FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PEDIATRIC ADVISORY SUBCOMMITTEE

OF THE

ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE

8:15 a.m.

Monday, March 3, 2003

Advisory Committee Conference Room
Food and Drug Administration
5630 Fishers Lane
Rockville, Maryland

ATTENDEES

ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE MEMBERS:

MARY GLODE, M.D.
University of Colorado Health Sciences Center
Children's Hospital of Denver

ANTIVIRAL DRUGS ADVISORY COMMITTEE MEMBERS:

JAN ENGLUND, M.D.
Children's Hospital and Regional Medical Center
Seattle, Washington

COURTNEY FLETCHER, PHARM.D.
University of Colorado Health Sciences Center
School of Pharmacy

LAUREN WOOD, M.D.
HIV and AIDS Malignancy Branch
National Cancer Institute

CONSULTANTS: (Voting)

ELLEN GOULD CHADWICK, M.D.
Northwestern University

PATRICIA CHESNEY, M.D., Meeting Chair
Professor of Pediatrics
University of Tennessee College of Medicine

DAVID DANFORD, M.D.
Associate Professor of Pediatrics
University of Nebraska Medical Center

ROBERT FINK, M.D.
Chairman, Department of Allergy and Pulmonary Medicine
Children's National Medical Center

NORMAN FOST, M.D., M.P.H.
University of Wisconsin Hospital

RICHARD GORMAN, M.D., FAAP
Pediatrician
Pediatric Partners

ATTENDEES (Continued)

CONSULTANTS: (Voting) (Continued)

MARK HUDAK, M.D.
Professor and Chief
Division of Neonatology
University of Florida at Jacksonville

ROBERT NELSON, M.D., PH.D.
Associate Professor of Anesthesia and Pediatrics
Children's Hospital of Philadelphia

KEITH RODVOLD, PHARM.D.
Consumer Representative

VICTOR SANTANA, M.D.
Associate Professor
Dependent of Hematology/Oncology
St. Jude's Children's Research Hospital

JOHN SEVER, M.D.
Children's Hospital National Medical Center

GUEST SPEAKERS: (Non-voting)

LYNNE MOFENSON, M.D.
National Institute of Child Health and Human Development
National Institutes of Health

BENJAMIN WILFOND, M.D.
Bioethics Research Section
National Institutes of Health

GUEST INDUSTRY REPRESENTATIVE: (Non-voting)

STEVEN SPIELBERG, M.D.
Johnson & Johnson Pharmaceutical

ATTENDEES (Continued)

FOOD AND DRUG ADMINISTRATION STAFF:

MELISSE BAYLOR, M.D.
JULIE BEITZ, M.D.
MIN CHEN, M.S.
TERRIE CRESCENZI, R.PH.
SOLOMON IYASU, M.D.
LINDA LEWIS, M.D.
DIANNE MURPHY, M.D.
SHIRLEY MURPHY, M.D.
THOMAS PEREZ, R.PH., M.P.H., Executive Secretary

ALSO PRESENT:

JAMES OLESKE, M.D., M.P.H.

C O N T E N T S

ISSUE: ANTIRETROVIRAL DRUG DEVELOPMENT
IN HIV-INFECTED AND HIV-EXPOSED NEONATES

C O N T E N T S (Continued)

ISSUE: PEDIATRIC UPDATE

P R O C E E D I N G S

(8:15 a.m.)

DR. CHESNEY: Good morning. I think we're ready to get started. I wanted to welcome everybody here this frigid morning.

We're gathered today to discuss the issue of the need and importance of continuing to request pharmacokinetic and safety studies of antiretroviral drugs in infants under 28 days of age, as I understand it. If the recommendation is to continue to study these agents, the FDA has asked us under what conditions they should be studied. That will take up most of the day, and then we'll have two other topics I believe at the end of the day.

Before we do the introductions, I wanted, for the benefit of the committee, to try to clarify for you, as I think I have clarified for myself, all the changes in the office, and Dianne is probably also going to review that. But I think it bears repeating for all of us. We can't hear it too many times.

But Dianne, as you know, is going to speak next, and she's the Director of the Office of Counter-Terrorism and Pediatric Drug Development within the Center for Drug Evaluation and Research.

Dr. Shirley Murphy is now the Director of the new Division of Pediatric Drug Development. Shirley, can

you put up your hand? Okay.

Dr. Susan Cummins is the lead medical officer in the Division of Pediatric Drug Development. Susan?

And Rosemary Addy is the project manager in the new Division of Pediatric Drug Development. And Rosemary has just stood up.

So Rosemary Roberts, who we're all familiar with, is now on temporary assignment with Dr. Dianne Murphy. And as they joke in the group now, they're looking for Rosemary Murphy. She will have an instant job.

(Laughter.)

DR. CHESNEY: You have to be either a Rosemary or a Murphy to work in the new Division of Pediatric Drug Development.

So I think the first order of business is for us to go around the room and introduce ourselves. Let's start with Ben.

DR. WILFOND: I'm Ben Wilfond, a pediatric pulmonologist with the National Human Genome Research Institute in the Department of Clinical Bioethics. And I'm here as -- I'm not quite sure what exactly I am.

(Laughter.)

DR. CHESNEY: It's a good way to start.

DR. MOFENSON: I'm Lynne Mofenson. I work in the Pediatric, Adolescent and Maternal AIDS Branch at the

National Institute of Child Health and Human Development, and I'm here to talk to you about perinatal transmission this morning.

DR. SPIELBERG: I'm Steve Spielberg, Vice President for Pediatric Drug Development at Johnson & Johnson, representing PhRMA.

DR. GLODE: I'm Mimi Glode and I'm a pediatric infectious disease doctor at the University of Colorado and Children's Hospital, Denver.

DR. RODVOLD: I'm Keith Rodvold. I'm a clinical pharmacist at the University of Illinois in Chicago, Colleges of Pharmacy and Medicine.

DR. FLETCHER: I'm Courtney Fletcher. I'm Professor and Chairman of the Department of Clinical Pharmacy at the University of Colorado Health Sciences Center.

DR. ENGLUND: I'm Janet Englund, Department of Pediatrics, University of Washington in Seattle.

DR. WOOD: I'm Lauren Wood. I'm a senior clinical investigator in the HIV and AIDS Malignancy Branch, NCI.

DR. SANTANA: I'm Victor Santana. I'm a pediatric oncologist at the University of Tennessee and St. Jude's Children's Research Hospital in Memphis, Tennessee.

DR. NELSON: Robert Nelson. I'm in pediatric

critical care medicine in the Department of Anesthesia and Critical Care Medicine at Children's Hospital, Philadelphia.

MR. PEREZ: Tom Perez, Executive Secretary to this meeting.

DR. CHESNEY: Joan Chesney. I'm a pediatric infectious disease person at the University of Tennessee in Memphis, and also more recently at St. Jude's.

DR. GORMAN: Rich Gorman in private practice of pediatrics in Ellicott City, Maryland and presently the Chair of the American Academy of Pediatrics' Committee on Drugs.

DR. HUDAK: Mark Hudak. I'm a neonatologist at the University of Florida at Jacksonville.

DR. FINK: Bob Fink, pediatric pulmonologist at Wright State University and Children's Medical Center in Dayton, Ohio.

DR. CHADWICK: Ellen Chadwick in the Division of Pediatric Infectious Diseases at Northwestern University in Chicago.

DR. DANFORD: I'm Dave Danford. I'm a pediatric cardiologist in the Joint Section of Cardiology, University of Nebraska Medical Center and Creighton in Omaha.

DR. SEVER: I'm John Sever. I'm at the

Children's National Medical Center here in Washington, D.C. I'm a co-investigator on the AIDS Clinical Trials Group there and I'm chairing three IRBs.

DR. FOST: Norm Fost, pediatrician at the University of Wisconsin, head of the bioethics program and chair of just one IRB there.

(Laughter.)

DR. BAYLOR: Melisse Baylor, medical reviewer, FDA.

DR. LEWIS: Linda Lewis, medical officer, FDA.

DR. DIANNE MURPHY: Dianne Murphy. I'm the Director of the newly formed Office of Pediatric Therapeutics and the Office Director for Counter-Terrorism and Drug Development, as Joan noted. Thank you.

DR. CHESNEY: Tom Perez, our Executive Secretary, will read the meeting statement.

MR. PEREZ: Thank you.

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

The Food and Drug Administration has granted waivers to the following special government employees which permits them to participate in today's discussion: Drs. Joan Chesney, Robert Fink, Keith Rodvold, Ellen Chadwick.

A copy of the waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, room 12A-30 of the Parklawn Building.

In addition, we would like to note that Drs. Robert Nelson, Victor Santana, David Danford, Richard Gorman, Mark Hudak, Mary Glode, Lauren Wood, Jan Englund, Courtney Fletcher, John Sever, and Jeffrey Botkin did not report any financial interests in the products or firms that could potentially be affected by the subcommittee's discussions. Therefore, they do not require a waiver to permit their participation in today's meeting.

Further, Dr. Victor Santana and Dr. Courtney Fletcher reported financial interests in the pharmaceutical companies covered under C.F.R. 2640.202(b)(2) de minimis exemption.

The topics of today's meeting are issues of broad applicability. Unlike issues before a committee in which a particular product is discussed, issues of broader applicability involve many industrial sponsors and academic institutions.

The committee participants have been screened for their financial interests as they may apply to the general topic at hand. Because general topics impact so many institutions, it is not prudent to recite all potential conflicts of interest as they apply to each

participant.

We would also like to note for the record that Dr. Steven Spielberg is participating in this meeting as an acting industry representative, acting on behalf of regulated industry. Dr. Spielberg reports that he is a full-time employee of Johnson & Johnson and also owns stock in the firm.

With respect to other invited guest speakers, Dr. Lynne Mofenson and Dr. Benjamin Wilfond, employees of the National Institutes of Health, have been screened for conflicts of interest and have been cleared to participate in today's meeting.

FDA acknowledges that there may be potential conflicts of interest, but because of the general nature of the discussion before the committee, these potential conflicts are mitigated.

In the event that the discussions involve any other products or firms not already on the agenda for which FDA participants have a financial interest, the participants' 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 upon.

Thank you.

DR. CHESNEY: Thank you.

I wanted in advance to thank all of the speakers for the day and the FDA for all their time and effort in preparing for today's meeting. It's really overwhelming when you think that it's not just sending us the materials, but preparing the Federal Register notice, being sure we are all identified in Tom's statement appropriately, meeting all the regulatory issues, and keeping us all in touch. It's really a huge effort and we're really very appreciative of that.

Our first speaker is Dianne Murphy, and again, at the risk of repetition and for those of us who don't really understand the FDA structure, Dianne is now officially the Director of the Office of Counter-Terrorism and Pediatric Drug Development in the Center for Drug Evaluation and Research and Director of the Office of Pediatric Therapeutics within the International Activities and Strategic Initiatives in the FDA Commissioner's Office. So she has two very official sounding titles. Dianne.

DR. DIANNE MURPHY: We try to keep it that way.

Again, I wanted to thank everybody for being here, welcome you, particularly those who came from more hospitable, warmer climes.

