40 p.m. off the record until 3:16 p.m.)

CHAIR CRAIG: Now we come to the time for Committee discussion. Let me just quickly summarize what has happened today. I think we started off this morning hearing about the previous history of this topic being discussed by the Advisory Committees. We then heard about the increasing resistance in strep pneumo and clearly the possible need for a new class of antibiotics in pediatrics. We then heard about one of the really concerning toxicities, the arthropathy in juvenile animals. We heard a lot about the pathology and the physiology of cartilage. But really in terms of hearing something about the mechanism of it, that was something that clearly is still lacking.

We then heard a lot about the uncommon association of arthropathy in humans. Probably the highest percentage seemed, at least from my overview of what we saw, to be with pefloxacin. But again, this is an association and the data bases were quite

limited. We did hear from some of the specific data bases from the companies. But again, if we look at the number of children that have been exposed, the number in very young children still is quite low. They tended to be in older children. So that tends to be an area that is still lacking.

Listening to the various consultants and also the people from industry, I think there is pretty much consensus from just about everybody that the drug should be studied in children. The question is in what way. I think there were a couple of votes that said no restrictions whatsoever, but there were other recommendations that this be done in an incremental way.

And I think that that is what we are coming now to with the first question. Of the following three options, which does the Advisory Committee recommend for the development of quinolones in pediatric populations. And let's start with the first one, which is continued restricted development only in patients with cystic fibrosis and hematologic oncologic disorders. And if there is anybody that wants to speak in favor of this approach, raise their hand. So everybody is in agreement, I would say, from the Committee that number one would not be the

approach that we would take. Okay.

Seeing no hands, I will assume that is unanimous therefore. Do you want a specific vote on each one of these items as we go down?

EXECUTIVE SECRETARY MCGOODWIN: Well, since no one spoke --

CHAIR CRAIG: Yes. Okay. It is unanimous. Good. Some could abstain you know. The next item on the list is no restrictions on the type of indications for which quinolones may be developed. Again, anybody that wants to voice this method -- and I think Dr. Lietman was one of them that commented on this earlier. Yes?

DOCTOR LIETMAN: I believe there should be no restrictions on the types of indications for which the quinolones may be developed. I think that it would be an unusual stance, I think, for the FDA to make the decision as to what can be studied. I think that if there is a possibility that the fluoroquinolones may be of value, then I believe given an acceptable feeling of safety -- and I believe we ought to have that at the moment for fluoroquinolones in humans -- I believe the drug companies should be encouraged -- not discouraged but encouraged to study the drugs for those indications.

Let me say also that I believe the pediatric rule should be very important in this issue. I believe that it should not be necessary to show that your fluoroquinolone for every indication works in children if it has already been shown to work in adults for that indication. So, for example, we heard a list of lower respiratory infections for which four or five fluoroquinolones have been approved. I would argue that for those indications, one need not show that the drug is good in children with pneumonia as well as adults with pneumonia. That if you simply show that the exposure -- that you can produce the same exposure, and if you show to some degree of acceptance that the toxicity is acceptable, then I believe you ought to be allowed to market the drug.

The question, I think, that needs to be defined by this Committee then would be how many patients have to be studied before the FDA should feel acceptably comfortable in terms of marketing the drug. Is it 100? For example, people have expressed a concern about children less than 5. Well, what should we tell the drug companies? Should we tell them that if you study 100 patients, we would allow you to market the drug if you promised to study the next 1,000 somehow diligently in post-marketing

surveillance? Should the number be 500? Should the number be 1,000? How many should it be? A number that is realistic and attainable and that doesn't simply squash research and squash the development of drug for that purpose. So I believe that number 2 is a good answer.

CHAIR CRAIG: Is there any antibiotic that has been approved for pediatrics previously that has had a question of a toxicity that might be specific for the pediatric age group?

DOCTOR LEISSA: No, I cannot think of any. The only issue that I know that has been brought up that has been a concern of being unique for pediatrics was with nalidixic acid and I believe it increased intercranial pressure.

DOCTOR LIETMAN: And that was in the immediate newborn period.

DOCTOR LEISSA: I am sorry?

DOCTOR LIETMAN: That was in the immediate newborn period I think.

DOCTOR LEISSA: And then also was raised would be the tetracyclines relative to the teeth.

DOCTOR LIETMAN: But that came after drug development. So also with chloramphemical and the gray baby syndrome.

CHAIR CRAIG: Dr. Melish?

DOCTOR MELISH: Well, I was just going to mention that pediatricians are used to avoiding certain drugs that are available for children. So that that is very much in the culture of children's medicine. Avoiding tetracycline at certain ages and being aware of special toxicities.

While I have the floor, if I do, I would like to say that I am very uncomfortable about the idea of using quinolones for otitis media in children. I think that this is an invitation to disaster. And although I am certain that in the short-term marketing, this might be worthwhile, I am very afraid that by opening up quinolones to use in pediatric ear infections, I think 50 to 75 percent of the use is probably not indicated and this is a breeding ground for resistance for the whole population which may ultimately do in the quinolones as effective drugs against strep pneumoniae. So that is my fear about what would happen if you allow number 2.

On the other hand, I don't see how we can answer the safety question without allowing research that involves no restrictions on the type of indications. Because the special serious indications that are mentioned in terms of incremental development

are quite uncommon. And to get a decent body of information on these indications would be very difficult. Whereas for respiratory infections in pediatrics, large numbers of patients could be studied. And I would just like to say at this point that I am very concerned about whether we are going to have an adequate safety profile that would tell children's doctors -- and this does include large groups of primary care physicians -- would tell children's doctors that it is safe to use these drugs in children under the age of 6.

So I would really like to see well over I would think actually multiples of 1,000 patients studied with good attention to both clinical and as much as possible MRI evidence to prove that they are not having this acute detectable cartilaginous lesion. Because as far as I know, this is a unique lesion. And if you say, oh well, lots of people will show up in later life with osteoarthritis. We don't know that this is going to be plain old ordinary osteoarthritis 20 or 40 years down the line. This could be a much more severe degenerative disease.

So I guess I am in favor of number 2, no restrictions on the type of indications provided we insist on good safety. And in a way, if we do prove

that quinolones are useful in various conditions, they will be used in other conditions if the safety is okay. So I think number 2 makes the most sense for planning development.

CHAIR CRAIG: How about from the point of view of using patients for otitis media that have failed previous therapy. In that way, one takes a chance of getting a -- at least from the puncture studies that I have seen -- a chance of getting a higher percentage of resistant organisms where one really does have the potential for needing this drug. I still think that you would be able to find a significant number of those kind of individuals and thereby still be able to study the drug but without putting it out there for everyday common otitis media.

DOCTOR MELISH: Well, I think that that is a better indication for use of the drug. But I think we have to seriously -- and probably there is plenty of failed otitis out there. But then you would have just one restriction.

CHAIR CRAIG: Any -- yes, Dr. Abramson?

DOCTOR ABRAMSON: I would like to speak to the issue of the pediatric rule and pneumonia or lower respiratory tract infections. I think lower respiratory tract infections in children, especially

young children, are very different than those in adults. We don't see chronic bronchitis. I think it is a major leap of faith to say that because it is approved for adults that therefore it will be useful and work in children.

CHAIR CRAIG: Dr. Klein?

DOCTOR KLEIN: I wanted a point of clarification from Dr. Ellis. If we were to embark on a group of pediatric studies whose major goal was to establish safety and the absence or presence of arthropathy, what survey instruments would you suggest for the arthropathy? How would you follow those children to assure that they did not have cartilage damage?

DOCTOR ELLIS: Truthfully, I don't really feel qualified to answer that question because I am not a clinician. So I don't know how one would relatively easily and ethically follow a human population. When you are dealing with animals, we get to cut them open and have a look. That is not the kind of data that we are going to be able to get from the human population obviously.

DOCTOR KLEIN: But there is a model that we might build into that, Bill. There are some kids who are having arthonoscopy. Now admittedly it is not

going to be the younger age group probably. But it is conceivable, just like we asked for say antibiotics a couple of hours before the placement of ventilating tubes to get information on middle ear levels. It is possible we can construct a model for children who are to have elective surgery in some joint -- weight-bearing joint.

But I think to a certain extent, to follow up on your point, which I agree with, we need to know what the techniques will be to follow those patients. We have to be comfortable that they are sufficiently sensitive so we haven't enrolled a large number of children and then find that the data are inadequate.

CHAIR CRAIG: Let me just interrupt a minute here. We have a message for a Dr. Richard Gural. You are supposed to call Laura immediately and I have a telephone number here if that individual wants to pick it up.

DOCTOR LEISSA: Dr. Craig?

CHAIR CRAIG: Yes.

DOCTOR LEISSA: I just wanted to comment on the issue about how to follow these children potentially. One thing that had been recommended in the -- I believe it was the 1999 Advisory Committee -- one of the members suggested that children should be

-- after receiving the drug, they should be followed for two years, presumably to look at growth charts and see if there had been any changes. I guess in retrospect, I wonder if that is really a reasonable suggestion. Because it doesn't appear that any of the toxicity is related to the epiphyseal plate. So growth shouldn't presumably be affected really as an issue. I just wanted to bring that up as something that I don't think probably should be an issue.

CHAIR CRAIG: Julie Parsonnet?

DOCTOR PARSONNET: I think one place I would like to see people start is with autopsy studies of children who have cystic fibrosis and leukemia. Because presumably a fair number of them have received ciprofloxacin or are currently receiving -- or were receiving ciprofloxacin at the time of death. Which would give you the opportunity to look at both the chronic effects on joints and the acute effects on joints at the same time.

Now that would be reassuring if all the joints looked normal or six months after ciprofloxacin and they looked normal, that would be somewhat reassuring. That doesn't necessarily say that that would be the same thing that would happen in more healthy children. But it at least would give you some

sense. And you shouldn't need hundreds of children for that. You should be able to look at children of different ages and get at least some idea.

CHAIR CRAIG: How many children would you think that have cystic fibrosis never get ciprofloxacin, which you would need for your control?

DOCTOR PARSONNET: Well, I think --

CHAIR CRAIG: I would expect it would be pretty small that you would find somebody that had never gotten the drug.

DOCTOR PARSONNET: But you could get leukemics that hadn't received ciprofloxacin.

CHAIR CRAIG: Okay. Yes.

DOCTOR PARSONNET: So I think there are enough children who --

CHAIR CRAIG: Yes, leukemics would. Yes.

DOCTOR KLEIN: But isn't there an arthropathy associated with cystic fibrosis as well?

DOCTOR PARSONNET: Right. So I think you would have to look at a variety of children to see. Leukemics who had received ciprofloxacin, leukemics who hadn't, and then cystics as well to take a look at their joints. And the cystics who had received ciprofloxacin in the distant past and the ones who had received it very recently. I think you could at least

get some sense of what was going on in the joints of these children. You wouldn't even have to do a total autopsy. You could just get the joint.