I also wanted to make an introduction that we

did not have and that's Debbie Birnkrant. Debbie is the Division Director, the Division of Antiviral Drug Products, and it is that division which has asked you all to come here today for the first half of the day because they had a very important question, as you can see.

I was telling Lynne this reminds me of many years ago when we were discussing 076. Ellen Cooper was the division director then, and there were adamant and sincere thoughts, feelings, and opinions on both sides of whether that study should go forward.

One of the adamant opinions was that it should not go forward because of the exposure of uninfected infants at a time when the transmission rate was much higher. As you know, it was one of the success stories in this arena.

I think that we are now coming back with the same question in a very different context. The division has had numerous conversations, discussions, and thoughts about what they should be doing not only from the scientific and the ethical perspective, but also from the perspective of should FDA use or continue to use the tool that Congress has given us called exclusivity in which a company obtains an additional six months of marketing. Should we continue to use that tool in this arena?

This committee does not get the simple stuff

like here's a product, here are the studies that were done, should we approve it or not. You guys get some really difficult scientific questions, groundbreaking questions really, about does this disease even occur in kids. Should we be marketing drugs to these children of different types? I'm talking about prior questions you guys have addressed. What kind of studies should we be doing? Is it ethical to do these kind of studies? In every meeting that you all have had you have had to deal with not only a scientific question, but also an ethical question.

Today is no different. We look forward to your deliberation and, believe me, it will be very important in how we proceed as to what you say today. Thank you very much.

DR. CHESNEY: Thank you, Dr. Murphy.

Our first speaker is Dr. Mofenson. I should say Dr. Cummins has prepared very nice introductions for everybody for me. She is a board certified pediatrician with special training in adult and pediatric infectious disease. She joined the Pediatric, Adolescent and Maternal AIDS Branch at the NICHD in 1989 as Associate Branch Chief for Clinical Research and became Chief of the branch in 2002. She's been involved in many studies, of which we're all well aware. She's chair of the Department of Health and Human Services Public Health Service Task Force that

makes guidelines for the treatment of HIV-infected pregnant women and participated in the development of the recent WHO antiretroviral treatment guidelines for resource-limited settings.

Dr. Mofenson will briefly update us on the state of the art of perinatal HIV transmission.

DR. MOFENSON: Good morning. I've been asked to provide you with an overview and update on prevention of mother-to-child HIV transmission both in the U.S. and globally.

What I'm going to do first is talk a little bit about perinatal transmission in the United States and in particular talk about the mechanisms by which AZT is effective in reducing transmission in 076, risk factors for transmission in this new era of antiretrovirals, transmission that we're seeing now in the post-076 era, and challenges that we have.

Then I'm going to talk about perinatal transmission on a global basis, giving you a short and rapid overview of the short-course antiretroviral prophylaxis trial results, relevance to the U.S., and end with challenges in that area as well.

So, first, the United States. In the U.S., about 6,000 to 7,000 HIV-infected women give birth annually. Prior to 1994, transmission was approximately 25

percent, and thus we had 1,500 to 1,750 infants newly infected with HIV born every year before 1994. And more than 16,000 HIV-infected children have been born in the U.S. since the beginning of the epidemic.

Now, in 1994, there was a dramatic change to the landscape of perinatal HIV in the United States, secondary to the results of PACTG 076. Now, this regimen was designed to target multiple potential time points of transmission because in 1987, when the trial was first designed, we really didn't know when the large proportion of transmission was occurring.

Thus, AZT was given from 14 to 34 weeks of gestation to start for the rest of pregnancy to target transmission occurring in utero after the first trimester. It was given intravenously during labor and delivery to target transmission occurring during the intrapartum period, and then it was given to the infant for 6 weeks postpartum to target transmission that might be occurring through infected cells or free virus that had entered infant either through swallowing of infectious maternal genital secretions during the process of birth or through blood-to-blood transfusion during microtransfusions with uterine contractions.

This regimen resulted in a 67 percent reduction in the risk of transmission, from 26 percent in placebo to

8 percent with AZT.

So I think an important question for you to discuss and think through is what were the mechanisms by which AZT lowered perinatal HIV transmission since you are discussing issues around neonatal drug testing.

Well, effect on viral load may be one part, but in PACTG 076, change in HIV RNA accounted for only 17 percent of the observed efficacy of 076 of AZT. I'll show you that on the next slide.

Two other important mechanisms through which AZT reduces transmission include pre-exposure prophylaxis of the baby, and this is through transplacental passage of the AZT given intravenously to the mother to achieve levels in the baby during the birth process capable of being virucidal, and post-exposure prophylaxis of the infant through continued administration of AZT after birth.

This slide just gives you some of the data from 076. The mean entry RNA in these women was relatively low, about 5,600. This was a relatively healthy group of women who enrolled. The median change from entry to delivery in RNA was only .28 log, and the proportion of AZT efficacy explained by HIV RNA levels at delivery was only 11 percent and the change from entry to delivery only 17 percent.

Now, additional evidence that AZT works by more than just lowering viral load is the fact that AZT lowers

transmission even in HIV-infected women who have a very low viral load. These are data from a meta-analysis of seven prospective cohort studies and clinical trials by John Ioannidis and colleagues, and he looked at 44 cases of transmission among about 1,200 women, all of whom had delivery HIV RNA under 1,000.

Transmission differed by receipt of AZT. In mothers receiving AZT, transmission was only 1 percent. In mothers not receiving AZT, transmission was 9.8 percent. And on a multivariate analysis that adjusted for maternal CD4 count, mode of delivery, and infant birth weight, AZT still independently reduced transmission. And these data illustrate the importance of infant pre- and post-exposure prophylaxis in addition to lowering maternal viral load as a mechanism of prevention, particularly in women with low viral load.

The importance of the infant pre- and post-exposure component of 076 can also be illustrated if you look at infants who are born to mothers who received different components of the regimen. These are data from a population-based study in New York State by Nancy Wade and colleagues, and you can see when all three components, antepartum, intrapartum, and postpartum, of 076 were received, transmission was very low, 6 percent. But even when the mother did not receive antepartum therapy and only

intrapartum and postpartum therapy was given or postpartum therapy alone was given, but started within 24 hours, transmission rates were still low, 10 and 9 percent, compared to those who started after 48 hours or who had no AZT. Thus, even when no maternal AZT is received, infant AZT started within 24 hours reduces transmission.

Why might pre- and post-exposure prophylaxis be important? Well, we now know that the amount of cell-free and cell-associated HIV found in the cervicovaginal canal is associated with transmission. I've given you two illustrative studies.

The first one is from a short-course AZT trial in Thailand I'll talk a little bit more about later. They looked at quantifying HIV RNA in cervicovaginal lavage and found that the presence of RNA was associated with a 3.4-fold increase in the risk of transmission, and this effect was independent of plasma RNA and was actually greatest when plasma RNA was low, and the post-exposure prophylaxis component can become more obvious. Antepartum AZT was associated with a median .8 log decrease in RNA in CVL.

Ruth Tuomala and colleagues in the Women and Infants Transmission Study looked at cell-associated HIV DNA in cervicovaginal lavage in women who were receiving antiretroviral and found that detection of DNA was associated with transmission, and for every 1 log increase

in HIV DNA in CVL there was a 2.3-fold increase in the risk of transmission.

Now, why would this be important? Well, the infant exposure to HIV in vaginal secretions and the swallowing of this HIV both in cells as well as free virus likely infects the baby through the intestinal mucosa of the infant either by infection by cell-free virus going to lymphocytes in the lamina propria, or through cell-associated virus again going through to cells in the lamina propria, or virus going through specialized M cells that bring it more directly to cells in the Peyer's patch.

These are data from the PETRA study I'm going to talk a little bit more about later. This is presented to you to illustrate that pre-exposure prophylaxis of the infant without post-exposure prophylaxis is not effective. This study looked at a three-part regimen, short course prenatal, intrapartum, and 1 week postpartum; a two-part regimen, intrapartum and postpartum. Both of these regimens were effective with the three-part regimen being most effective, the two-part regimen being next effective. But the intrapartum regimen alone, which is giving pre-exposure without post-exposure prophylaxis, was ineffective.

I'd like to now turn to risk factors for transmission now in women and infants in the post-076 era.

Probably one of the most important risk factors is delivery plasma RNA level. These are data from the Women and Infants Transmission Study, a prospective cohort study. And you can see a clear association between the level of RNA in the plasma of the infected mother and the risk of transmission to the infant, ranging from only 1 percent in women with undetectable virus under 400 up to 32 percent in women with high viral loads over 100,000.

As one might expect then, if low viral load is associated with lower risk of transmission, more potent antiretroviral regimens in the mother that are capable of significantly reducing their viral load is also associated with lower perinatal transmission. And these are again data from the Women and Infants Transmission Study, and you can see that as the potency of antiretrovirals increases, the risk of transmission decreases 8 percent with the 076 regimen, 4 percent with the dual NRTIs, and only 1 percent with protease inhibitors.

Now, importantly these two factors are independent. This is a somewhat complicated slide. Let me work you through it. This shows percent of transmission. This x axis here shows you maternal plasma HIV RNA at delivery, and here you see the type of maternal antiretroviral therapy which increases in complexity. So if you first look down across HIV RNA levels, you can see

that in most of these categories of treatment you can see a clear relationship between the level of RNA and the risk of transmission, high transmission when RNA is high, low transmission when it's low. But interestingly, if you now look within an RNA strata going this way, you can see also that with increasing complexity of therapy, you see a decrease in transmission even in women who have the same viral load.

Elective cesarean delivery. Mode of delivery is another important risk factor even in women receiving antiretroviral therapy. These are data from the International Perinatal HIV Group which was a meta-analysis of about 8,500 women from 15 different cohorts, and you can see that with elective cesarean delivery without AZT, transmission is 18 percent compared to 19 percent with other modes of delivery. When you're receiving the 076 AZT, you lower transmission in both groups, but there is an additive effect of elective C-section. So transmission is 2 percent with elective section and 7 percent without elective section. So the addition of an intrapartum intervention further reduces perinatal transmission even in the face of AZT prophylaxis.

I want to talk a little bit about what happened in the U.S. following the results of 076. In February 1994, the results of this trial were announced pre-

publication, and within six months, the U.S. Public Health Service had issued guidelines for use of AZT to prevent transmission. And about a year later, they issued guidelines for prenatal HIV counseling and testing recommending universal HIV counseling and testing in the U.S. These guidelines are periodically updated, with the last update of the prophylaxis guidelines being just a few months ago in November 2002.

So what are the current Public Health Service guidelines for prevention of mother-to-child transmission?

Well, when women have plasma HIV RNA levels over 1,000, the use of highly active antiretroviral therapy, usually two NRTIs and a protease inhibitor is recommended, as well as elective cesarean delivery if the mother remains greater than 1,000 copies near delivery.

For women with plasma RNA 1,000 copies or less, the use of either HAART or in this case the use of AZT monotherapy as in the 076 regimen is recommended.

For women with no treatment prior to labor -- and this is a significant minority of HIV-infected women. 15 to 20 percent of HIV-infected women lack prenatal care, particularly those who are illicit drug users. There are a variety of regimens recommended, in this case intrapartum/postpartum regimens, either AZT alone, AZT/3TC, nevirapine, or AZT/nevirapine. And near the end, I'll go

through the trials that have the evidence for this.