CHAIR CRAIG: Yes, Dr. Dowell?

DOCTOR DOWELL: I'll tell you what my concern is as I think about the data that we have seen today. It is with the data we saw this morning about the -- I forget what you called it, the NOEL or the no arthropathy level. There is a level in each of these animal models that you showed us below which you don't see arthropathy. It looked to me like this was an animal dependent level, perhaps a quinolone dependent level, but that this was a dose-dependent lesion.

DOCTOR ELLIS: I think that is fair to say it is dose dependent.

DOCTOR DOWELL: Okay. What I wonder then is what we are seeing in humans is the doses that we currently use are below that level. We are not seeing the lesions. How much below that level, I don't know. But I guess the concern I would have if you start to use ciprofloxacin not in hundreds of kids but in millions of kids that you would have kids who are dosed at four times what you intended or six times what you intended or even two or three times what you intended. And then those were the kids that you would

see the arthropathy. You might study hundreds and hundreds of kids who got a dose below the level and see absolutely nothing.

So I would argue for in monitoring safety being careful to get per kilogram dosages in kids who have the reported arthropathies and kids who get the quinolones and don't have the reported arthropathies and at least have an initial look at whether there is a difference there.

CHAIR CRAIG: So we have heard from Dr. Melish as far as possibly favoring number 2 with maybe a modification of looking at least in otitis with children that have failed previous therapy. And that is primarily because -- your argument is that is what you need in order to try and develop the data base?

DOCTOR MELISH: I am much more concerned that we have answered the safety question. I think it is important to answer some efficacy, but safety -- in fact, I am not -- I would like to go on record as saying I don't approve of the pediatric rule. I think we should be doing studies in children primarily and not having to do pediatric role. And I think lower respiratory infections in children and otitis media in children are absolutely unique and certainly shouldn't be making these kinds of connections. But here I

think we have to get a large number of patients. I don't think I would be comfortable telling someone about this drug unless I knew that this effect, which is seen in all species although at different dose levels, doesn't occur in the human species in children -- no one can tell us, but it does seem as if the age of about four is the age suggested. So we are going to have to look at preschool children as well as school-age children who are active in sports while they are taking these drugs.

So if we want this drug to be a useful drug that conscientious doctors will prescribe, I think we have to lick the safety question ahead of everything else. So I think we have to have big studies. And I would just like to say I think it is good to take out the growth, but blinded evaluations by people who are used to looking at joints using a protocol and MRI, provided we have got good data showing that this is the best way to look at the lesions in dogs or I think that that was what was said, would really be needed on these kids.

CHAIR CRAIG: Even requiring anesthesia?

DOCTOR MELISH: Not necessarily, but you could do that in older children. Children over the age of four are usually easier to have exams than

adults. So I think they could get along without anesthesia.

CHAIR CRAIG: Well, I don't know other Committee members, but at least to me the most concerning group is the group under five, where I think at least from experience that has been presented already the number of individuals there is very low. So that is the group that I think I would want to see information and done very well, as best one could. I am less concerned as you go into the older age groups. Dr. Lietman?

DOCTOR LIETMAN: I didn't think we had heard that MRI was particularly good at picking up the lesions. In fact, I thought we heard that several studies had been done with MRI in humans which failed to pick up anything.

DOCTOR MELISH: Well, they may not have lesions.

DOCTOR LIETMAN: Well, similarly with x-rays. And then I thought the response to --

CHAIR CRAIG: It was animals I think that Dr. Leissa commented that at least in animal models it is a useful tool.

DOCTOR ELLIS: It can be, but it is not as sensitive as actually looking at the joint. It will

pick up things like effusion. But I have talked to some veterinary colleagues and there are some lesions in the joints that are caused in the animals by these drugs that MRI is not necessarily going to pick up.

DOCTOR LIETMAN: Would MRI be better than a veterinary clinician or just looking at the dog and seeing limping? Is MRI even better than that?

DOCTOR ELLIS: That I don't know. I don't know if there are any veterinarians in the audience who might have an opinion about that. Here comes one.

DOCTOR PETERS: I am just one of the team. I am Terry Peters, Division of Anti-Infective Drug Products. I have looked at a lot of these studies and the problem is that the MRI early on doesn't really do much for you. It is not until you have the eburnation of cartilage and the collapse that that can really give you any useful information other than just synovial effusion, which you are going to be able to see clinically anyhow. And when these dogs are lame, the MRI does not give you anything predictive at all.

DOCTOR LIETMAN: So I would argue that the MRI isn't the thing to demand, nor x-rays. And I would think that the blinded clinician as Dr. Melish has proposed is the best we've got right now and maybe good enough.

EXECUTIVE SECRETARY MCGOODWIN: Dr. Craig, perhaps in terms of thinking about some of the toxicity issues, at least in terms of -- we would have to think about it in terms of working with companies to design a clinical trial. Some categories that I think seem to be relatively obvious are the issue of acute reversible toxicity. The issue of -- and how common that might be and how -- at what level we would like to be able to exclude that or tolerate that as an event. Acute irreversible toxicity. Presumably, from what we have seen to date from all the reports, that is relatively uncommon or perhaps even very uncommon. On the other hand, I think most people probably would agree that that is something we would have a very low threshold for. And as Bob Hopkins showed in his slides, if we, for instance, felt that that level needed to be below 1 in 1,000, just as an example, then you are talking in a prospective trial of having to study 3,000 patients to exclude -- you know, with a 95 percent chance -- one event. That is a big undertaking, but I think it is important to talk about.

And then the issue which we are not really sure if it is an entity or not -- perhaps irreversible toxicity occurring relatively soon after therapy

stopped, in which case we are talking about some issue of monitoring after the conclusion of the study. We have heard figures up to two years. We may very well be talking about something much shorter.

And finally the issue that has been touched upon several times and poses significant problems, and I think this is where Dr. Klein and others have talked about using data bases, et cetera, the issues of latent effects to the joint with longer term predisposition and how important that is to address and how we might deal with that.

But from our point of view in terms of thinking about the design of clinical trials and talking with companies, it is helpful to have some advice about those different issues because that is what we would confront as we were trying to set up a protocol.

CHAIR CRAIG: So, does anyone want to --

DOCTOR LIETMAN: Just a clarification. What was the evidence that the cartilaginous damage can occur after you've stopped the drug?

EXECUTIVE SECRETARY MCGOODWIN: I am not sure, sir, that there is any evidence. The question is --

DOCTOR LIETMAN: Then we don't need to address that.

EXECUTIVE SECRETARY MCGOODWIN: -- do we think that that is a concern that we need to address in a clinical trial. Normally follow-up would occur in a trial like this a couple of weeks after the conclusion of therapy roughly. And that may very well be sufficient. The question comes up -- that blends into the issue of latent injury. I am not sure that there is any evidence, but we would like the Committee to give its opinion about this issue. If everyone, for instance, agrees with what I think you are suggesting that this is not an issue, then it is something we might not worry about in the design of a clinical trial. But we would like to try to get as comprehensive advice as we can at this point in time so that we will not have to come back frequently over the next couple of years as we talk about specific clinical trial issues. I am quite happy if people have the consensus that this is not an issue. We would then use the normal follow-up that was appropriate to the study of the infection in question.

DOCTOR LIETMAN: Well, I would submit that there is no evidence for either of those and we have enough problems in areas where there is evidence. And

to deal with problems where there isn't any evidence may be going too far.

CHAIR CRAIG: Yes, Dr. Parsonnet?

DOCTOR PARSONNET: I have two comments. First of all, I agree with many of the comments that we should not have restrictions on the type of indications. I agree with that. I think it will be very difficult to do a trial for otitis media in children less than five just because there are other drugs available and there are risks that we can't quantify at this point. And to tell some parent that we are going to try to put your child on a drug for which we think there might be adverse side effects when we know that there are many drugs available that don't would be very difficult to do such a study and it would be difficult ethically to do such a study. I don't see one happening in the near future, especially in young children, where otitis media is the most common problem.

With that, I think there are some retrospective data that haven't been looked at that should be looked at, specifically on nalidixic acid, which has been used for a long time and has been used commonly in children, particularly in Navaho Indian reservations, where it has been for the last 10 years

the treatment of choice for shigella. And many of those children have been studied and have gotten courses in nalidixic acid and have never, as far as I know, been looked at or studied or evaluated for the effects of that drug. So I think there are some children that you can look at who are healthy and who have been treated in the past with a drug that may be more toxic to the joints than ciprofloxacin is and we should start by looking at those children before we start proposing studies on otherwise healthy children.

CHAIR CRAIG: Any other -- yes, Dr. Abramson?

DOCTOR ABRAMSON: Well, there is another issue that hasn't been brought up and that is the palatability of the fluoroquinolones. It is going to be tough to get them down children. Just from a practical issue of studying otitis media, forgetting other issues, I think that has to be taken into consideration. So I think there is enough of other things that we have talked about, including diarrheal disease, that we can get a good data base and we can get much more comfortable that we are today about young children.

CHAIR CRAIG: In that age group. So that what kind of numbers would you be talking about? I

mean I think the acute reversible toxicity, if you are going to pick that up, and you are using not a very common disease but a less common disease, you are probably talking about hundreds, not thousands.

DOCTOR ABRAMSON: Right.

CHAIR CRAIG: And low hundreds.

DOCTOR ABRAMSON: Yes. And things like shigella occur frequently enough and outbreaks of shigella occur frequently enough that you can get three and four-year-olds who may be able to take small tablets or such to where you can actually get that drug in.

DOCTOR KLEIN: Bill, may I ask a question?

CHAIR CRAIG: Yes, Dr. Klein.

DOCTOR KLEIN: It is just a clarification. Have attempts been made to make suspensions of the other quinolone products and failed or are they available?

EXECUTIVE SECRETARY MCGOODWIN: Ciprofloxacin is currently available in a suspension dosing form. I don't think we have any reason to believe that there are technical obstacles to the creation of a suspension dosing form.

CHAIR CRAIG: Dr. Bradley?

DOCTOR BRADLEY: Two observations. First

I think that it actually won't be that difficult to enroll children in a study of otitis media, particularly if they are enrolled after having failed the first round of antibiotics. And that is based on the paper that just appeared in CID looking at 7,000 cases. It is not enough to reassure me that the drug is going to be safe, but it is enough to reassure me to tell the parent that this is worth studying. I think the risk is low, but we are going to be doing all of these tests on your child and let them help make that decision with you. But I think the data can be collected.

Dr. Van Sickle and I were talking about the possibilities of taking sera from these children and hopefully finding some marker of joint inflammation that would hopefully predict the toxicity. There is urinary tubular enzymes that are present in all aminoglycoside-treated children. It is such a sensitive test that it is too sensitive to predict toxicity. I know he is working on a marker and probably a number of pharmaceutical companies are working on a marker. But if we could correlate the marker with histology and MR in an animal and can hopefully use that in children, it would be an easier way to follow toxicity, just like we get liver

function and kidney function tests on every child treated.