And then there is the situation where the mother has neither antenatal or intrapartum therapy and therefore you only have post-exposure prophylaxis open to you, and in this case infant prophylaxis for 6 weeks with either a combination regimen is recommended for nosocomial post-exposure prophylaxis or with AZT alone.

This is just to show you some data about what we're seeing in the U.S. in terms of antiretroviral prophylaxis. These are data from PACTG sites between 1998 and 2000 from an observational study that we're doing, and the main message I want you to get here is that the vast majority of women, 99 percent, are receiving some kind of therapy during pregnancy, and the vast majority, 78 percent, are receiving combination therapy primarily with protease inhibitors although there are a variety of other types of regimens being received.

This is data also to show you the increasing rate of elective cesarean delivery among women in the United States from the Pediatric Spectrum of Disease project of the CDC. You can see that rates were relatively stable between '94 and '97, a slight increase in '98, but then in 1999 when the international perinatal meta-analysis was published, as well as the clinical trial became available, rates jumped to over 40 percent and are nearing

50 percent now.

This is really the punch line. What have we seen in the United States with this? We've seen a dramatic decrease in the risk of transmission. These are data from a variety of different studies and clinical trials that I've combined to show this decrease, rates of 25 percent from the Women and Infants Transmission Study in 1993, down to 8 percent with PACTG 0786. In another clinical trial 185 where all the women were receiving the 076 regimen, transmission was 5 percent. In 1999, beginning to see combination therapy used, 3 percent, and 2001 and 2002, transmission down to 1.5 percent when most women are receiving combination therapy.

Along with this, we've seen a significant decrease in perinatally acquired AIDS as one might expect. You can see the increase in cases over time until about 1994. Here the results of 076 were announced, and soon after, the U.S. Public Health Service made their recommendations. And you can see an 81 percent decline in the rate of pediatric AIDS from 1994 to 2000.

So in summary, we've made great progress in the U.S. in reducing transmission. It's currently under 2 percent for women who are in prenatal care. The number of infected infants born every year has decreased from about 1,500 to 2,000 before 1994 to an estimated 300 to 400

currently, and this reduction has been achieved through enhanced prenatal HIV counseling and testing, recognition of the importance of viral load, and the increased use of HAART by pregnant women, and an increase in elective cesarean delivery.

However, we shouldn't be too complacent. Many challenges still remain. There are significant barriers to eliminating perinatal HIV in the United States. One of the most predominant is continued HIV transmission to women, particularly adolescent women who have high rates of unintended pregnancy. I already talked a little bit about lack of perinatal care, particularly in women who are illicit drug users, and a significant minority of HIV-infected women lack prenatal care. Failure to identify HIV infection during pregnancy and antiretroviral drug resistance, which I'd like to take a minute or two to talk about in a little bit more detail.

The frequency of antiretroviral drug resistance mutations in virus identified among newly infected persons in the U.S. and Canada is increasing. A study in San Francisco compared the rate of resistance, 1996-1997 to 2000 and 2001, and found about a quarter of patients had resistance to nucleoside analogs. It didn't really change. The rate of resistance to non-nucleosides increased from 0 to 13 percent; to protease inhibitors, 3 to 8 percent. And

this resistance appeared to potentially be clinically important.

Additionally, studies from 10 cities in the U.S. and Canada comparing '95-'98 to '98 to 2000 found an increase in any drug resistance from 8 to 23 percent and in multi-drug resistance from 4 to 10 percent.

We're also seeing that more HIV-infected pregnant women are antiretroviral-experienced and have drug-resistant virus. These are data on resistance from women in PACTG 316 which was a study where women were receiving primarily combination therapy and it was evaluating whether single-dose nevirapine offered any added benefit. You can see that 44 percent of these women at delivery had the M184 mutation consistent with resistance to 3TC. 8 percent had resistance to AZT; 2 percent to NNRTIs, although these women had not received non-nucleosides before; and 9 percent had primary protease inhibitor-resistant virus.

What is the impact of resistance on prevention of transmission? Well, I think that that's still very debated but there are some studies that suggest that there may be a significant impact. We did a study, PACTG 185 I talked about before. All of the women were receiving AZT, and we had 24 transmissions in this study. The transmission rate was 5 percent. And we did a case-control

study comparing transmitters to controls, and you can see that at delivery AZT resistance was found in 25 percent of women who transmitted versus 11 percent of non-transmitters. This was not statistically significant. Small numbers. And any nucleoside analog resistance, 46 percent in transmitters, 25 percent in controls.

Additionally Seth Welles and colleagues in the Women and Infants Transmission Study did a case-control study. They had about a quarter of their women having prevalent AZT resistance, and in a multivariate analysis, genotypic AZT resistance was associated with a 5-fold increased risk of transmission.

At present I think most cases of antiretroviral failure where you have transmission despite maternal prophylaxis are probably not due to drug resistance, but this may change as resistance becomes more frequent in the U.S.

I want to then turn to the global picture. Globally over 2 million HIV-infected women give birth annually, most of these in resource-poor countries where the 076 regimen is too complex and expensive to use. Transmission rates in breastfeeding women who have not received prophylaxis range between 25 to 40 percent, and currently about 2,000 children become infected every day globally. And an estimated 3.2 million children are living

with HIV.

This slide is to illustrate for you the importance of breastfeeding postnatal transmission in resource-limited countries. The colors show you the blocking of the proportion of infections occurring at different time points. About 20 percent of transmission occurs in utero, with a majority of that probably occurring late in utero, about 40 to 50 percent during labor and delivery, and you can see a full 40 percent occurring both early and late postpartum through breast milk transmission. So in a breastfeeding population, breastfeeding postnatal transmission is extremely important.

Following 076, there was clearly a need to develop shorter, less expensive regimens that are more applicable to resource-limited settings. Studies first looked at modifying AZT-alone regimens to see whether shorter regimens would be effective. They then also explored whether short-course combination regimens might be better than AZT alone. And they also looked at whether similar efficacy to combination therapy could be achieved with alternative drugs in what might be simpler regimens.

This is just a schematic, and I just put this up here to illustrate to you the types of questions that were asked in the trials that have currently been completed. These trials focused on prevention of in utero

and intrapartum transmission. This up here is the 076 regimen, starting at 14 weeks, 6 weeks to the baby, and the yellow is antepartum regimens. And you can see the questions being asked were what is the minimum duration of antepartum therapy needed, and is it needed at all, a question whether intrapartum therapy alone might be effective. Then a variety of different postpartum durations were looked at, and the questions were what's the minimum duration and is it needed at all.

I'm going to give you the punch lines first to the results of the trials. Short-course AZT prophylaxis is effective, although longer antenatal therapy starting at 28 weeks is more effective than shorter antenatal therapy starting at 36 weeks, and that shows that some portion of antenatal transmission is occurring between 28 and 36 weeks. And efficacy of prophylaxis is diminished by breastfeeding but still persists at 24 months, at least with the short-course AZT regimens.

This illustrates for you two trials that looked at the same regimen. They looked at AZT starting at 36 weeks and given intrapartum, no infant regimen at all. This is first looked at in Thailand in a formula-feeding population with an efficacy at 6 and 24 months of 50 percent. You take the same antiretroviral regimen, you put it into a breastfeeding population in Africa, and you see

there is still efficacy but it is significantly diminished: 37 percent at six months compared to 50 and down to 26 percent at 24 months. Still statistically significant, but clearly less than 50 percent.

Another study in formula-feeding infants tried to assess whether the duration of antepartum or postpartum therapy was important. This looked at an 076-like regimen, started at 28 weeks, and given for 6 weeks to the baby, and then looked at a very short regimen starting at 36 weeks and 3 days to the baby and the different variations in between. They found that the most effective regimen, which is not surprising, was the longer regimen, transmission of 4 percent compared to 11 percent in the short-short regimen. With the variance, you see that the transmission rate was intermediate with those who had long antepartum therapy being more like the long-long regimen, those with short antepartum therapy being more like the short-short regimen. Indeed, when they looked at the in utero transmission in this study and they compared long and short antepartum therapy, they found a significant difference in that longer antepartum therapy was associated with a transmission rate in utero of 1.6 percent compared to 5.1 percent with short antepartum therapy.

Now we move to the short-course combination regimens. After short-course AZT was found to be

effective, researchers then asked whether short-course combination regimens might be more effective than AZT alone. AZT/3TC prophylaxis does appear to be more effective than AZT alone, and a three-part regimen appears more effective than a two-part intrapartum/postpartum regimen. As we talked about earlier, intrapartum only is not effective, showing the importance of this post-exposure prophylaxis component, particularly if the mothers do not receive antenatal care.

And in this particular AZT/3TC regimen, efficacy did not persist at 18 months. This first looks at the combination of AZT/3TC in formula-fed infants. This is a study in France. They took the 076 regimen and added 3TC to the mother starting at 32 weeks and also added 3TC to the baby for 6 weeks. So the baby got AZT and 3TC. Transmission was 1.6 percent compared to their historical control of 6.8 percent.

A study in Thailand took their standard short-course regimen, 36 weeks and 4 weeks to the baby, added 3TC to the mother antepartum/intrapartum, and found a transmission rate of 2.8 percent compared to a historical control of short-course AZT alone of 12 percent.

This is the PETRA study I talked about before. This is AZT/3TC, three-part regimen most effective; intrapartum/postpartum also effective; intrapartum-only not

effective. But you see at 18 months in a breastfeeding population a real severe diminishing of the efficacy of this regimen.

How about alternative prophylaxis regimens? Researchers then asked whether alternative drugs that had some significantly different properties like nevirapine, long half-life, very good penetration into tissues, might provide efficacy similar to the short combination regimens. The bullet point is that when only intrapartum/postpartum prophylaxis is given, single-dose nevirapine is superior to intrapartum/postpartum AZT alone and similar to intrapartum/postpartum AZT/3TC. Efficacy is diminished by breastfeeding, but unlike the PETRA study, nevirapine appears to retain significant efficacy at 18 months in breastfeeding populations. The addition of single-dose nevirapine to the mother and baby to short-course AZT appears to improve efficacy, but adding it to standard regimens in the U.S. does not offer benefit.

Now, to just show you these studies that support those statements. This is the HIVNET 012 study. This compared a single dose of nevirapine given to the mother at the onset of labor to a single dose of nevirapine given to the baby at about 72 hours, and it compared it to an ultra-short regimen of AZT/3TC given orally intrapartum and for 1 week to the baby. The key point here is that the

nevirapine regimen was significantly more effective than ultra-short AZT, efficacy 47 percent at 14 to 16 weeks and still significant, 41 percent at 18 months.

Well, the next question would be, now we've got two intrapartum/postpartum regimens, single dose nevirapine and AZT/3TC. Is one better than the other?

The same trial, which was actually just published this week in the Journal of Infectious Disease, compared the 102 regimen, a variant of it -- they gave two doses to the mom instead of one -- to the AZT/3TC PETRA regimen, and the end result here was that the transmission rates in two groups, 12.3 percent with nevirapine, 9.3 percent with AZT/3TC intrapartum/postpartum, are not significantly different. So similar efficacy.