And the second comment I wanted to make has to do with -- if we do any kinetic experiments in kids with gastroenteritis, it is not likely to represent serum levels of drug that you would achieve in a child without gastroenteritis. And there is nice data to show that increasing your GI transit time decreases your absorption with many antibiotics.

EXECUTIVE SECRETARY MCGOODWIN: Do you think that that would be an issue then in terms of the usefulness of that particular patient group for a safety data base if the systemic exposure is likely to be decreased?

DOCTOR BRADLEY: In gastroenteritis, I don't think the safety data would --

CHAIR CRAIG: It becomes inefficacy.

DOCTOR BRADLEY: Right. Efficacy would be okay, but safety I wouldn't trust.

CHAIR CRAIG: Yes, Dr. Norden?

DOCTOR NORDEN: The more I listen, I find myself thinking that probably option 2 is going to be the way to go. But I think that we have hinted around and I guess based on Dr. Leissa's presentation earlier this morning, I think we need at least 1,000 kids

under the age of 5 with the incidence of arthropathy that was predicted, if occurs, to be comfortable. To do that, I think you have to -- you are not going to find it in meningitis, osteomyelitis, septic kids. I don't think you are going to find enough. I like Marian's suggestion that otitis should be restricted to kids who have failed. I think it also makes it more likely that they are a difficult population to treat than every kid who has otitis. And I think that I would go more now toward option 2, even though I initially thought I wasn't -- I was clearly favoring incremental development.

CHAIR CRAIG: Yes, Dr. Leissa?

DOCTOR LEISSA: When we were formulating these questions, one of the concerns we had was relative to number 2 and 3 in that if one would recommend incremental development, one might take the strategy of, fine, let's get some more data from children with severe infections. And if everything looks fine, then we could go into more garden variety infections. Yet the concern is -- and some of this is based on the preclinical showing that animals who are suspended who don't have or aren't using their joints are less likely to show the arthropathy. The concern would be is if you are treating hospitalized

infections, severe infections, and these were not ambulatory children, and at the end of this you didn't have any arthropathy whether you would say, fine, we can go ahead. Obviously if you saw something then that would be important. But if you didn't, you may not be any closer to addressing the issue of whether you should be able to pursue otitis media.

CHAIR CRAIG: Very true. Dr. Parsonnet?

DOCTOR PARSONNET: That was somewhat of my point with the gastroenteritis. I still think there is value in looking at those patients. Because it is true if you find nothing then it doesn't tell you for sure what is happening. But if you find something, I would be pretty concerned. So I think that there still is merit in looking at that since it is being used for that purpose and trying to evaluate what is happening in the long-term with those children.

CHAIR CRAIG: Getting back to your osteomyelitis. If this is really dose-related, that is a disease where people would get it for a long time. But even if you got every single kid, it would probably take a huge number to still be able to do it. So I agree with you it is hard in these other more severe infections to see that you could get a large enough population base that you would be able to feel

comfortable in terms of those potential side effect. Dr. Parker?

DOCTOR PARKER: I'm not sure that I am going to agree with you about this huge number to make some kind of decision. I refer to Dr. Hopkins, I believe, paper on showing that we can make some judgments on a sequential basis. That is, using his numbers -- I don't have my calculator -- if we were to run 300 patients and we didn't see any ruptured Achilles tendons -- 300 I think I could find in almost or in a lot of these categories -- then I would be 95 percent confident that the incidence is less than 1 percent. If I want to restrict it further, you know he has got some other numbers here that we could use. But I think that we could make some decisions as to, gee, it is not really a big number, on a relatively small number of patients -- say the 300 -- restricting it to 1 percent. What I am not hearing anybody tell me, and once they would tell me that then I could go to my computer and give you some numbers, is how many ruptured Achilles tendons are we willing to tolerate? 2 percent? 5 percent? One in a thousand? Give me the number you want to tolerate and I will tell you the number of patients you would need to have a certain probability of detecting it.

CHAIR CRAIG: And a lot of that --

DOCTOR PARKER: But, you know, I haven't seen any -- one, how much we are willing to go with, and two, from the data I have seen here, I don't have a good estimate of what that prevalence is or the incidence would be.

CHAIR CRAIG: And I think a lot of that would depend also on the situation. If resistance continues and the only drug one has is the fluoroquinolones and the alternative is death, you could tolerate a lot of ruptured Achilles tendons.

DOCTOR PARKER: Statisticians don't make those equivalents.

CHAIR CRAIG: Dr. Azimi?

DOCTOR AZIMI: So it seems like a group of severe nosocomial infections in children under 5 years of age, which we see not really infrequently -- a variety of infections, osteomyelitis and endocarditis -- quinolone seems to be -- by susceptibility testing seems to be a drug that you can use and other agents are not so much available -- multiple resistant organisms. I think that would be the population where there is definite clinical indication. It would be easier ethically also to use this agent in that population rather than otitis media even after one

failure where we still have other alternatives. And I think this could be done on a multi-center trial and reach the numbers that you are talking about.

CHAIR CRAIG: Yes, I think the -- just again, the question that Dr. Leissa brought up earlier is that those are primarily hospitalized patients that aren't going to be that active. And the question is if you need activity in order to really manifest the toxicity, we might not see it in that population.

DOCTOR AZIMI: You mean the movement of extremities and so forth?

CHAIR CRAIG: Yes.

DOCTOR AZIMI: I think a lot of that could be evaluated.

DOCTOR LEISSA: Yes. It was a weight-bearing issue in the animals.

CHAIR CRAIG: Dr. Rodvold?

DOCTOR RODVOLD: Well, I think that -- you know, I am tossed between 2 and 3 here. But what I am hearing and I would like maybe for other people to see if they are hearing the same thing, is that there is this age around 5 or less that we don't have much data on and that we are really uncomfortable and then someplace after 5, we have got a different comfortability level. And then what numbers you need

to study that. The same thing kind of holds up with whether or not you have children that are ambulatory and maybe more weight-bearing versus in-patients that may be less weight-bearing, and does that influence your selection of number or your safety evaluations. And those two issues get to be then what studies and what indications do you go to get the answer to what issue you are looking for. Because will you answer your safety question with in-patients versus out-patients? Will you answer the same question on in-patients of less than 5 or on in-patients greater than 5 years of age. So I think you've got a couple of things that we are in the dark with that may influence this type of thing.

With that, if you can take those variables and account for them and put them in, then maybe 2 is reasonable.

CHAIR CRAIG: Dr. Abramson?

DOCTOR ABRAMSON: I guess what I am missing here is the compelling reason not to do it step-wise. For the diseases of otitis media or sinusitis, we have alternative antibiotics. For diseases of pseudomonas of a nail through the foot where you can keep a child out of the hospital, we don't have that kind of alternative. So if we can

sequentially do this -- get the data even with a few hundred patients -- that makes us feel more comfortable in those less than 5, I don't hear the compelling argument to do it all at once. It is not to preclude doing it down the road, but there is a level of safety that one gathers by doing 200 or 300 patients.

CHAIR CRAIG: I guess one of the things that I might raise and I think somebody else raised this as well is that there is a lot of off-label use of the drug already. And if it is already being used out there and people are being exposed, shouldn't we have the obligation to try and at least collect some prospective data that will help us really identify whether this is a population where we should be a lot tougher and put out the word that they shouldn't get the drug as compared to letting it continue to be used off-label for a long period of time, potentially exposing a large number of kids to a toxicity that with prospective data we would be able to identify.

DOCTOR ABRAMSON: Well, if I can answer that, I think the off-label use in pediatrics is clearly not in otitis media. It is not in sinusitis. It is in chronic draining ears due to pseudomonas. It is for the nail through the foot. And these are the

things that you would be studying, where it is being used. At some point -- I think at some number of patients, you may well expand it out. And though I have some trouble with that, I have less trouble -- my trouble with that revolves around the issue of resistance and ruining an antibiotic. It is a different question at a different time.

CHAIR CRAIG: Okay. Dr. Lietman?

DOCTOR LIETMAN: My answer would be that the reason not to do it incrementally is time. That that will be slower and furthermore it will send a message to the pharmaceutical industry that there will be delays and that there will be restrictions on your development of the drug, which I think will simply deprive kids of the drug for years younger. So I think the reason not to do it incrementally is it sends the wrong message and it will delay the development of drugs.

CHAIR CRAIG: Dr. Henry?

DOCTOR HENRY: Well, I have been mulling this over and I looked at the material that was so nicely sent to me that I had to drag back with me to D.C. But one of the things that I was so sure of when I got here last night was that the third option was really the best way to do it and it is greatly

influenced by my concerns about having quinolones be used for the respiratory tract indications that as pediatricians we are all very much against. But after listening to all the discussion, I think that there is no way you can get beyond the fact that you have to have the safety data. So it means sort of allowing pharmaceutical companies to go ahead and develop the drug for other indications only to get the safety information, knowing that once those indications have been studied, that information is there and it will most likely serve as a marketing tool. But as you have pointed out, the fact that the drug is out there for a number of different off-label uses, that at least we would have more information to know just exactly what we are doing. And the population of kids that are getting it off-label primarily are the CF kids and the leukemics. I mean, I have used it in those settings myself, though not in kids under 6. But the problem in looking at those kids is that even the leukemics -- I mean, when you think of all the other drugs that they are getting, there are drug/drug interactions. You don't really know what the pharmacokinetics are. So if you find joint abnormalities on the articular cartilage surface, do you really know that it is going to be ciprofloxacin?

The CF kids, what is there metabolism of the drug? I mean, some of them their GI transit time is so fast that are we really having a reliable population of patients to know that the quinolones were there in sufficient concentration to cause those problems. So we really are stuck looking at patients who are by and large healthy and have no other factors that are going to obscure the results. And then once we have safety data, we are going to have to decide now that we have these indications, are we going to let a pharmaceutical company actually have an approval for that indication.

So I think right now if I had to choose, I would have to say number 2, primarily because of the safety issue taking precedence.

CHAIR CRAIG: Dr. Norden first and then Dr. Bradley.

DOCTOR NORDEN: I want to come back to what Dr. Parker said, though. I mean, one of my reasons for saying that I thought you probably needed to open it up to many indications is the sample size that you would need to demonstrate convincingly safety in a population under the age of 5, where I don't think we have the data now at all.

And although I agree with Paul that time

is important, if a sample size of 300 really gives the numbers here and if someone who is skilled at statistics like Dr. Parker tells me that is fine, I am more comfortable in saying you could easily do it incrementally and in a reasonable period of time and you don't have to bring in kids with otitis media necessarily. So I think sample size does become a real issue. At least for me, the only reason to open it up wide was to achieve a larger sample size.

CHAIR CRAIG: But again, we are talking a sample size of ambulatory people and a sample size of hospitalized-prone individuals. They may be two different things in regards to this toxicity. Dr. Bradley?