The next question is whether the addition of single-dose nevirapine to the proven effective short-course AZT regimens might improve efficacy. Now we're beginning to move to studies that are still ongoing.

This is a study in a formula-fed population in Thailand. They looked at a baseline short-course AZT regimen and added single-dose maternal and infant nevirapine and single-dose maternal nevirapine only. At the first interim analysis, the placebo arm, the AZT-alone arm, was discontinued because transmission was significantly higher than in this arm. So the study is

still ongoing, and I don't have the actual transmission rates to give you.

In a study in the Ivory Coast, this was an open-label study where we again had short-course AZT. Single-dose nevirapine to the mom and baby was given. Transmission was only 7 percent at 3 months compared to 13 percent with a historical control.

Now, nevirapine appears to add efficacy to AZT alone, but what about to the standard regimens that we're receiving in the U.S. now, most of which is combination? And this was addressed in the study, PACTG 316, conducted in the U.S., in France, Brazil, and the Bahamas, that looked at women receiving standard therapy during pregnancy, intravenous AZT during labor, and AZT to the infant, and they were randomized to single-dose nevirapine to the mom and baby or placebo. Transmission rates were remarkably low, 1.4 and 1.6 percent, but not significantly different.

Infant prophylaxis. Now, many women may not present until labor. In the U.S. I talked about 15 percent of HIV-infected women do not have prenatal care. In resource-limited settings, it is a much higher percentage of women who do not present to the health care system until they are actually in labor. Therefore, they can't receive antepartum therapy.

Epidemiologic data suggests that AZT for 6 weeks after birth reduces transmission. That's the Wade data I already showed you. And the Wade data also showed that infant prophylaxis must begin within 24 to 48 hours after birth if it's going to be effective when the mother has not received antepartum/intrapartum drug.

Preliminary data again from studies that are still ongoing show that single-dose nevirapine given to the infant may have similar efficacy to AZT, but that single-dose nevirapine plus AZT may have better efficacy than nevirapine alone.

And these are the two studies that have shown that. This is a study that compared single-dose newborn nevirapine only to 6 weeks of AZT, found similar transmission rates at 6 weeks. This study is still ongoing. There was a lot of lost to follow-up, so I don't know that we can draw any definitive conclusions.

And this study here I want you just to concentrate on the top part. Here they compared newborn nevirapine, single dose alone, to single-dose nevirapine plus 1 week of AZT, and found that the combination had a significantly lower rate of transmission, 14 versus 22 percent.

In the U.S., we use the standard 6 weeks AZT, but the transmission rate even with 6 weeks AZT, is still

relatively unacceptably high, 10-12 percent. So we're currently doing a study in Brazil and the U.S. that's going to look at whether combining 6 weeks of AZT with additional drugs might be more effective in reducing transmission in this circumstance. And it's comparing 6 weeks of AZT, 6 weeks of AZT with three doses of nevirapine, and 6 weeks of AZT with three doses of 3TC and nelfinavir. This study should be enrolling in April.

To finally move to what is currently planned in terms of international perinatal trials, clearly the largest problem in the resource-limited setting now is how do we reduce postnatal breast milk HIV transmission in areas where formula feeding is not safe, is not sustainable.

This is the design of ongoing infant prophylaxis studies. Again, this is just a schematic for you to look at. Whereas before with our completed studies most focused over here on antepartum duration, now we see they're focused over here on postpartum duration in the infant. Questions being asked include what's the optimal duration of antepartum therapy. Do you need it? And postpartum, a number of questions are being asked. What's the optimal duration of prophylaxis of a breastfeeding baby? Will it work if it's given alone? What drugs should you give? Is combination better? What about exclusive

breastfeeding?

This just gives you a flavor of the type of drugs that are being looked at antepartum/intrapartum and focus on the infant postpartum here. Duration varies from 1 week, 6 weeks, 14 weeks, to 6 months looking at a variety of drugs, AZT, nevirapine, 3TC, and a number of different combinations.

Additionally, probably most importantly, a number of studies are looking at maternal prophylaxis during breastfeeding where the mothers are receiving highly active antiretroviral therapy. These studies are all very similar. They start HAART at 34 to 36 weeks, and they give 6 months of HAART to the breastfeeding mother. Some of these are open-label and some of them are comparative.

So in terms of global perinatal transmission, shorter, less expensive regimens than 076 have been found to be very effective in reducing in utero and intrapartum transmission by 41 to 63 percent. Although breastfeeding decreases overall efficacy, most of these trials still show a significant decrement at 18 to 24 months. However, we've only lowered transmission in these populations to what we saw in the U.S. pre-076. We've lowered it to 25 percent instead of 40 percent.

Thus new approaches, and importantly including infant and/or maternal prophylaxis that are targeted

against reducing postnatal breast milk transmission are clearly needed.

And finally, implementation of what we know are effective regimens is now key in developing countries.

Thank you very much.

(Applause.)

DR. CHESNEY: Thank you very much. That was superb. Just as one had a question, you answered it.

Dr. John Sever is going to speak to us next. We are scheduled to have questions on the presentations at the end of the three presentations.

Dr. Sever has had a long and distinguished academic and research career in pediatrics and pediatric infectious diseases with a special focus on pediatric HIV and other perinatal infections.

Currently he's Professor of Pediatric Medicine and Infectious Diseases at Children's National Medical Center and Professor of Pediatrics, OB-GYN, Microbiology, and Immunology at George Washington University School of Medicine. Prior to this, he was Chairman of the Department of Pediatrics at George Washington University School of Medicine and Vice President for Medical and Academic Affairs at Children's Hospital National Medical Center.

He's also an associate investigator in the Washington Regional Consortium, Pediatric AIDS Clinical

Trials Unit for the NIH.

And Dr. Sever has published extensively with over 500 publications.

He will address the ethical issues that arise when conducting neonatal research.

DR. SEVER: Thank you very much. It's a pleasure to be here this morning to discuss some of the ethical issues in the area of concern here.

I'd like to bring forward some of the issues which I think are important to keep in mind for you to consider as these discussions proceed today.

First, I'd like to refer you to a couple of references. One I think is particularly worthwhile. Those of you who are here on the panel have a copy in the FDA briefing document. It's the reference to the American Academy Policy Statement on the Guidelines for Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations. That does a very thorough job of discussing some of the important things in pediatric studies in general and I think is particularly useful for you to review. Again, it is in the briefing material that you have in your package.

Another reference, of course, is the Code of Federal Regulations. This one, Title 45, part 46, subpart D, deals specifically with pediatric studies. There's a

parallel document for the FDA. This details the issues which are perhaps the minimums that we have to consider in relating studies to newborns and pediatrics specifically and provides us with general guidance that's used by the institutional review boards in considering pediatric protocols.

Now, I'd like to take up some of the principles that are guidance for us in general in looking at areas of research and specifically how they apply to pediatrics and newborns and HIV in newborns.

First, of course, is respect for persons. This deals with the participants voluntarily consent to participate in research, that you obtain an informed consent, and that there's privacy and confidentiality.

You can see immediately, of course, in pediatric studies we're under the constraints that the participant cannot voluntarily consent to the research, and we have to then determine that we will have to obtain consent from some reasonable surrogate for that individual. The parent or the legally appointed guardian has to be the one that would be able to then consent.

Usually in pediatrics we also require an assent, and that is for children over 7. We look to the child also to participate in the consenting process. Here again in studies for neonatal investigations that's also

impossible.

So two of the main issues that we have to consider is this respect for persons and we have to be particularly careful in our electing to proceed in studies to protect the child in that consenting process.

Now, the second major area is beneficence which concerns the risks for research are justified by potential benefits to the individual or society. The study is designed so risks are minimized and conflicts of interest are managed adequately.

Of course, in many of these studies for pediatric patients, they're early studies. They're phase I studies, phase II studies, so we may not know what the risks and benefits are particularly for children in that age group. That has to be something that you have to keep in mind. We don't know the benefits because although we may have some indication from other studies what the benefits are in adults, whether that same benefit will be present for the issue that you're trying to accomplish, such as a lack of transmission of infection as opposed to treatment of infection. And the risks to the child, of course, are often unique and serious.

The last main area we have is justice and that vulnerable subjects are not targeted for convenience and people who are likely to benefit from research

participation are not systematically excluded. That means looking carefully at the populations we study and how they match up with the populations at risk and the need for these studies. Do we go to other populations simply because there are more infected patients and it's easier to complete your study, or do we do it because of consideration for the true need for that type of a study?

Now, taking this into a greater, more specific area, I'd like you to consider neonatal research which is what I was asked to talk about and specifically neonatal HIV research. Here under respect for persons, we have to look at the issue of voluntary consent. Again, we have to use a parent or a guardian.

The concerns we often are undertaking are is there a good understanding of what this means to the child, as well as to the mother.

Are we communicating that adequately by the consent process? Often the consents get very long and detailed because they have to be to get in all of the issues about risks and potential benefits. But can the individual really understand the issues? We find, for example, in dealing with pregnant women who are HIV-infected that they're particularly willing to be compliant while they're pregnant for the benefit of their child, but what about the continued issue of their understanding about

the drugs and their potential toxicities which has to be communicated?

Their ability to cope becomes important. In so many of these instances, as you know, of course the mother has HIV and the child has HIV, and if that's the total family, the issues of coping with the mother taking the medicine she needs, getting the appointments she needs, as well as getting that drug to the child at the time that the child needs it, getting the visits that the child needs to have become a real problem in coping with being able to be employed, as well as taking care of these issues. And if the mother isn't really present -- the child is being taken care of by another individual in the family -- the ability for that regime to be administered and to be followed often becomes very difficult.

And then the motive of the individual. I will discuss that a little bit more, but I think it's important to understand why the parent or guardian would want to participate in this study. Why would they want to have their child receive this drug if we don't know much about the drug and its possible toxicities? Are they altruistic and interested in that, or are there other motives present which are understandable but must be recognized?

We look at these phase I studies. And this is often a problem in pediatrics. Is there going to be direct

benefit in a phase I study? And if not, is the benefit important and how must we approach that? In most phase I studies that have been followed -- and I've been discussing this with Dr. Nelson because we get involved in this in our oncology phase I studies too -- it's unlikely that the child will benefit. Estimates have been made that in adult studies it's somewhere around a 5 percent chance that in a phase I study you'll have any benefit whatsoever, and that takes into account even no observable clinical benefit but some laboratory type benefit.

Now, it's said that perhaps you have a 10 percent chance in children because you're using drugs that hopefully have had some evaluation in adults. But increasingly we're seeing drugs that have had little or no evaluation in adults and have not had evaluation certainly for some of the issues that you may be applying them in the pediatric patients or the transmission of infection.

Is better care an important issue and is that important in the decision to volunteer, as well as the benefit of the study? Frequently patients will tell us they volunteered because they know it's better surroundings and they can see the same doctor every time when they participate in a clinical trial, whereas that rotation -- and there will be fellows and residents they'll be seeing -- does not pertain if they're not in the clinical trial.

Is there a certain assistance that's participating in this decision making in their effort to participate? Will they receive some compensation for it? Yes, we'll compensate them for their travel and perhaps for their time away from work, but is that the important factor that's motivating them to participate?