DOCTOR BRADLEY: In trying to answer some of Dr. Abramson's questions, the data presented by Dr. McCloskey this morning on ciprofloxacin prescriptions written shows that in 1995, 2,000 were written in the age group 0 to 1 year, and in 1996, 12,000 were written. Now these aren't being written for kids with CF and they are not being written for kids who stepped on nails, because they are barely even walking. What are they being treated for? And who is treating them?

DOCTOR LIETMAN: And wouldn't it be better to get information from those rather than no

information?

CHAIR CRAIG: Dr. Leissa?

DOCTOR LEISSA: Obviously the challenge for the advisory committee in making recommendations is trying to put a handle on how much information we actually have. The way we typically acquire information is obviously through protocols that are done under an I&D and they are usually done specifically for an indication. But there are also compassionate use protocols that go on for other products where any patient that would receive the product would somehow become part of the data base. This can be a broad kind of treatment I&D that can occur.

So I guess that is one avenue potentially to consider which would be that where one perceives that the quinolone will be used or somehow that you can still try to capture that information and that it not be specifically in one of the typical well-controlled clinical trials for an indication.

CHAIR CRAIG: Well, let me bring up another point in terms of looking at it from an incremental form. It is the question of at least limiting the diseases that are going to be looked at to those diseases which are due to organisms where the

fluoroquinolones are needed. And looking at them as another alternative for uncomplicated urinary tract infections as a first group to look at right from the very beginning would not be the group that I would pick. But I would pick the group that has otitis media that have failed other therapies because the general trend is for those organisms in terms of their MICs to other drugs to be getting worse and that we may need these drugs in the future. So that would be a group that I would include in the study, but not for uncomplicated urinary tract infections. I think we have plenty of other agents and the need to use quinolones in that group is not there.

So I can see an incremental approach from looking at the organism, but I feel that you need to get in both the ambulatory patients as well as the others in order to get the data and also to use it in the patients where these drugs will eventually be needed a year or two down the line. Dr. Melish?

DOCTOR MELISH: Well, actually I was very reluctant to endorse number 2 because of all of the things that have been said, but I can't imagine a clinical trial that would -- maybe it can be developed, but would companies support a well-controlled clinical trial in which the safety issue

was addressed? That means at each institution you have to have a rheumatologist or a person trained in joint evaluation who is going to look at it blindly and things like that. So that is not likely to happen if you just -- every severe case that might need a quinolone. That is going to show up in different institutions with limited numbers of patients. I am afraid you are not going to be able to address the safety issue. And that is, I consider, the most important thing here is addressing the safety issue. Efficacy can only be addressed for an indication if you are able to mount a large number of patients. If they think they can design a trial where multiple, multiple indications at multiple centers could be studied well for safety, I would be comfortable with incremental. But otherwise, I am afraid you need to get numbers. And I would still think it needs to be in excess of many thousand or several thousand patients. Because I think what we want to know is that there is no joint involvement due to the quinolone. If there is, we are going to go for other drugs.

CHAIR CRAIG: Well, but I mean if we are running into that area where we are not going to have other drugs.

DOCTOR MELISH: Well, it is less than 1 percent.

CHAIR CRAIG: Then it is a different story. Yes, Dr. Parsonnet?

DOCTOR PARSONNET: I think naturally this is going to be incremental.

CHAIR CRAIG: Yes.

DOCTOR PARSONNET: I think just right now there is already a substantial amount of data that has been collected on seriously ill children. The first place that people are going to really be successful in getting these drugs approved is going to be for seriously ill children. And then we are going to get more experience with that and it is going to be naturally incremental. I would like to see things move forward very quickly on that because I think that there are a lot of children who could probably benefit from quinolones who are not in academic centers and whose physicians should know that they can use those drugs safely in children who are seriously ill.

EXECUTIVE SECRETARY MCGOODWIN: If I could just follow up on that?

CHAIR CRAIG: Yes.

EXECUTIVE SECRETARY MCGOODWIN: I think that it is clear that when we talk about incremental

here, there are a couple ways of looking at it. Perhaps a clarification would be helpful. I think what Dr. Parsonnet has said is correct. As a practical matter, of course development will be incremental since we are not going to have companies coming in for every conceivable indication at the same time. However, there is the issue of incremental development based solely on how things happen to come in and perhaps incremental development based on what you had said a few minutes ago, Dr. Craig. Differentiating development based on need versus development based on activity. I think those two are very different. It is clear that the development will, in fact, as a practical matter be incremental. The question is whether it should be incremental based on some level of need versus the fact that the quinolone is active against that particular organization or likely in that infection. That would be helpful to get some advice on that.

CHAIR CRAIG: Okay. Dr. Reller?

DOCTOR RELLER: To follow up on that. As I have been listening, it seems like there has been a subtle transformation where the objective has become to demonstrate safety as opposed to looking at those components perhaps of common infections, the less

common ones, where all things considered there seems to be a sufficiently compelling need that would override the concerns for safety. In some ways, we are sort of dancing around the issue. I mean, if we really don't think there is any problem with safety, you throw open the door to number 2 and let developmental market conditions decide what protocols are going to come forth.

I agree with Dr. Melish's earlier comment. I would think for the public's health it would be a disaster to have the multiplicity of quinolones used in the 24 million patients treated with otitis media with something currently. I don't think there is a demonstrated need for that. But the FDA can't consider need. They have to consider safety and efficacy. So it seems to me that unless we really have no concerns for safety, we ought to have a focused approach -- incremental or however you want to put it -- to delineate those infections where there is sufficient return in terms of information to be able to use the drugs appropriately that would suspend, at least temporarily, until the data were in hand -- suspend the concerns about safety to allow us to get the data in the most controlled way possible. So that I think that there should be -- and we can do the

focus of discussion about what components of common infections and which less common infections would be appropriate to study. Because safety, it seems to me, can span indications. I mean, you can get safety information from a multiplicity of multiple studies looking at efficacy. Whereas efficacy can only come from singular indications, one by one. So in the aggregate, the needed components of the more common, as Bill has pointed out -- those who have perhaps failed otitis media -- and the other indications where these drugs may fill a niche where we don't have other drugs in the aggregate could provide a data base for safety as opposed to simply going with number 2, that I don't favor at all, of simply having no restrictions and let nature take its course.

CHAIR CRAIG: And I think -- at least I would think -- and I am just asking the members on the Committee, but I think most of the Committee members at least are talking about some form of incremental involvement, whether it is looking specifically, as you say, to diseases where it is going to be needed or those that would give us the best information in terms of safety of the drug as compared to just throwing it open. Am I right on that? Seeing everybody's eyes -- so at least we are somewhat with 3 but not necessarily

where we are starting just in the most severe infections and moving to the milder infections. I think there is some feeling, at least for some people, that some other individuals should be included.

So the question is -- if we go to 3, then the next question is specifically what indications should be studied first?

DOCTOR RELLER: Bill, are you sufficiently clear on that? I mean a modified 2 and an expanded 3 look pretty much the same to me. I mean as worded it is pretty clear. No restrictions versus some restrictions -- fewer or more. Do you want to vote and get this clear so we know exactly what we are working on?

CHAIR CRAIG: Dr. Abramson?

DOCTOR ABRAMSON: Can I make the point that if you are talking about -- and I could certainly live with it -- when you are talking about restriction to somebody who has failed initial treatment, are you talking about only failed one drug, two drugs? I mean, there are many, many kids who go on three drugs to clear up an otitis. Are you talking about failures defined by 14 days -- of developing disease again in 14 days or after 3 days and no improvement? Those are things that you have to define.

CHAIR CRAIG: If you can give me which ones give the highest yield for the organisms for which the drug might be useful so that I could get the efficacy, that would be the ones I would look at.

DOCTOR ABRAMSON: Well, I think we were talking at lunch that the point is that a lot of kids who fail at 14 days really have simply a second infection. Kids who fail at 3 days and who have to go immediately onto another drug are much more likely to have failed on the basis of antibiotic resistance or non-compliance or issues like that.

CHAIR CRAIG: But let's get back to Barth's question, and I guess the question is whether number 3, instead of calling it incremental development of indications is some restriction in the diseases that are actually studied. Is that more what --

DOCTOR RELLER: Well, I mean a pure 2 is no restrictions. 3 is an open discussion of where trials might be beneficial for the health of children.

CHAIR CRAIG: That is what the second question is once we get to 3. I guess I would ask is anybody in favor of no restrictions at all for number 2? Raise your hand. Okay. So that leaves number 3.

DOCTOR LIETMAN: We can't vote as

consultants.

CHAIR CRAIG: You are not voting. Sorry, Paul. Not even with both arms.

DOCTOR LIETMAN: But I have to say this is micromanagement. And furthermore, I am not even sure it is within the FDA's province to decide what can be studied and what can't. That is, if there is a possibility that the drug works, that --

CHAIR CRAIG: From a safety issue. I mean I think the whole point that this Committee has been saying is the reason that we feel that we are not going to number 2 is because there is a question of safety with this compound.

DOCTOR LIETMAN: You are doing the same thing you did five years ago.

CHAIR CRAIG: And we feel that the population that this might be even a higher incidence in has not had a large enough number of individuals studied.

DOCTOR VAN SICKLE: You are doing the same thing you did five years ago.

CHAIR CRAIG: Dr. Reller?

DOCTOR RELLER: I had thought that it was not only the province but it is the responsibility of the FDA to actually approve all studies in patients

done in this country. Is that not true?

EXECUTIVE SECRETARY MCGOODWIN: It is not -- in other words, there are certain circumstances under which a clinical trial could be conducted without ever referring protocol to the FDA. This does not fall into those certain circumstances, however. There are some circumstances where that can occur. But here clearly this would be something we would need to review the proposal for the clinical trial. Obviously there are concerns that have existed going back years to 1989, 1993, and now about what we understand to be the safety versus the possible benefit. The fact that we are having the meeting today is a recognition of the fact that we think circumstances may have changed somewhat since 1993.

Nonetheless, there is a concern that in certain circumstances the lack of safety information as we understand it today would make it inappropriate at present to conduct a clinical trial in that indication. I mean that is an issue that at least we think we need to confront. Now if we say there are no restrictions on the types of indications, then in theory companies, presuming that the drug has activity and presuming that they have done appropriate pre-clinical information and say it is no different than

other fluoroquinolones, would be permitted, for instance, tomorrow if they had the appropriate information and perhaps the appropriate formulation to begin a study in routine otitis media. That no restrictions in essence means they would go ahead and do that and we would find that appropriate, only having to work out certain things with regard to the numbers.

There are some concerns whether that course of action is something that is appropriate and that is why I had specifically mentioned otitis this morning in terms of the kind of advice we would like from the Committee as to whether this is an appropriate thing to do. If the Committee feels that this would not be safe, then that is something that we could tell companies that it was not appropriate to do at this time.

CHAIR CRAIG: Dr. Parsonnet?