Is the social support and aid, the fact that they're going to have a lot more social workers around them and available to them in our settings, important to them and, therefore, that's why they're going to participate?

And for some individuals, the important thing appears to be that they get food and formula and diapers free if they participate, and I think we have to be careful about understanding that motive in balancing that against the situation that we're giving to the family.

Other things, of course, come up. What about the inconvenience? And the inconvenience becomes very large. Frequently we are providing the subsidy for taxi travel in order to make it convenient for the individual to come.

The time away from their work and the fact that their visits and their time away, in addition to their own visits and time away, becomes really important. So obviously we all try to combine those together to make it a joint visit.

But the concern often is that their work or their fellow workers will learn of their diagnosis by the fact that they're away so much or they're being called. The way the calls are made to their offices to tell them about canceled appointments or changes become very important so that they can keep their privacy about their own diagnosis, as well as about their child. Very often, of course, they do not want the child's father to know the diagnosis, and that adds to the complications.

The travel, the extensive use of medications is an inconvenience. Side effects for the medications, both to the mother and to her child, certainly are important.

Then any additional costs that we don't cover that are necessary to be paid for become an important issue for the consenting and for retaining their interest and participation in ongoing studies.

Well, in beneficence then we would like to have as much background information, first of all, as we can from laboratory studies, from animal studies, and from adult studies. This gives us the greatest amount of it, if we have all three, as we enter into our first phase I pediatric studies.

But we may not have the information we need or it may not be appropriate for the age group that we're dealing with, particularly if our questions are not exactly

the same as those in adults. Obviously, prevention of transmission is different from treatment studies.

Then the risks that are involved, of course, as Dr. Mofenson has pointed out, are that most of the patients are not infected so that if we're doing studies in pregnant women in this country, we have to realize that only about 2 percent of the children will be actually infected and 98 percent will be exposed to these drugs with really no benefit to them.

Also in the immediate newborn period, again dealing with the neonatal period, the diagnosis may not be made until several weeks have passed so that if you're going to initiate a study and you feel you must initiate it in the immediate newborn period, you may not know again whether that child is infected. I think here is a role for intensive evaluation of the rapid tests in making the diagnosis in newborns and documenting it at birth whenever possible and selecting on that basis.

But there may be particular toxicities in newborns. They have different metabolism. The studies of drug levels in the newborns would be important to document, and now, fortunately with tandem mass SPECT, we're able to do that a lot better, getting rapid drug levels in children, which we're doing in our studies at the Children's Hospital here in Washington. They have

different metabolism.

Also you may have long-term effects which you don't appreciate in studies done in adults. Certainly the effects on growth and development of the child we have to monitor and we won't find out for a long period of time whether there has been a detrimental effect on growth and development or mental development. Neurological findings are not going to be apparent as readily in relation to these children being exposed very early in life and what might occur many years later.

And then the effect of maternal treatment. How does that affect the child, the drug effects themselves, as well as the development of resistance which may be occurring in the mother, and therefore the effect on the treatment of the child has to be consider.

Some of the benefits, of course, could be the better suppression of infection, lower risk of transmission, perhaps less side effects if we choose the drugs appropriately and then are able to use drugs with less side effects.

Easier to administer, very important in children obviously. The mixtures, some of them that have been developed over the years, have been just terrible tasting, atrocious. Some of them taste like kerosene and the children won't take it. They'll spit it out. So drugs

that are easier to administer, more palatable drugs, become important for us to have available and to be thinking about in terms of benefits.

Again, some of the benefits are better medical care because they are participating in these studies, social support for the family, and benefit to other children as an indirect benefit in the long run.

Now, as to justice, again these are vulnerable subjects. They're newborns and they shouldn't be targeted for convenience. They don't have either consent or assent, and so not only do we have to ask the parent or the legal guardian to be concerned about this, but we have to ask the investigators and those of us who are reviewing the protocols in general to be sure that we're protecting the child as appropriately as we can.

There's a question about general availability, the location of the center. There are these centers which do studies and then there are other areas of the country where there are usually less HIV-infected patients that may not have centers. Those locations still have these HIV-infected children and they may or may not be able, therefore, to participate in studies because they are in a low incidence area and there are no centers in that particular area.

We have to be very careful about our

recruitment procedures, be very conscious of the way that we induce patients or discuss with patients their participation and the benefits. While there is the constant pull for increasing accrual in protocols because the study wants to get it done, we still have to be careful about ensuring that the recruitment is reasonable.

Now, the IRB has to look at protocols and consider them, first of all, that they may be not more than minimal risk and they may, therefore, number one, have a direct benefit or they may have no direct benefit. And if the IRB determines that it is not more than minimal risk, in that category it has the authority to approve or disapprove that study.

But some of the studies have some risk. Are bone marrows going to be required? Are other procedures going to be required that would not normally occur in these children? One has to then decide is this a study that's a minor increase over minimal risk where there is either a direct benefit or no direct benefit.

The IRB can approve that level, but the decision there is a difficult one often. There is not good guidance in the decision as to what is a minor increase over minimal risk. So what one IRB decides is a minor increase over minimal risk and another one decides is not acceptable will differ. We ourselves go through that

frequently. So that's a hard decision to make. Is this particular drug study a minor increase over minimal risk and therefore something that we can approve or not?

If it's more than minimal risk and you can feel quite sure that there is direct benefit, the potential for direct benefit is reasonable, then the IRB can approve it.

However, if the study involves more than minimal risk and there is no evidence of direct benefit but the IRB continues to feel that the study is worthwhile doing, this can be referred to HHS for a panel decision. That's a much longer route and more complicated. So this decision point between a minor increase over minimal risk for no direct benefit study and a more than minimal risk for no direct benefit study becomes very important and puts us into a different area. But studies can be done if there's more than minimal risk and no anticipated direct benefit if the IRB supports it and sends it on for this panel and if the panel supports it.

So in conclusion then, I've summarized some of the things that I think are important for us to consider when we look at these protocols. Some of the benefits certainly have been demonstrated by 076 and other studies, but now we're down to the point where we only have 2 percent infection rates, and as we realize from the start, this then puts both a difficulty in conducting the studies

and a difficulty in considering the risks which we are taking and the child is taking as a result of participating in this study.

Again, I would suggest that if we had an emphasis on the support of the use of rapid tests in the immediate newborn period, that would help us a great deal to at least identify at that point the infected child immediately rather than a month later or so.

The use of foreign studies is certainly important because of the availability of more infected patients to participate in those studies, but the information from many of those studies using shortened regimes and less effective protocols, as we know, may not be applicable to the information we need to try to get down to 0 infected children in this country.

Thank you.

(Applause.)

DR. CHESNEY: Thank you very much, Dr. Sever.

The next individual to present to us is Dr. Linda Lewis who is a board certified pediatrician with subspecialty training and board certification in pediatric infectious disease. She's been with the FDA since July of 1999 and is a medical officer with the Division of Antiviral Drug Products.

Prior to joining the FDA, she was a senior

clinical investigator at the Pediatric Branch of the NCI where she supervised phase I and II clinical trials of antiretroviral drugs in children. She also has served as a pediatric ID consultant for the DuPont Hospital in Wilmington, Delaware and was a medical consultant to the Delaware pediatric HIV program.

Dr. Lewis is going to present to us the FDA perspective regarding the need for reevaluation of antiretroviral drug development in neonates, and she will close with a presentation of the questions for our consideration today.

Dr. Lewis.

DR. LEWIS: Thanks, Dr. Chesney.

As Dr. Chesney says, I have been on pretty much every side of this debate over the last many years, but I am here today on behalf of the Division of Antiviral Drugs and would like to thank the committee and all of the other people who are in attendance for participating in this meeting.

We would like to obtain from this meeting advice on the best approach to drug development for all pediatric populations. You've just heard a very concise description of where we stand with perinatal transmission programs both in the U.S. and globally and some thoughts on the ethical issues that are involved in performing studies

in neonates.

We're here today to ask specifically for advice regarding the development of HIV drugs in neonates, that is, infants from birth to about 4 weeks of age. During the next few minutes, I would like to present some of the issues that have been brought to the Division of Antiviral Drugs that have led us to ask for this reevaluation of our standard request for studies in this age group.

I'll begin my presentation with a description of the written request as a mechanism for requesting pediatric studies. I'll present our current standard request issued to sponsors of HIV drugs. After that, I will present some of the issues that have been raised regarding the feasibility of conducting HIV drug development studies in the neonatal age group. Many of these concerns have been brought to us by our pharmaceutical sponsors. The next several slides will provide a little more detail on each of these topics.

First, a description of the written request for pediatric studies. Those of you who are on the Pediatric Subcommittee have heard a little bit more about written requests and pediatric exclusivity than some of our guests who participate in the Antiviral Advisory Committee.

The Best Pharmaceuticals for Children Act of 2002 reauthorizes the exclusivity provision that grants

sponsors six months of market exclusivity for conducting pediatric studies as outlined in a written request. This legal provision was originally passed in 1997 as part of the FDA Modernization Act and has been instrumental in providing pediatric data on many drugs.

A written request comes in the form of a letter sent by the FDA to the sponsor describing the studies that must be done, the number of patients who must be studied, and the time frame for completion of these studies in order for the drug to be eligible for pediatric exclusivity. The FDA requests studies in a written request that we believe will provide a public health benefit. That's one of the keys in the legislation. Agreement to conduct these studies as outlined in the written request is entirely voluntary on the part of the sponsor. The incentive to perform these studies is the potential financial benefit provided by six months of patent protection.

In order to provide a consistent approach to pediatric drug development, the Division of Antiviral Drugs developed a standard written request for HIV drugs. A copy of our written request template for antiretroviral drugs was included in the briefing package that was sent to all of the committee members.

In general, a written request is issued when enough data is available in adults to indicate a drug's

potential efficacy and preliminary safety profile. This is usually occurring during phase II or phase III of drug development or occasionally after an accelerated approval. The Division of Antiviral Drugs has issued 20 written requests for HIV drugs that are either approved or already in development.

To date, five of our drugs have been granted pediatric exclusivity, and these include abacavir, lamivudine, didanosine, stavudine, and nevirapine.

You might notice that zidovudine, which is our original first antiretroviral drug, is not on this list, and that's because most of the pediatric data that was required during those studies had been submitted to the FDA and reviewed prior to the initiation of this program.

As I stated, the division has developed a standard template for antiretroviral drug written requests, and this slide really gives pretty much the exact wording that is included in our template. We identify the type of studies that are requested and these include multiple dose, PK, safety and activity studies of drug X in combination with other antiretroviral agents in HIV-infected pediatric patients. These studies are designed to support the use of the drug in HIV treatment regimens for children. We do not generally require that the sponsors perform randomized, controlled phase III studies in children if there are

adequate data confirming the drug's efficacy in HIV-infected adults.

We also request multiple dose, PK, and safety studies of drug X in HIV-exposed neonates, and by that we mean neonates born to HIV-infected mothers. These studies are designed primarily to identify the PK profile and some safety data in this age group and not to show the efficacy of a treatment or prophylaxis regimen.

The template also identifies the age group in which studies will be performed. These are HIV-infected pediatric patients from 1 month to adolescence and HIV-exposed neonates.

These patient groups were originally designated to allow the inclusion of the larger population of neonates whose HIV status had not yet been determined at a time when the rate of perinatal transmission was significantly higher in this country and other countries where most of the research was being performed.

Over the last year, a number of issues regarding the development of HIV drugs in neonates have been raised. Sponsors have voiced concerns regarding the feasibility of conducting studies in neonates and some have been asked to be released from their commitment to study drugs in this age group and to have their written requests amended. Amending a written request would allow a sponsor

to be granted the six months of exclusivity for that drug without performing the neonatal study component.

Some of their concerns include the size of the population available for study, the characteristics of this population available to be studied, the ethics of including uninfected neonates in clinical studies, and the ability of parents to understand and give informed consent during the first few weeks of an infant's life.

Lynne has given you a very good overview of the size of the population involved in the U.S., but just to recap a little bit, it is estimated that 300 to 400 HIV-infected infants are born annually in the U.S. It is now standard practice for infants born to mothers with known HIV infection to receive prophylaxis through 6 weeks of age or until a definitive diagnosis can be made, whichever comes first. Current pediatric guidelines recommend treatment for HIV-infected infants less than 1 year of age.

Diagnosis of HIV infection in the neonate can clearly be made by 4 weeks of age using the Public Health Service's recommended testing schedule. In practical terms, although many centers who are familiar with HIV have gotten much better at identifying infants early, it is not always possible to identify a newborn as HIV-infected prior to leaving the hospital and is not always possible to confirm early positive test results with a second

confirmatory test before the infant is 4 weeks of age. Consequently, the number of infants diagnosed with HIV infection and presenting for treatment during that time is relatively small.

The total number of infants born to HIV-infected women in the U.S. is a little more difficult to determine. Reporting of HIV infection is not required in all states and there is no linking of infection status to pregnancy in the states that do require reporting. The CDC HIV/AIDS Surveillance Report identifies approximately 50,000 women reported to have HIV infection through December of 2001. That's the last time period for which appropriate statistics have been compiled. This number includes women only from the jurisdictions that require reporting, but does include all female patients greater than 13 years of age.

We know that rapid HIV testing of women in labor whose HIV status is not yet determined are being evaluated and it is hoped that these studies will provide the identity of more women and infants who are at risk, but it is not clear how the identification of these infants will impact on neonatal studies.

We know that studies have shown that in the U.S. and other countries using current HIV treatment regimens, the rate of perinatal transmission is less than 2

percent in pregnant women receiving appropriate HIV treatment. If you calculate backwards from the estimated number of HIV-infected infants who are born, you can come up with a number of thousands of HIV-infected women delivering infants in the U.S. each year. These estimates range from the 6,000 or 7,000 that Lynne says up to 12,000 or 15,000 in other estimates.

Worldwide the size of the population potentially available for study is quite different. It has been estimated that 600,000 to 800,000 infected infants are born annually worldwide. Compared to the number estimated in the U.S., the population of infants born to HIV-infected women outside the U.S. is tremendously larger. As we all know, these women and infants reside predominantly in resource-limited countries. Rates of transmission are decreasing in some of these countries but not in others, and certainly treatment of HIV-infected children remains much less common in resource-limited countries than in the U.S.

Clearly there have been studies successfully conducted in neonates. Four of the five drugs that have already received pediatric exclusivity were evaluated in infants less than 4 weeks of age. Also, the Pediatric AIDS Clinical Trial Group has been instrumental in performing studies in this age group by enrolling pregnant women in

clinical trials and following them and their infants through the postpartum period. I have a couple of examples listed here of neonatal studies that were reported last year at the 9th Conference on Retroviruses and Opportunistic Infections.

PACTG 354 evaluated ritonavir in pregnant women and their infants and enrolled from November 1997 to November of 2000. This study enrolled 7 pregnant women. There were cord blood drug levels available in 4 infants and full PK assessment in 3.

PACTG 353 evaluated nelfinavir in pregnant women and their infants and enrolled from December 1997 to November of 2001. Cohort I of this study enrolled 10 mother-infant pairs and determined that the dose of nelfinavir being studied in the neonate did not provide adequate drug levels. Cohort II enrolled 23 pregnant women. Cord blood levels were available in 16 infants and full PK assessments were available in 10 neonates.

These studies and others provide valuable information about how to use the HIV drugs in neonates, but they also point out the pros and cons of conducting studies in young infants. These studies require years to enroll very small numbers of mother-infant pairs, and even in these well-conducted studies, only about half of the neonates remained on study and completed the pediatric PK

portion of the study.

However, both of these studies pointed out that the initial doses of ritonavir and nelfinavir that were being studied resulted in inadequate drug exposure. This confirms that appropriate dosing of at least some antiretroviral drugs in neonates cannot be predicted accurately on the basis of PK modeling or dosing in older children.

In terms of the characteristics of the population available for study, we know that the vast majority of infants born to HIV-infected women in the U.S. and increasingly in other countries as well will be uninfected. Their HIV status may not be confirmed for 2 to 4 or even 6 weeks. Therefore, most of the HIV-exposed neonates available for research studies will be uninfected. Because they are not infected, most of the HIV-exposed neonates enrolled in drug studies are unlikely to derive direct benefit from participation in these studies.

Is the risk/benefit assessment in this subpopulation of HIV-exposed infants, those whose HIV infection status has not yet been determined, different when the rate of transmission is less than 2 percent compared to 20 percent or compared to 10 percent?

In the case of HIV drug development, the major concern expressed by our sponsors involves the ethics of

studying this population of uninfected infants. Uninfected neonates enrolled in clinical studies would be subjected to the risk of drug exposure and study procedures without the potential to directly benefit from the knowledge obtained. We know in many of our studies HIV drug PK assessment often requires multiple blood samples. Many of our newer drugs are not amenable to single-dose PK and require multiple days of dosing for accurate assessment and steady state levels.

Also, many of our drugs have significant potential for toxicity, including bone marrow suppression, hepatitis, hyperlipidemia, mitochondrial toxicity, and hypersensitivity reactions. Some of these events have been seen not only in adults and children who are receiving the drugs in HIV treatment regimens but also in HIV-negative adults who were receiving the drugs as part of post-exposure prophylaxis.

In 1999, the Ethics Working Group of the Pediatric Advisory Subcommittee recommended that the FDA adopt the principles described in subpart D of the Code of Federal Regulations, as Dr. Sever alluded to. This section provides for additional protections for children involved as subjects in research. At that time, the Pediatric Subcommittee strongly suggested that children enrolled in clinical trials should have or be susceptible to the

disease under study.

In the case of HIV drug development, this concept has been interpreted and discussed broadly. HIV-exposed infants were believed to be at sufficient risk for a uniformly fatal disease to warrant their inclusion in drug studies. This concept was discussed at length prior to the initiation of study PACTG 076, the first study that proved the value of prophylaxis for perinatal transmission. That study represented the first example of a proposed protocol being discussed at an advisory committee, and as you have heard from the previous speakers, it engendered a lot of debate on both sides of the question.

At the time of that discussion, the rate of perinatal transmission in the United States was between 20 and 25 percent. Clearly now if infants are not likely to derive direct benefit, we must agree that the benefit to the public health still outweighs the potential risk to an individual neonate who does not require HIV treatment.

Last, the FDA works to encourage ethical conduct of studies through protocol reviews and other communications with sponsors and convening advisory committees like this one. But study sites are required to report to an institutional review board, and that IRB is the final judge of a study's acceptability to the local community. IRBs at different institutions in different

communities may not agree on what is ethical and acceptable.

Finally, some concern has been raised by our sponsors regarding the ability of parents to provide informed consent. We know that parents of newborn infants are very protective regarding painful procedures. As in the PACTG studies, they may initially enroll in a study but later withdraw their infant before the study can be completed. We know that parents of HIV-exposed infants may be very anxious over the unknown HIV status of their infant until the diagnosis can be confirmed. Similarly, parents may express feelings of guilt regarding the possibility of infecting their child with a potentially fatal infection.

However, those of us who have worked with parents in this setting acknowledge these issues but have learned never to underestimate the ability of parents to assimilate information and make difficult decisions.

In summary, the Division of Antiviral Drugs has tried to encourage the study of neonates as part of antiretroviral drug development through the incentive mechanism of the written request and pediatric exclusivity. The sponsors who have completed studies or agreed to conduct studies should be commended.

However, we believe that the issues raised by some of our sponsors regarding the study of neonates are

legitimate and are worthy of bringing to public discussion because of the changes that have been brought about by improved perinatal prophylaxis. We would like the advisory committee to consider the risks and benefits of antiretroviral drug studies in this age group, especially in uninfected neonates, and whether we in the Division of Antiviral Drugs should amend our request for sponsors to perform clinical trials in this youngest age group. We recognize that this is an area of great interest to many individuals and groups and we doubt that this is the last discussion we'll have on this topic.

Thank you.

(Applause.)

DR. CHESNEY: Dr. Lewis, did you want to introduce us to the questions or can we pick that up?

DR. LEWIS: I can either do that now or later.

DR. CHESNEY: Maybe we could do it later after we do the questions for the presenters.

So the floor is open. Dr. Nelson.

DR. NELSON: A question for Dr. Mofenson. Thank you for your clear presentation.

You emphasized efficacy. I'm wondering if you could briefly comment on safety, in particular two questions. Do you anticipate the safety profile would follow drug class, and can you extrapolate safety from

preclinical or from older children and adult studies to this population?

DR. MOFENSON: That's about another half an hour talk. Let me first address safety of neonatal prophylaxis as used in prophylaxis regimens as opposed for treatment, and I can provide you an article recently published in JAIDS. Is it in here? Okay, good.

I think that the data show for the prophylactic regimens we're currently using, that toxicity is minimal and transient with probably AZT having the most toxicity, bone marrow toxicity, with anemia being more frequent in infants receiving AZT.

The issue of long-term toxicity is more difficult to address. Data from our studies of long-term follow-up have followed children from 076 through maybe 10 years of age and not found any problems to date. But the French have reported a mitochondrial toxicity syndrome associated with lactic acidosis and some neurological disorders in a small number of children. I estimate, based on reading their articles, that the incidence of this would be about .5 to .7 percent, if I remember my calculations correctly.

Following the presentation by the French of their 7 children who had those disorders, 2 of whom died, we did an in-depth analysis of our database of children in

the U.S., including data from the CDC and all of our clinical trials, over 16,000 uninfected infants followed since the early years through 2000. We did not identify any deaths similar to the deaths reported by the French.

There has been a study of uninfected babies within the PACT study, which is a CDC natural history study, and they looked at their uninfected infants for the prevalence of disorders that the French described and did not find those. That's been published.

I know from the European collaborative study, not published, but through verbal conversations, that they have also not seen this event.

So is it real? Is it not real? I think that it may be real. I think that it is very rare and in my view doesn't outweigh the potential benefit to the infant in terms of prevention of transmission.

Can you extrapolate? Well, I guess I was just trying to think whether the mitochondrial toxicity with in utero exposure could be extrapolated. We haven't seen any toxicity in newborns and children that haven't also been reported in adults is what I would say to date.