DOCTOR PARSONNET: I guess there are two levels of question. One is would it be inappropriate because it is not safe? And the second is would it be inappropriate because when you come to us 3 years from now with your results, it is very unlikely that it would be approved for that indication because there are a lot better drugs for it that may have better

safety profiles? So I guess there are two questions and what is our role in respect to both of those questions?

EXECUTIVE SECRETARY MCGOODWIN: Well, let me say this. I think we always have to be cognizant -- to address really the second point first -- we have to be cognizant of the perspective from the industry. It would be unreasonable to tell the industry that it is fine for you to go ahead and do a clinical trial on uncomplicated otitis media with X numbers of children. That we will obviously be very interested in the safety data that is generated as well as the efficacy data from that trial. But of course even if nothing untoward occurs which is certainly possible with those numbers, we would probably not approve it because we are still concerned that the drugs might be unsafe. I think we could not really tell companies that that is what was going to happen. We need to have an agreement going into such a trial that if they do it and if the efficacy is there and if we do not see anything out of the ordinary, that that would be sufficient for approval even if there are better products out there on the market. That is something that we could discuss in more detail, although I don't know that this is the right venue. But we are not in

the business of saying because something else may be preferred, you cannot be approved. We can put a proviso in the label if it looks like there are some differences in activity between the comparator arm, et cetera, but I think we can't be in the position like that.

We are more concerned here with whether or not the safety information as we understand it now might raise concerns about doing that. We would like to get your advice about it because I think that questions like this are most appropriately handled with input from an independent body as opposed to our making a judgment ourselves internally, which we could do but I think is not as preferable.

CHAIR CRAIG: And I guess I would respond to Dr. Lietman in terms of his response that we are doing the same thing as before. In terms of toxicity, there has not been a lot more information that has been learned since the last time outside of that the drug appears to be safer in older children. But again, the very young ones is still a group in which we don't have the data. What has changed and the reason why I think it is appropriate for this committee to relook at it and start identifying groups that it should be studied in is that the organisms are

changing and clearly this drug may be needed for organisms that in the past it might not have been needed for. So it is important to go ahead and do those studies.

DOCTOR LIETMAN: There has been a change. You have more data. You may not have enough in the age group that you are interested in. The best way to get that is to allow unrestricted study of that.

CHAIR CRAIG: No.

DOCTOR LIETMAN: Yes.

CHAIR CRAIG: There is a difference.

DOCTOR LIETMAN: It reminds me of a saying of my favorite professor of pharmacology, Dr. Talalay, who said there are so many questions we don't know in medicine that it is really premature to practice medicine.

CHAIR CRAIG: Dr. Klein, you had a point?

DOCTOR KLEIN: I had three points that aren't necessarily the same, but I think they come to the same conclusion. One is there are a lot of kids who have been treated under 5 years of age. These data add up to 54,000 children under 5 years of age having received ciprofloxacin. Presumably that would be the vast majority of quinolone usage. As far as we know, there hasn't been any ripple among

rheumatologists or orthopedists that they are all of a sudden seeing a burst of children with joint manifestations. That doesn't help, but I think it suggests that whatever safety study we feel comfortable with is going to require large numbers. We are not going to get away with a couple of hundred on the basis of no real blip on the screen from this data base, inadequate as it is.

The second thing to keep in mind is even if we started tomorrow, to get a sufficient number of cases is a three to four-year period before a drug would be established as effective and as safe and possibly effective.

The third point is if you are going to study it for severe otitis or otitis failures, you accept that the drug is going to be used for otitis. Because by progression, it would mean that it faced a challenge of the failures and worked. Therefore, it would be an effective drug for those initial cases as well.

So I think that those are all steps that you have to enter into with your eyes open. That it is going to take a long time. That if otitis is the disease area to be studied then in fact it is going to get an otitis approval. And that may or may not be

the way that you want to enter. But I don't see another cohort of children that would yield 3,000 cases, which I think is probably what you are going to require to get over the hurdle of safety.

The safety issue is a perception one. We feel uncomfortable because we don't have an adequate data base. The data that are available are inadequate, but they don't suggest that there are large numbers -- 2 per 100,000 may in fact be reality. But I think to get this to the point in the year 2001 where we may be faced with a more significant pneumococcal problem, then we have to begin thinking of a study of safety and efficacy in an area that likely will be approved if it is established that the drug works and is safe.

CHAIR CRAIG: So I guess the question we are at right now is really number 2. At least that is what I thought we got to. And that is, which indication should be studied first?

DOCTOR MELISH: I was going to say that I am still uncomfortable with this issue. I am not willing to say that I am against option 2 until I see what is practically possible within option 3. Because I really think we need to answer the safety question. Whether these drugs are used a lot in kids will

probably depend a lot on resistance and we don't know where we are going to be in the future. So I am not willing to say that I am against 2 until I know whether we can do good studies quickly with 3.

CHAIR CRAIG: Okay. I guess the questions would come up -- which indications, if someone does want to do number 3, are we going to recommend. We have heard recommendations earlier for some of the more severe infections -- meningitis, pneumonia, sepsis, bacteremia, complicated urinary tract infections, osteomyelitis I think was another one.

DOCTOR KLEIN: I have three that I think would be suitable and by enrolling the appropriate institutions, one could see a light at the end of the tunnel. One would be chronic suppurative otitis media that comes to eye and ear hospitals. So it is not just the draining ear. It is the kids who appear to have tissue invasion. The second is from the same eye and ear hospitals, external otitis with tissue invasion. And the third would be recurrent and severe otitis. I think you could get numbers there. And I would add the others to the data base, but I would restrict the number of investigators and the number of institutions that are involved and try to get their recent experience, so at least you know the numbers

that are likely to be accrued over the next couple of years. But I think having recruited that group and established -- and it has to be randomized because there has to be a control that will be equally evaluated. That you recognize that you will have an otitis media pool.

I used to say it is like the Defense Department has plans for invasion of Grenada and I stopped saying that because of the reality, but it happened.

CHAIR CRAIG: So you would limit it to that group?

DOCTOR KLEIN: No. I think that would be the largest pool of patients.

CHAIR CRAIG: Yes.

DOCTOR LIETMAN: And if we are talking about recruiting a couple thousand children, recognizing that it has to be randomized and there has to be a control group. So your numbers even are larger than you would have anticipated just on the basis of quinolone-treated children alone.

CHAIR CRAIG: Any other suggestions of diseases that we have or is it sort of that group that we have that are already the hospitalized patients that have serious infections? To me the organisms

that I am most concerned with are the pneumococcus, and especially with the gram-negatives, the extended spectrum beta-lactamase producing organisms where are organisms where I think in the long run we may eventually need these drugs. Dr. Bradley?

DOCTOR BRADLEY: Well, I think investigating both hospitalized patients with parenteral quinolones with the indications that you listed, that is easy. I think the drugs are necessary and the risk/benefit ratio is much more in favor of therapy. In terms of the otitis group in terms of getting safety data with oral therapy, I agree entirely with Dr. Klein. I think otitis represents one of the largest groups of children who receive oral therapy. I think the safety issue -- if the safety issue can be solved by one, two, or three thousand patients, then if the drug is approved for use in otitis, then it is our job as clinicians to teach our colleagues when and where to use these drugs. The safety issue is the one that worries me the most. And if it is safe, then it is our job to put it in perspective as second line or third line or whatever.

CHAIR CRAIG: And I guess the question comes back again to the various forms of toxicity. What sort of toxicity are you willing to tolerate in

terms of acute toxicity or chronic toxicity. And I think what Dr. Melish is most concerned about is the latent effect on joints, which is a topic that is going to be very difficult to sort out and be able to obtain data. Yes?

DOCTOR ABRAMSON: As far as the latent toxicity, I saw us hold up the varicella vaccine with that being one of the main concerns, and I cannot see that as a reasonable reason. 40 years down the road just cannot be a reason to hold up this drug.

DOCTOR MELISH: Well, I would have to say I completely disagree. The only reason we are concerned about safety at all is because we have evidence that in every species looked at, an irreversible cartilaginous lesion can occur depending on the dose and the species. If an irreversible cartilaginous lesion can occur, it is very likely that is going to cause problems down the line and we can't even anticipate what they are like. So I think that is a reason for being strict in this case. If we saw acute joint problems similar to the beagle dog, then I think it would be -- I personally would teach and avoid use of quinolones until there was no alternative. Because I am concerned about what a child of 5 is going to be like when they are 40 or 50

or something like that. I think this is a unique sort of toxicity, and that is really why I would like to get a large enough number of cases. I would be willing to go for incremental use if companies and others would tell us that they are willing to -- I mean, to look at the hospitalized patients. There is no hospital that is going to have a large number of these except for the CF clinics. And certainly in the CF clinics, they can be taught to do good joint evals by whatever means we want. But as far as chronic osteo and hematologic things, you would have to have so many institutions that it would be hard to do an adequate control trial with a good look at the safety.

So I guess that is why I am holding it up at all. I mean I have been tempted to use quinolones in children with chronic draining ears and have been stopped from doing -- or mastoiditis -- stopped from doing it because of worry about what they would be like when they were 40 or 50. So if the FDA or the industry can say that it is easy -- or it would be possible to design a multi-condition trial in which safety would be looked at, then I would go for limited indications. Otherwise, I think you would start having to get into otitis.

CHAIR CRAIG: Yes, Dr. Azimi.

DOCTOR AZIMI: I wanted to come back to Dr. Klein's comment and the categories that you mentioned about studying -- chronic suppurative otitis media or draining external otitis and so forth. If you select several hospitals to do these studies and you either prove or disprove any kind of problem with safety data, you are going to get an indication for otitis media and the drug is going to be used for otitis media. So why not just use it in otitis media and get your safety data right from the beginning. The difference is your 2,000 or 3,000 patients. That is it.

DOCTOR KLEIN: I think the reason is probably the indication in these selected groups is more presentable to a parent that this child does have a likelihood in the first two cases -- the chronic suppurative and the external otitis -- of having a pseudomonal infection. So at least with those two, which will not be the larger proportion of numbers, we have a basis for the specific use of this drug. The recurrent and severe otitis I think is another issue where we are using it because it may have failed because of bacterial resistance to others. So I prefer to have the population be the one who would be most benefitted from the use, and I think that those

three would be. I can make at least a rationalization to myself that there is reason for the special use of this agent rather than one of 14 drugs that are approved for otitis media.

CHAIR CRAIG: Dr. Reller? Because I am going to take some votes here in a minute. Go ahead.

DOCTOR RELLER: I would like to strongly endorse this focused approach that Dr. Klein has mentioned. One of the benefits seems to me is that if tolerable safety were demonstrated in such patients, the more complicated patients in general would be treated by investigators or enrolled by investigators who might, because of past experience, more carefully gather the data that we really want or we also want having to do with safety. And that any indication that might come out of that would be for the population studied -- the complicated, the refractory, et cetera. It wouldn't preclude down the line practitioners from using it in acute uncomplicated that we have heard earlier, many of which don't need anything and for which there are many other agents. But at least you wouldn't start out with that population and then have the extrapolations potentially going the other way for which there are not the efficacy data, if that is the way the trials

would turn out.