DR. NELSON: And then the final thought is if resistance in future is one of the issues that will have to be addressed, would you anticipate seeing different toxicity profiles as you move from drug class to drug class

so that the data you've got now may or may not be relevant to that?

DR. MOFENSON: Well, we have data in neonates on all three of the major drug classes, the NRTIs, the NNRTIs, and the protease inhibitors, not all drugs in all classes, but we have data on all of those and haven't seen anything unusual.

There are two new classes, the nucleotide tenofavir, which has not been tested in newborns yet, and the T20 fusion inhibitors have not been tested in newborns yet.

But we haven't seen anything surprising in terms of the three classes that we use most frequently. Linda talked about the protease inhibitor ones. Nevirapine had a phase I study prior to the HIVNET 012, and AZT and 3TC and ddI and d4T have all been studied in neonates.

DR. CHESNEY: Dr. Mofenson, could you comment for us on the accuracy of diagnosis in the first 24 hours, the current state of the art?

DR. MOFENSON: Yes. I think that you can diagnose at birth the kids who are infected in utero. So it depends on the proportion of children infected in utero. Probably that's around 20 percent, so that means 80 percent of infants will potentially be infected but not have a positive culture at birth.

This may change as we see women receiving antiretroviral therapy for prolonged periods during pregnancy. In 316, the most recent perinatal trial, about 40 percent or so, I think, of the kids who were infected were positive at birth. So you may see a change as you have more effective intrapartum interventions put in, but I'd say most people would say 20 percent or so positive at birth.

DR. CHESNEY: Would there be any reason to think that if a mother had received prepartum and intrapartum therapy, that the test may not turn positive within the first 24 hours?

DR. MOFENSON: There have been studies with AZT and there doesn't appear to be any problem with AZT monotherapy. With the other drugs and in particular with combination drugs now we're talking about being given to the newborn, I don't know. There haven't been that many studies of diagnostic tests in newborns who have received more than just AZT. AZT alone doesn't appear to affect.

Let me just comment. If you're using DNA PCR, one might not think that you'd see a delay, and that's because even adults who are undetectable for many years, in terms of plasma RNA, still have positive DNA. And in children who have received treatment starting at 3 months of age or more and have been RNA negative and have

seroreverted, they still are DNA PCR positive. So if you're looking at the virus in the cell, you may still be accurate.

DR. CHESNEY: Thank you.

Dr. Fink and then Dr. Danford.

DR. FINK: One comment and one question. The comment is, as the presentations went on, I was confused. Although it's medically correct the use of the term "prophylaxis" versus "prevention" of transmission, particularly to IRBs and lay individuals, I think it would be very helpful to talk about prevention of transmission because this really to me doesn't seem to fit prophylaxis in terms of talking about neonatal treatment.

But my question is, as we look at PK data and discuss studies in neonates, what is going to be the effect of the issue that we have mothers who have received vastly different amounts of prenatal antiretroviral therapy and how will this allow you to interpret PK data in neonates, some of whom may have been exposed to multiple drugs prenatally and some of whom have been exposed to no antiretroviral drugs prenatally?

DR. LEWIS: That's a very difficult issue for some drugs but not for others. Not all of these drugs cross the placenta well. In the studies that I outlined, the PACTG studies, what we found is that the protease

inhibitors really don't cross the placenta in identifiable amounts. There may be some effect, but it is likely to be minimal.

Drugs like AZT and nevirapine and probably some of the other nucleoside reverse transcriptase inhibitors do cross the placenta in varying degrees, sometimes widely variable. But that was the purpose of looking at cord blood levels in many of those infants as well as then doing direct PK analysis on the infants.

DR. FINK: But isn't it possible or likely that even prenatal exposure to AZT may alter postnatal metabolism of a protease inhibitor?

DR. LEWIS: No. Those drugs do not interact. So some of the protease inhibitors interact with each other, and that's why if you're going to look at mother-infant pairs, it makes the most sense to look at the same drugs in the mother and the infant so you don't have too much conflict or too much interaction. But again, most of these drugs, the newer drugs, don't cross the placenta in substantial quantities.

DR. MOFENSON: Just a comment as to how we studied this with nevirapine, which has a plasma cord blood ratio of about 1, was we first studied nevirapine in the mother and did not give drug to the baby, looked at the fade-out pharmacokinetics in the baby to determine when

giving another dose of nevirapine would be warranted. So that is how that was done. And the half-life of nevirapine was prolonged. In the cord blood, it was prolonged in the baby, and we didn't have to give a second dose until 72 hours.

DR. CHESNEY: Dr. Danford.

DR. DANFORD: Before we have to face the question of whether it's ethically permissible to enroll neonates who are not actively infected to study the pharmacokinetics of these drugs, I think an important question is, would the study of such groups be scientifically valid? Are uninfected neonates known to be or thought to be the same in their pharmacokinetic handling of these drugs as infected infants? And I'd be interested in comments about whether this is known by any data that we already have or if there is scientific reason to believe these populations are different.

DR. MOFENSON: The data we have from earlier studies, such as AZT and nevirapine, showed no differences in metabolism between infected and uninfected babies. So I don't anticipate that's an issue.

DR. LEWIS: Just as an addition, most of the neonates who are born to HIV-infected mothers are born healthy, so they have no real identifiable abnormalities of renal or liver function. Occasionally there is a sick

infant or a premature infant, and then all of the metabolic processes that go along with extreme prematurity are in play and that's a different group entirely. But in terms of most neonates, they're mostly indistinguishable whether they're infected or non-infected.

DR. CHESNEY: Dr. Wilfond.

DR. WILFOND: Yes. I had two questions for Dr. Mofenson. The first was a clarification. While people were making the distinction between HIV-infected and not infected, my impression was the recommendations are for the treatments for HIV-exposed patients. And my question for you is whether before there ever would be a change in the clinical recommendations for those HIV-exposed patients, would PK data ever be sufficient or wouldn't you want data about efficacy before using a new drug in those children?

DR. MOFENSON: You're correct that the U.S. Public Health Service recommendations for neonatal treatment are for HIV-exposed infants because you won't have their diagnosis.

Back in 1994, when we had the first Public Health Service meeting, people without any data but with natural history epidemiologic data felt that even though we didn't have efficacy data for intrapartum/postpartum or postpartum only AZT -- we didn't know for sure that that was effective -- that they felt that there was suggestive

enough evidence to go ahead and make those recommendations. So even in 1994, those recommendations were made and that was way before we had the studies showing intrapartum/postpartum efficacy.

The second meeting of the group was 1998, and there was extensive discussion in the recommendations for the intrapartum/postpartum when the mom hasn't received antepartum therapy or when the mom hasn't received antepartum/intrapartum therapy. So here you're dealing with pre-exposure and post-exposure prophylaxis or only post-exposure prophylaxis.

And we have to remember that the 2 percent transmission rate is only for those mothers who are in antenatal care early, get HAART treatment, perhaps elective cesarean delivery. 15 percent of HIV-infected women are not seen until labor, and those women have a transmission rate even with intrapartum/postpartum or only postpartum prophylaxis of over 10 percent. So it's a very different situation.

There was extensive discussion in the group about whether to recommend anything other than AZT, and the clinicians and obstetricians and pediatricians and experts that were part of that group felt the data from nosocomial prophylaxis where they recommend two to three drugs for prophylaxis was enough to put combination therapy of the

baby into the guidelines with the comment that we don't have a lot of data on pharmacokinetics and safety of these drugs in the baby. We now have an increased amount of information on that based on the studies that Linda has talked about.

So I would say that having efficacy data for use of the drugs postnatally on every drug that gets used postnatally probably will never happen, and that if we have pharmacokinetic and safety data, that would probably be enough.

I think maybe the pediatricians in the group who care for HIV can comment as to whether they use combination antiretrovirals in neonates in selected circumstances. It's my feeling that many HIV experts do do that. I see nods over here.

DR. LEWIS: Just a regulatory comment. We in the Division of Antiviral Drugs, because of primarily numbers and the feeling that there would never be controlled clinical efficacy trials in young infants, determined many years ago that we would accept the efficacy of a drug in an adult population as proof of concept that there would be efficacy in the pediatric population because the virus isn't any different.

DR. CHESNEY: Dr. Mofenson, I had one more burning question and then Dr. Fletcher has a question.

I wonder if you would give us your take. Because you've, I think, participated in trials in other countries, given the diminishing population in our country, what are your thoughts about doing these studies? Say we were to advise continuing these studies in neonates. What are the issues involved in doing these in other countries?

DR. MOFENSON: Well, the HIVNET 012 study had, as a prelude to it, a phase I study of nevirapine in pregnant women and neonates in Uganda. We did the study first in the U.S. That was PACTG 250, the study that I talked about where you gave it to the mom first and then to the baby. And then that study was repeated in Africa because the Ugandans wanted data in their own population. The pharmacokinetics were basically the same.

I think that there are reasons to want to do those phase I studies in resource-limited settings because the children there may have co-existing conditions that are not necessarily present in U.S. children. There may be a higher incidence of anemia, for example. So there may be more potential for toxicity in children in resource-limited settings. Having said that, we have not seen that to date.

So I think that there are strong reasons for doing the studies there as well because the issue in resource-limited settings, as I tried to emphasize, is postnatal transmission. That's the issue, breastfeeding

transmission. How can we make breastfeeding transmission safer? And if one way you're going to do that is by doing infant prophylaxis with drugs for 6 months, you have to have the data on pharmacokinetics and safety. So I personally feel it is essential to continue to gather that data because that's going to be the only way that we're going to be able to prevent postnatal transmission.

DR. CHESNEY: Thank you.

Dr. Fletcher.

DR. FLETCHER: My question is really for Dr. Lewis, and it really just follows Lynne's last point. It's like one of these "what if" questions. So if the FDA is going to contemplate changing the requests to obtain neonatal data, what is the alternative given the scenario that Lynne just identified that in this country there will certainly be infants, newborns that receive these agents and in other countries there will clearly be infants, newborns that receive these drugs? So if relaxing the rule is on the table, is there some alternative contemplated?

DR. LEWIS: Well, that's one of the reasons why we wanted you guys to come.

But there are certainly other options. Organizations like the PACTG would certainly be encouraged to continue doing studies that they felt were of benefit globally.

The written request, as I said, is a voluntary mechanism. We can continue to ask sponsors to provide those studies and they can choose not to do it because they may say that the potential financial benefit does not compensate them for the cost and difficulty of doing those studies.

The written request has been our best incentive. We don't have much in the way of requirements.

We could make some of these studies phase IV commitments. Again, those are being tracked a little more closely now than they were in past years, but there's very little enforcement for making sure that the companies actually complete their phase IV commitment studies. So we know that if we don't have the data for use in the U.S. population, we clearly won't have it for use in the global population either. So it is a very difficult process.

DR. DIANNE MURPHY: And I just want to point out one thing too from a regulatory point of view. I'm sure many of you are aware of this, but for some of those who are not on the Pediatric Advisory Subcommittee, the pediatric rule, as you know, has been enjoined. So that is a tool which we no longer have in which we could require a company that came in with a product -- that was, the disease occurred in adults. We could require them to study it in children and we are now enjoined not to do that. So

that mechanism is not available to us.