So it seems to me that a measured, responsible, detailed, careful documentation of both efficacy and safety in that population would be the way to approach this issue.

CHAIR CRAIG: And not look at it in other situations?

DOCTOR RELLER: No, no. Not precluding those, but that they would be additive for the safety. But the recognition that the numbers may not be there or the difficulties in interpretation with absorption of drugs and diarrheal disease. That sort of will take care of itself. But these would be a reasonable balance between numbers and responsible need that would be a reasonable way to start out with increments to that based on what the population numbers are and what the perceived need is.

CHAIR CRAIG: For those that have done those kind of trials, what kind of numbers do you think you could get with that? I mean just so that the rest of us know what number of outpatients one would be getting with recurrent otitis.

DOCTOR KLEIN: I think it is a question of dollars and investigators and on how fast a track you want to achieve it. But recurrent and severe otitis

media or otitis media failures are about 5 percent of all otitis. So it is not -- you know, you are getting down to a child in each of the first three years of life has one episode. So you need a population that is going to have -- that is 12 million episodes a year just in kids under 3 years of age, 5 percent of which would be eligible.

CHAIR CRAIG: 600,000.

DOCTOR KLEIN: And then I would have to go to the Mass Eye and Ear Infirmary and other like institutions to see their experience with the chronic suppurative otitis. Because we know that just a draining ear is not what we are talking about. We are talking about tissue invasion as well as the malignant external otitis. But I would bet that those institutions that gather cases from a large area would see 50 to 100 cases a year. If you have a handful of those over a two or three-year period, you would probably get a substantial number.

CHAIR CRAIG: Now your otitis studies in adults -- you really don't have any, but let's say what kind of numbers would you normally have if you were comparing it with another agent to show similar? Would you get 200?

DOCTOR LEISSA: Probably going into -- the

issue would be of being able to have adequate power to base equivalents on a 95 percent confidence interval and the issues there would be how many patients were drop-outs, et cetera. But I would think in general that 200 patients would be adequate for that.

CHAIR CRAIG: Per arm. And then you would need two studies. So that you would be getting up to somewhere around 400? I mean, the second one would need to be comparative if I remember right.

DOCTOR LEISSA: Right. Typically -- at least the way the points to consider addresses it for the second study. That would be the uncontrolled microbiologically-driven study where it is just all micro-data, much smaller.

CHAIR CRAIG: So you might get up to somewhere in the range of 350 to 400 patients with such studies. Yes?

DOCTOR PARSONNET: The numbers you are talking about though are for efficacy and not for safety. And I would think that for safety reasons -- for issues of safety, you would need a lot higher numbers than that. Because for otitis media, you would want the risk to be quite low for any therapy that you would want to give somebody -- 1 percent. With that number, 1 percent would be high.

CHAIR CRAIG: But I guess the question is that in some of these situations, it may be a relatively low incidence. It may be actually in post-marketing where one obtains that kind of data. It may be difficult to get that many enrolled in initial trials.

DOCTOR LEISSA: The only way to address that is if multiple indications are developed at once.

CHAIR CRAIG: Right. Yes.

DOCTOR LIETMAN: Dr. Parker told you if you tell him what incidence you are willing to put up with, he can then tell you how many patients you are going to need to study to rule that out with 95 percent confidence. Isn't that what you said?

CHAIR CRAIG: Sure. That is why I was trying to get -- our number was less than 1 percent if we had none.

DOCTOR LIETMAN: So why doesn't the Committee try to tell him what percentage they want to be sure to rule out?

CHAIR CRAIG: Well, I will start off unless somebody else wants to. Dr. Danner?

DOCTOR DANNER: I actually had a different question. How long do these patients need to follow them up to determine that there is not some sequelae

that occurs later in terms of the joint? And in terms of the length of time that you are evaluating, what is feasible? We clearly want to encourage development of these drugs for use in pediatrics. So we don't want something that is punitive. But we want to get the correct answer.

DOCTOR LEISSA: You are raising the question of how long to follow relative to the joint toxicity?

DOCTOR DANNER: Yes. Do you need to redo an examination or at least do some kind of questionnaire and ask if there are joint problems a year later or three years later?

DOCTOR LEISSA: Sure. Maybe that is part of question 3 in terms of -- we are really asking you what your recommendations are to us about what kind of safety follow-up should occur relative to the joint issue. I don't think we know.

CHAIR CRAIG: But let's get back up to number 2. Julie, did you have a -- so I think what I would like to do is try and -- I think we have one proposal of at least to include chronic suppurative otitis, external otitis, and recurrent otitis media as one of the data base. That group, at least from the studies we have, would probably get up to about 400

patients, which would tend to be mostly in that young age group? The otitis would be, but how about the --

DOCTOR KLEIN: The chronic suppurative and the external otitis would probably be a minority of the patients that are seen at Mass Eye and Ear, but we would have to get the numbers.

CHAIR CRAIG: But at least with over 300 patients in that area, we would be able, if I remember what Dr. Parker said before -- if we had no cases, we would be less than 1 percent. Is that correct?

DOCTOR BRADLEY: A point of clarification. In studying children who have failed treatment with otitis media, there is a large group of children who come in with a bulging erythematous TM who are given antibiotics and 48 hours later still have persisting high fevers and on recheck the ear drum is still bulging and red. And that is the group where the clinician will switch antibiotic therapy.

CHAIR CRAIG: So we can say recurrent or persistent?

DOCTOR BRADLEY: Right. It failed therapy. A child who has failed initial therapy. So that selects out for the higher likelihood of a drug resistant organism, but it is a different group and much more prevalent than the group with chronic

draining suppurative otitis.

CHAIR CRAIG: Okay. Well, let me start first and see how many people are in favor of studying that group. I don't want to limit you to those numbers right now, but let's just talk about that group of patients with chronic suppurative otitis, external otitis, and recurrent otitis as one of the groups in which quinolone should be looked at. Okay. It looks all but Dr. Azimi. Any comments?

DOCTOR AZIMI: Well, I don't know why we are not including in there other serious infections where --

CHAIR CRAIG: We will come to those. We will do those too.

DOCTOR AZIMI: This would be just one part of it?

CHAIR CRAIG: This would be like the more outpatient group.

DOCTOR AZIMI: Okay. You can count me in.

CHAIR CRAIG: Okay. So it is unanimous in that. And then I guess the question comes also that they wanted to know -- and I guess that really comes under 3. We can get into the questions, but we might touch on it here. Would the numbers that would normally be generated in a trial which would bring

about 350 patients in from this group be sufficient for an initial look? We would obviously get other patients from other indications. Or do you think the number needs to be larger in this group as well? Are the numbers okay? All in favor of the normal numbers, which as we said would probably be in the range of 350. Raise your hands if you are for it. If you are for more, we will take another vote.

DOCTOR DOWELL: May I ask a question?

CHAIR CRAIG: Yes.

DOCTOR DOWELL: I am not sure I understand the gist of the question there.

CHAIR CRAIG: The question is whether you feel that you need to look and restrict the possibility of having this to even less than 1 percent. That you feel that you need to have arthropathy developing to be even -- find it even at a lower percentage, which therefore then is going to increase the number of people that you would have to have safety data on.

DOCTOR DOWELL: I felt like one of the goals was to collect data both on efficacy for otitis media, which you are designing a study to do, and also on safety that would reassure you a little bit. It seems like we have seen safety data on trials with

more patients than that even already and that adding another 350 patients, would that really give people more reassurance that there is not cartilaginous toxicity with the quinolones?

CHAIR CRAIG: What we haven't seen, and again I may be wrong in this, is data in that age group where it has been objectively assessed, even if it is only clinical, which is our best tool, in people of that age group. The data at least that was presented for ciprofloxacin had a relatively small number that were in that lower age group where they were assessed very regularly for any changes. So I think that is the reason. Looking at an age group or at least diseases that is in the age group where we are most concerned by the lack of data. But the question is how many people would one feel comfortable looking at in that age group in order to feel like you are starting at least to make it such a relatively uncommon problem that the ratio between the need for the drug and the toxicity start to fall in favor of using the drug.

DOCTOR LIETMAN: But screw up your courage. Gary Tide has pointed out to you that 15,000 kids of this age apparently have had prescriptions written for ciprofloxacin and we don't hear shouts and

hollers from him.

CHAIR CRAIG: But you also commented about how poor that data is in the past.

DOCTOR LIETMAN: Well, but it is not going to be that far off. It is not going to be that there is an incidence of 1 in 100. If 15,000 patients have gotten the stuff and --

CHAIR CRAIG: But again, the population that has not been looked at, as was mentioned earlier, is the people that have been probably getting that drug, which are the people that have been in the hospitals, not the patient that are out in ambulatory and especially with these particular diseases. So it is looking at a different group, we think, than what we have data currently available. Yes, Dr. Melish?

DOCTOR MELISH: I think it is absolutely critically important to have the clinical evaluation by a blinded expert reviewer. I know, for example, that arthritis occurs in 35 percent of patients with Kawasaki disease because I have had the advantage of doing that or evaluating those patients with an expert rheumatologist. This is nothing -- no one else has seen that many cases of arthritis in patients with Kawasaki disease, but they unquestionably are there. So what you have is practitioners giving out this drug

and not necessarily noticing whether or not the children are not walking or not using a limb or that sort of thing. So I think it is very important to see how well the studies are designed. I am not at all -- I think it is not just a question of we don't look at the children under 5 at all. We haven't looked at them in a systematic fashion. Even the older children I am not so certain have been looked at in that effective a fashion.

CHAIR CRAIG: Right. And as I say, that is one of the things we will be covering in the next question, looking at a little bit more specifics. But I wanted to get back again to whether people feel a level of less than 1 percent is a sufficient value for trying to look for, and what we would be looking for in this disease would probably be acute potentially reversible toxicity or a more chronic toxicity that may last for a period of time. Obviously such studies would be very difficult to design for looking at the later part, which is 20 years down the line. Yes, Dr. Parsonnet?

DOCTOR PARSONNET: I think for hospitalized children, I would accept higher than 1 percent. But for healthy outpatients, I think 1 percent is too high.

CHAIR CRAIG: So you would want to see more patients?

DOCTOR PARSONNET: Yes, I think so. There are alternative drugs for this and there are alternative therapies and these are healthy ambulatory children who you are saying you may be causing serious injury to joints. I would want less than 1 percent. 1 percent is 1 in 100 children might have adverse effects of this and I think that is too high.

EXECUTIVE SECRETARY MCGOODWIN: Again, as we spoke earlier, we are obviously interested in getting recommendations to distinguish arthralgias, which may very well occur in any clinical trial, from something more severe. And then I guess if you are talking about 300 children, you are talking about the more severe arthropathy, still only excluding it at around a 1 percent level. As to whether everyone is comfortable with that.

CHAIR CRAIG: But I mean the question is later down as time proceeds, we may have the need for these drugs where it almost becomes like the situation in the hospital where the need outweighs the risk. And the question is do we wait until that occurs or do we go ahead and study now so that at least we have some idea of what that is going to be when and if we

need these drugs more extensively.

DOCTOR PARSONNET: My own personal feeling about it is you start the study now and if the risk gets higher, then you change your cutoff. But you don't put the cutoff now for an anticipated change in risk that hasn't occurred yet.

CHAIR CRAIG: Okay. Now I guess -- there was a whole list of a variety of different, more hospital-associated infections that one could also include and obviously should include in these. Are there any that members on the Committee feel shouldn't be studied? I think the ones that we had there were recurrent urinary tract infections, osteomyelitis, pneumonia, meningitis, sepsis, and infections like that. Are there any that specifically should not be or should be restricted from being studied if the sponsors so wanted to do it?

DOCTOR BRADLEY: Septic arthritis?

CHAIR CRAIG: Septic arthritis.

DOCTOR BRADLEY: I think that might impair the assessment of joint toxicity.

DOCTOR KLEIN: I think the wider the net you throw -- you have to look at each option. I would be concerned only with meningococcal disease as a cause of meningitis with its own arthropathy and

arthritis. So that I would probably not choose meningococcal disease because of that variable that would enter into the analysis.

CHAIR CRAIG: But how about from the point of view that if we continue to see penicillin resistance occurring that might be a disease in which the use of the drug might be very appropriate. And for that reason, efficacy data should be obtained.

DOCTOR KLEIN: Well, I think you could approach it by other techniques. I would like to have more pharmacokinetics. I would like to know in infants an appropriate dosage schedule, diffusion in to spinal fluid, diffusion in to middle ear fluids. So I think there are parallel studies that are tangential to the central focus of the safety issue that should be encouraged.

CHAIR CRAIG: Any from any members of other potential diseases that they would restrict which would be of the variety that we have talked about already? I am not seeing any. So I think that at least in terms of restriction, it is primarily -- we have got a group that we are telling you would be the group from the outpatient area of the diseases that we would look at from the more severely infected patient and looking at the variety of diseases where

the drug clearly could be very beneficial outside of the possibility of bacterial arthritis. That those diseases would be acceptable to be studied. Julie, were you about to say something? Okay. Yes, Dr. Reller?

DOCTOR RELLER: The position that we have come around to, it seems to me, is a reasonable balance. Because the message is that if there be a body of patients where there is a use indication that that would be reasonable to add incrementally for the safety issue. But to start with the more complicated patients where the aggregate numbers would be far more than we have seen so far in the younger age group with the cystic fibrosis patients and the hematology oncology patients presented earlier. And in a controlled situation that would provide better data, far better than the 54,000 youngsters that we saw earlier that is totally uncontrolled. And what that means is anybody's guess.

CHAIR CRAIG: Another possibility. Now, is it efficacy in the more complicated patients, the 350, 400 that have been discussed, and one can only put a statement that if there be joint problems that they are in the order of one percent or less, whatever the appropriate figure is from the statistical analysis,

to put that in, I mean if it comes to an indication later to put it in, that this has been studied in more complicated patients, and in those patients it was, you know, an estimated incidence of under one percent, or between whatever the confidence limits were. So that, you leave open whether or not with less serious infections, if these were, you know, if the drug were used in those patients in the future, whether or not there may be a frequency that was under one percent but still may preclude the appropriate indication for that drug if you weren't willing to tolerate that list, in other words, to look at it carefully, get the best information we can, and then to say where we stand, and we may know more down the line but it's a place to start, and I think an important place to begin documenting what the real risk may be in these younger children in a controlled way, data that we currently don't have.

DOCTOR LEISSA: Doctor Craig?

CHAIR CRAIG: Yes.

DOCTOR LEISSA: On the less severe list, obviously, is community acquired pneumonia, and I'd be interested in whether the committee believes that this might be an important indication to pursue because of the potential role of the quinolones in atypical

pathogens, some of their activity there, where there might be value in seeing those developed at this point.

CHAIR CRAIG: Any interest from the committee? Doctor Melish?

DOCTOR MELISH: I would not be interested in studying that at this time. There are lots of other options. It's difficult to say, you'd have multiple pathogens.

I would like to add one, though, to the severe ones, and that is MAI infections in children with HIV. I think that's a place where quinolones are used a lot.

CHAIR CRAIG: Just for my own information, from the pediatricians, community acquired pneumonia, is that, I mean, in adults, obviously, for many patients it's an out-patient disease, does it become more of an out-patient disease the older you get, the younger you get it tends to be one that you'd pick up more in the hospital?

DOCTOR ABRAMSON: One of the issues is that it not only becomes more in-patient the younger you get, but it also often is more viral, and so you are treating a lot -- now, the big ability to make the diagnosis for bacterial infection, you are treating a

lot of viral infections.

And, the second thing is, as I said, I think it's a very different disease than the adults have. There are occasional cases where you know it's pneumococcal pneumonia and we have lots of options for that.

CHAIR CRAIG: Did you want to say something?

DOCTOR AZIMI: Well, the community acquired pneumonia in children, the organism it differs in different age groups, and if we are going to do this for safety purposes this is one thing, because you hardly ever know what organism you are dealing with.

So, from the standpoint if efficacy it's going to be extremely difficult.

DOCTOR GOLDBERGER: Could I just ask you about a couple other indications, the less severe?

CHAIR CRAIG: Yes.

DOCTOR GOLDBERGER: I'll just ask them altogether, acute sinusitis, streptococcal pharyngitis, uncomplicated UTI and uncomplicated skin, is there any -- what's the feeling about those right now, in terms of studying them?

DOCTOR ABRAMSON: I'd really like to take

on streptococcal pharyngitis.

CHAIR CRAIG: Yes.

DOCTOR ABRAMSON: Love to take that one on. I think there's absolutely no indication for it. There are a slew of drugs, which most of the time should just be penicillin.

DOCTOR GOLDBERGER: You understand, I'm obliged for a variety of reasons to ask these questions.

CHAIR CRAIG: Yes.

DOCTOR GOLDBERGER: Just to be on the safe side.

DOCTOR --: Do you want to vote? Well, if the committee, if no one is speaking up in favor of any of them, I would accept that as the will of the committee. You know, I'm quite happy with that.

Is it the sense of the committee that those were not appropriate, you feel, at this time, if that's what everybody thinks?

Then, I would like to ask -- come back to acute otitis media. The sense I get then is that at this moment in time that is not -- you do not feel that's appropriate. I wanted to ask a couple things about that. Is that because of the risk to the children enrolled in the clinical trial, or is to the

consequences of what might happen if a product was, in fact, labeled for that indication in terms of actual usage? I'd just like to distinguish that because it's helpful to understand that.

CHAIR CRAIG: Nancy, go ahead, start off.

DOCTOR HENRY: For me it's more an issue of what it would be labeled. I guess I can sort of, you know, accept the fact that if it's been tested in chronic suppurative otitis media things, a failed antibiotic course for acute otitis media, I mean, I can rationalize and feel comfortable ethically and morally giving that kid a quinolone, but, you know, I guess I would be afraid that if it was studied in that population it would be a whole lot easier to get the indication and market it, and I think that would really lead to some abuse. So, I'd have to accept sort of this, you know, approach where we are looking at it for something just a bit worse than acute otitis media that could respond to, you know, many of the other drugs available.

CHAIR CRAIG: And also in my mind, also to provide data, efficacy data, for those organisms where the fluoroquinolones may be needed, so that by looking at those that have failed or have recurrent infection one has a higher chance of having some of the

resistant organisms there and so one can get that needed efficacy data for those organisms.

DOCTOR GOLDBERGER: Okay.

I had wondered, just in passing, if, for instance, one were today to do a clinical trial of a fluoroquinolone against high dose amoxicillin in routine otitis media, how the fluoroquinolone would really stack up, because although it would work presumably well against those few very resistant organisms one wonders if, in fact, it would work as well against the rest of the pneumococci, whether, in fact, it might not turn out to be somewhat inferior, whether or not that's worth studying, and whether that result would be important in terms of what actually goes on in the community, as opposed to how a product is labeled, I'm not in a position to say, but I did want to just raise that at least in passing.

CHAIR CRAIG: Yes, Doctor Klein?

DOCTOR KLEIN: The answer is that it probably would turn out, as the other multiple agents have turned out, it would be equivalent. And, part of that is built into the numbers issue, that 60 to 70 percent of kids with acute otitis media resolve without antibiotics, so you are focusing on a relatively small group.

I think I'd just reiterate what was said, I couldn't go to my Human Studies Committee to get approval for a drug of potential toxicity for a disease that spontaneously resolves in 70 or 80 percent of the cases.

DOCTOR GOLDBERGER: So then, let me just ask so we have this information should we get inquiries from the industry, what, if anything, would it take to change your opinions about doing a study then in acute otitis media?

DOCTOR KLEIN: I think the responses that you have established, that in the worst case you are getting efficacy, then it's a slam dunk that you could do a study in one season that would establish its general applicability for all acute otitis media.

I think you are placing worst case scenario, and if it turns out to be effective then for less severe cases it is most likely going to be equal or better.

CHAIR CRAIG: But, you are looking at, first of all, of course, getting an adequate safety database.

DOCTOR KLEIN: You need that, yes, that's right.

CHAIR CRAIG: Doctor Bradley?

DOCTOR BRADLEY: Your question was originally whether the concerns were more for safety or more for drug resistance, and I think, the answer is yes and yes. From my standpoint, safety is the overriding concern, and if safety is proven then I'll let it go out into the community for acute otitis media and we'll try and teach the doctors not to use it for every ear infection that comes along.

However, Doctor McCracken feels very strongly that he doesn't want fluoroquinolones used as primary therapy for otitis media because of real fears that it will be used inappropriately and indiscriminately, and that especially in day care centers that you'll have spread of resistant organisms which then go to the adults, and it will be a very difficult time for the fluoroquinolones.

CHAIR CRAIG: Okay.

I guess the last part of the question, question number three, I think is fairly -- the first part of it we can add right away, does the committee believe the safety profile of quinolones for adults and children differs significantly for arthropathy? And, I think, at least from what I heard from everybody, is we don't know. And, I think we can't answer that yes or no, at least from the feeling I've

been getting from everybody, and that's why the need for getting safety data is important. Am I right in that, as far as the members?

So then, it comes to the last part of it, if so, how does the committee recommend that the FDA address the concern? In other words, what specific clinical testing, duration of exposure, and we've touched a little bit on the size of the pediatric safety database, but if people want to comment a little bit more, does anybody from the committee or any of our consultants have suggestions as to specifically what kind of studies need to be done?

Doctor Norden?

DOCTOR NORDEN: I think we are lacking the information, and I think that information is available and it's probably available with skilled rheumatologists. I mean, the veterinarians here couldn't really answer how they would approach it in humans, and it seems to me that if you describe to a skilled rheumatologist, who is particularly interested in cartilage, what the lesions are, that they should be able to tell you what the best way to do this is, apart from the general clinical exam done by an expert rheumatologist. And, I think it would be a waste of time, personally, for us to try and answer that now,

because I don't think we have the expertise.

DOCTOR DOWELL: I have a --

CHAIR CRAIG: Yes, Doctor Dowell?

DOCTOR DOWELL: -- suggestion on the safety issue. Just to come back to what I was discussing before, I think a lot of information could be gained by a carefully conducted case control study, comparing cases of patients who have arthropathy, reported even if it's two per 100,000 controls who had received a similar quinolone and have not developed arthropathy, comparing the dose that those two groups of patients received, comparing the ages of those two groups of patients, comparing the history of weight bearing on the joints during the administration of the drug. So, I think there are data out there, as Doctor Klein said, that could be collected that would help to address some of the concerns about safety relatively easily.

I also wanted to say a little bit about Doctor Goldberger's question about efficacy, because as I mentioned I think earlier the DTSB Therapeutic Working Group registered concern about recent approval of otitis media drugs because they felt that these drugs were approved without showing that, in fact, the drugs that were approved were not efficacious against

pneumococci, and so knowing that there are fluoroquinolones that are more active against pneumococci and less active against pneumococci I would hope that in considering application for otitis media that there would be careful consideration about the in vitro activity against pneumococci, and also microbiological efficacy of pneumococcal eradication.

CHAIR CRAIG: Proven and not presumed.

DOCTOR DOWELL: Yes.

DOCTOR GOLDBERGER: Well then, let me ask a question then related to that. In terms of both getting efficacy against pneumococcal isolates and also to get a better understanding of the overall safety profile of the drug, do you think it would be preferable that a drug that is to be developed with quinolone in children be something that has already been approved for indications in adults?

We are operating under, though, that would be the assumption, because we have many quinolones out there, but there is nothing to say that future quinolones now under development could not be developed in parallel for both adults and children. The question comes up, given some of the uncertainties at present, whether that's prudent or whether a drug should have been evaluated in adults. There are a

number of indications, for instance, where activity against pneumococcus would be assessed, plus some general information on safety before one goes into children. And, that may be something in terms of thinking about the safety database.

It occurs to me that that may be something worth discussing, or at least getting a little advice about, because that issue may come up to us.

CHAIR CRAIG: Any suggestions from the group? I mean, obviously, I would think that if you don't have a large database, like you obtain, I mean most of the time you are up somewhere probably about 3,000 to 5,000, that what we've been talking about, if someone wanted to just develop something for otitis media, and you would be talking about 350 cases, I would think you would clearly want to get a larger database than that before it could be approved for just that one indication.

DOCTOR GOLDBERGER: Yes. The other thing is that even though a total application, if it had adult and pediatric indications simultaneously, might have a relative large amount of data, it would, of course, not have the post-marketing experience for certain less common adverse events that might otherwise be detected. That would be the other

advantage of --

CHAIR CRAIG: Of doing it with adults first.

DOCTOR GOLDBERGER: Yes.

It would be helpful if we could actually get, not that this issue has come up, the committee, perhaps, on record about this point, if people wouldn't mind voting or expressing a little more of an opinion about it. It is concern of mine that this may happen in the future, and I would just like to get a good sense of that.

CHAIR CRAIG: Well, further, I guess we should probably discuss it a little bit further, so I guess the question is, should a -- could a drug be approved for pediatric indication without being initially approved for adults. Doctor Klein?

DOCTOR KLEIN: We've been discussing a drug that's been used in 7 million or some huge number of patients and feeling a level of concern for the use in children, and we haven't been able to get over that hurdle, so I think that I would suggest that those drugs with sufficient experience be the first to be considered candidates, rather than talk about a new drug with almost no or limited adult experience.

I think it would probably be one of the

those first things first issues.

CHAIR CRAIG: Barth, you look --

DOCTOR RELLER: No, I'm just listening.

CHAIR CRAIG: Any comments from -- how many people would be in favor of having it developed before it's developed in adults? Anybody?

DOCTOR LIETMAN: Well, yes, I'd like to go on record as saying that I think there are some diseases that are unique to pediatrics, and the drugs that have a possibility of being used for those diseases should be developed in children before adults. And, I see no reason that if there is a disease that is -- even if it's not unique in pediatrics, if it's primarily in pediatrics, that we should be developing that drug very early, if not first, maybe in parallel, or maybe very closely behind development for adults, to avoid what's happened in this case, which is years after the drug is used widely in adult medicines people are still arguing about whether we can even study it in children. And, that's got to be avoided.

CHAIR CRAIG: Doctor Melish?

DOCTOR MELISH: Well, I'd like to say that I agree with Doctor Klein as far as drugs that have already been evaluated. We've got the experience in

adults. We should use the ones that are most efficacious.

But, when he's talking about future development, certainly in situations like we are talking about, otitis media and community acquire pneumonia in children, I don't think it's fair to extrapolate from adult data, and I think that our children are losing out if they are not enrolled early in studies. This one has a particular safety issue that raised a question, but as a routine I don't think we are doing any good by protecting children from research. They are not necessarily getting to benefit from research.

CHAIR CRAIG: I guess in my own mind, too, I can't see a reason not to develop a drug in pediatrics if that's where the indication is primarily going to be, it's not going to be in adults, but I also have trouble thinking nowadays of an infection that one would go after that would be primarily just in the pediatric age group, outside of otitis.

And, I think if you did develop something that was just simply for otitis, because it's not a very common disease in adults, I think most people are going to go after sinusitis, they are going to go after community acquired pneumonia, they are the same

organisms, and so then I think you start getting into the adult population, so I don't see the situation occurring.

But, I wouldn't, at least to my mind, I wouldn't say that it couldn't be done if there is a sufficient database that's presented.

CHAIR CRAIG: Doctor Parsonnet?

DOCTOR PARSONNET: I agree with everything you just said, and I think there have been some drugs for infections that have been largely tested in children, like libroviron, for instance, and so I think -- which is specifically for an infection that infects children more than adults, and so I think that there may be circumstances under which you'd want to do that.

I can't think of it with fluoroquinolones, but --

CHAIR CRAIG: Yes?

DOCTOR HENRY: I guess I would just like to see them be investigated concurrently. I mean, I think you increase your pool of data lot faster if you would include both kids and adults, but I don't think that you always have to do adults first, but for most of these drugs you'd be using them in kids and adults, and you would have all that information, and just to

do both of them concurrently.

CHAIR CRAIG: Okay.

Have we answered the questions that I think that -- Doctor Leissa?

DOCTOR LEISSA: I guess what I heard as a response to question number three is that here in the room we don't have the expertise really to answer what kind of clinical assessments should be done.

However, I think I did also hear, though, some negative comments about --

CHAIR CRAIG: Following growth.

DOCTOR LEISSA: -- well, following growth, and also the MRI may not have a place, because --

CHAIR CRAIG: Well, that was the information that was presented to us, I don't think that is personal information from the committee members. So, I think, again --

DOCTOR LIETMAN: But, it's information based on the literature.

CHAIR CRAIG: Yes.

Barth?

DOCTOR RELLER: I'd like to reemphasize a point made by Doctor Melish earlier, and that is, if a relatively small number of studies, at least initially, are done under highly controlled

conditions, that there be built into those studies some long-term follow-up, because I think it would be a missed opportunity not to look at that very closely over time, I mean to keep in the database and have access to what happens to those children years later, because if we don't capture that now, we'll never have the long-term follow-up in a controlled way.

CHAIR CRAIG: Would you be happy with a telephone call, how they are doing once a year?

DOCTOR RELLER: Something.

CHAIR CRAIG: Something.

Okay. Doctor Hopkins, do you have --

DOCTOR HOPKINS: How long?

DOCTOR RELLER: Well, we don't know, but I just don't think from the pathology -- I'm not sure that everything that might be amiss with cartilage is going to be picked up, you know, with what's seen acutely, and the usual short-term follow-up.

CHAIR CRAIG: I think the easier you make it, the easier it is to go longer. If it's a relatively simple thing like a phone call, that's obviously something that's easy to continue.

On the other hand, if it's bringing the individual in doing an exam by a rheumatologist that starts to make it very costly and starts to, you know,

make it more difficult to do. So, I think you have to decide what you are trying to gain from the long-term follow-up, in terms of information. Is the patient going to be good enough to describe, at least in my mind, that's what we are looking at, is something that's going to affect the patient and maybe they are going to get osteoarthritis relatively early. I think the patient is going to probably come up with some complaints earlier than what they necessarily are going to be using an exam to find something early.

CHAIR CRAIG: Doctor Melish?

DOCTOR MELISH: Well, I don't know who would do this, but I think here is where you really would like to know what happened to the patients who got nalidixic acid, either in the trials in the Indian Reservations with enteric infections, or the people who got it 20 years ago in neonatal units and other places, but that's a quinolone, that's a quinolone that's very toxic to dogs at least, one of the things that raised the question, but that's a retrospective study.

However, those patients are out there ten and 20 years along.

CHAIR CRAIG: Doctor Leissa?

DOCTOR LEISSA: Just so the committee has

the information, nalidixic acid, the marketing company for that is Sandofi Pharmaceuticals, and it is still currently being marketed, the suspension, and I asked last week about what are their projected sales and they said that they are around $1 million a year in suspension. So, it still is being used, but it's not a large market for them, they are not doing anything in terms of promoting it or advertising it.

CHAIR CRAIG: And, they are not currently collecting any data, there's not any post-marketing data that you are doing?

DOCTOR LEISSA: Well, they would only be collecting the typical adverse event data to be spontaneously submitted, but there have been no big flags, red flags.

CHAIR CRAIG: Okay.

Any other comments or anything that anyone wants to bring up?

Okay. I'd like to thank -- what?

DOCTOR GOLDBERGER: One more thing. I wanted just to thank everyone.

CHAIR CRAIG: Okay.

DOCTOR GOLDBERGER: I think that --

CHAIR CRAIG: I was going to do it, too.

DOCTOR GOLDBERGER: -- your -- actually

was quite helpful in terms of -- I think in spite of Doctor Lietman's comments, I'm sorry he's already left, I think we probably have advanced from 1993 until now in terms of some things to do in terms of development.

I also want to take the opportunity to thank Ms. Fogarty, who, not only did all the administrative work prior to setting up this meeting, but actually, perhaps, more importantly, operated all the audio and visual equipment all day, without the slightest problem, so she never called any attention to herself, which is ideal from the point of view of that type of work.

CHAIR CRAIG: And, I'd also like to thank all of our consultants for spending their time and helping the committee with this difficult problem.

Thank you very much.

(Whereupon, the meeting was adjourned at 5:25 p.m.)