DR. CHESNEY: Could I just clarify timing? I'm aiming for us to go on our break in about 10 minutes. Although I don't know if we have anybody who wishes to speak at the open public hearing, we do have a number of people well-known to all of you, who have written letters who were not able to attend, and I wanted to be sure we had an opportunity to read some of those into the record before we begin our discussion of the questions at 10:50. So I just wanted to give you an idea of where we were at.

I think Dr. Nelson and Dr. Gorman both have questions. Dr. Nelson.

DR. NELSON: Back to pharmacokinetics. At what age in the first, say, 6 months of life do you begin to see a shift in the metabolism? What I'm leading up to is if we have a problem doing PK data in someone who is not infected, would it scientifically still be valid to wait until we were able to demonstrate or prove infection before doing that PK study, say, at 1 month of age or 3 weeks?

DR. MOFENSON: Probably Courtney should answer this. Let me give you my feeling and then Courtney should answer this because he's the pharmacologist in the PACTG.

I think it depends on the drug. A renally excreted drug is different than a liver-metabolized drug.

I think that we don't have a lot of data

sequentially on a drug from birth going all the way up. Usually what we've got is neonatal data and then -- I don't know -- 2-month, 3-month data, and there's this big blank period in between. For some drugs, there's a big difference between neonatal data and 3 months. So I think you need that data in between.

But, Courtney, you're the expert.

DR. FLETCHER: I'd probably like to see if I can't pass it to Dr. Spielberg.

(Laughter.)

DR. FLETCHER: But I think Lynne is right. It really is drug-dependent. There are changes that happen certainly over the first 3, if not into the first 6 months. I think AZT again has been one of the better studied drugs with PK within the first week that was showing half-lives of 14 hours. Within 2 weeks, it was down to about half of that. By 3 months, it really began to approach adult half-lives which are in the 1 to 1.5 range. They may have still been about 3.

The non-nucleoside drugs and the protease inhibitors have really been less intensively studied. I think as a general rule, the half-lives in the neonates are longer and then approach adulthood in some varying time after that.

DR. MOFENSON: One comment is that for a drug

like nelfinavir, for example, the original neonatal doses were based on extrapolating from children under 12 months but that were older, and it was wrong. Way wrong. I mean, we had to really double the dose on a milligram per kilogram basis to get adequate levels in neonates.

DR. SPIELBERG: I think the bottom line of what's been said is it depends and that's why you need data. That's the bottom line to the whole thing. There are drugs where a babe at a week is a very different biologic organism than a babe at 1 day of age. There are drugs where it really doesn't matter very much, and it depends on the mechanism of clearance and it depends on the nature of the compound.

Given that we're going to be seeing new compounds with varying different structures and varying different pathways of clearance, varying different metabolism by different cytochromes and other pathways, the bottom line is, if you're going to do it rationally and if you're going to provide adequate coverage of the organism and safety for the patient, you've got to have the data.

DR. CHESNEY: Thank you.

Dr. Gorman has been waiting patiently over here.

DR. GORMAN: I'm not sure who the question is for, but how comfortable are we with the non-treated

transmission rates in terms of placebo treatments? Are those 20 to 25 percent numbers stable over long periods of time, or are those numbers that we generated over a brief of time and now have little confidence in?

DR. MOFENSON: Do you mean the comment that the transmission rates in the U.S. are 25 percent? You think maybe they might be different?

DR. GORMAN: I'm asking how comfortable you are.

DR. MOFENSON: Well, I think that even back in the early '90s we saw differences between the U.S. and Europe, 25 percent here pretty consistently, 15 percent or so in Europe. This may have been due to differences in elective cesarean delivery between the countries.

What I'm not comfortable with is extrapolating from one country to another. If you took what happened in the United Kingdom, it was not the same as the U.S. which is not the same as Africa. Ideally you would have placebo controls for all of the trials. That's ethically not possible anymore.

DR. GORMAN: You've anticipated my second question which was, if all mothers who were HIV-positive had elective cesarean sections, what impact would you postulate on the transmission rate?

DR. MOFENSON: Based on the studies without

antiretroviral prophylaxis, it's 10 to 12 percent.

DR. GORMAN: And the third question that I have is, is the interruption of transmission from mother to child independent or dependent upon the continued treatment of the mother after delivery?

DR. MOFENSON: In the U.S. with our regimens, no, because the mothers don't breastfeed. The place where treatment of the mother postpartum may be important is in breastfeeding.

DR. GORMAN: Well, then I'll make my question more specific. With breastfeeding mothers, is the transmission rate independent or dependent upon continued treatment of the mother?

DR. MOFENSON: We don't know. That's why the trials I showed you are being done. I don't know.

DR. GORMAN: Those trials looked like they were addressing, at least in this arena, only the treatment of the infant. Is that an assumption on my part that's incorrect?

DR. MOFENSON: Yes. I showed two slides. One was the slides of the schema for infant prophylaxis, and the last schema slide was maternal HAART treatment.

DR. CHESNEY: Dr. Gorman, do you have fourth and fifth questions?

(Laughter.)

DR. GORMAN: Thank you very much, but no.

DR. CHESNEY: I think we'll take one more question and try to get back on track. Dr. Spielberg, I think you had your hand up first.

DR. SPIELBERG: Just a couple of comments. I think in the ideal world, those of us who worked hard on the Best Pharmaceuticals for Children Act went at it conceptually from the point of view that the incentives would really be a driver to do important public health studies. I'm encouraged that in fact the act has driven the development of many compounds so far in the HIV arena because, in fact, most of these drugs are not blockbusters. In fact, the issues of finances here do become tight. And I'm encouraged that the mechanism has worked.

I think what we're struggling with here is that the public health issues really do vary internationally and U.S.-wise. I would posit that all of us have a major vested interest in public health issues internationally because it's going to come back as an international issue to bite us if we do not, indeed, take into consideration the needs of kids internationally. And that's why the ICH effort and the efforts to move ICH out of, if you will, the first world into the rest of the world. We are all part of the same world.

It strikes me from what Dr. Mofenson has said

that the numbers of patients internationally are still staggering. They will remain staggering because of some of the issues we're dealing with with breastfeeding and transmission by other mechanisms, which makes it incumbent on all of us to understand how some of these drugs in fact are handled pharmacokinetically and safety-wise in the neonate.

And that's also in the U.S. public health interest because of the issue of emergence of resistant organisms. We are going to face this in our own situation here, and we have to figure out a way of doing the studies to get the information.

I'm encouraged by the safety that's been discussed here. We're not dealing with URIs or ear infections. We're dealing with a fatal disease. As such, the incidence and prevalence of the kinds of side effects that have been described, although very real and we have to take them into consideration in the newborn, appear to be reasonable, given the risks.

And I would also posit that the risks, when you're talking about 25 and 40 percent remaining risks for babies and large numbers in the rest of the world, that the risk/benefit of doing those studies in a distributive justice sense in those populations, if the drugs are made available to those populations subsequently -- and that's

one of the criteria, but if that's the case, then the risk/benefit in those populations becomes very different than the risk/benefit of waiting to get diagnosis in the kids here. If you already have a 40 percent risk of having a fatal disease, we're back to where we started with 076.

DR. CHESNEY: Thank you, Dr. Spielberg.

I think we could take a 15-minute break and we'll reconvene at 10:38.

(Recess.)

DR. CHESNEY: I think we're ready to start the open public hearing, if everybody could find their seats please. I'd like to start the open public hearing by reading into the record four letters that were e-mailed to the FDA based on today's discussion. We'll finish up with Dr. Jim Oleske who was able to come to the meeting.

The first letter is from Margie Rogillio, and she writes:

"Hi, I am a foster and adoptive mom and have so far lost six babies to this virus. And I currently have a foster child in end stage renal disease, and on dialysis at home daily, from HIV nephropathy. I am also a member of the Pediatric Community Constituency Group of the PACTG and a member of the CAB at my local site.

"It is so important to continue to develop medications that are effective and safe for our babies.

Yes, the rates are down due to 076, but the truth is many women do not get prenatal care and are still having babies born with or exposed to HIV. It is very disheartening now with the focus on adolescents and international -- not that these are not important -- money that was being used to help American infants is now being re-routed to these populations and there is no increase in funding. So we are losing money to fund studies for our kids.

"I think in some cases information extrapolated from the United States studies could be used internationally, but I am concerned about the reverse. We live in a very different way from the rest of the world.

"I know these babies are being born here because they come into my home. I would like to plead that we keep our children, our babies, in focus.

"Thanks."

The second letter is from Dr. Philip Walson, a professor of pediatrics at the University of Cincinnati who is Director of the Clinical Pharmacology Division and Clinical Trials Office. He says:

"This brief note is in response to the announcement of the upcoming FDA advisory committee meeting to discuss studies of anti-HIV drugs in infants. Unfortunately, I cannot attend the meeting, but I wanted to provide some comments.

"Clearly studies are needed and could be done in HIV-infected infants both in the United States and abroad. However, children whose mothers were given HIV drugs could provide subjects for useful PK/dosing information with little or no risk. Important dosing information could be obtained by merely doing population PK studies on children who were exposed only while in utero and even if not given additional medication after delivery.

"Such children will have blood drawn for HIV infection status and for other routine lab testing. If collected and analyzed correctly, these samples would provide much of the PK/dosing data necessary to dose infants who need postnatal treatment. Such studies would be ethically, financially, and practically fairly easy to do. Studies in children are clearly preferable to the only alternative, that is, the continued unregulated and uninformed use of anti-HIV drugs in such children."

The next letter is from Dorothy Shaw.

"To Whom it May Concern:

"As a parent of an HIV-infected child, I believe studies on new HIV meds for use in neonates should be limited to those that have proven safe and effective and useful in older children and older babies. I do not believe every drug needs to be studied in newborns since there are effective drugs currently available. As we

discover meds that do not have side effects of the current meds, or have improved results, we must first find them to be safe and effective in older babies and children, then they should" -- in bold -- "be tested in neonates. Since we do not have adequate numbers of neonates in the U.S., studies can be done with newborns throughout the world, where the numbers of HIV-infected newborns is not diminished. Studies must be carried out with the same ethical considerations, et cetera, as they would have been designed for U.S. newborns. The results of such studies would translate for use in newborns in the United States as well as throughout the world.

"Thank you for the opportunity to put in my two cents."

And the last is from Robert Reinhard. "I am not able to attend the March 3 meeting to discuss the announced issues. However, please consider these e-mailed comments on one of the three questions announced in your notice." And the question is, "If studies are conducted in resource-poor countries, where perinatal transmission rates are still unacceptably high, can the results be extrapolated to the U.S. population?"

And his comment. "Although the announcement was intended to be brief, it did lay out many factors affecting this drug development initiative, including the

use of current guidelines for study and considerations of minimal risk towards populations. Specifically, the announcement mentions 'current guidelines endorsed by the American Academy of Pediatrics, NIH and FDA, stating that infants who are unlikely to directly benefit from research should not be exposed to greater than minimal risk, and suggest that exposure of uninfected infants to antiretroviral drugs constitutes a greater than minimal risk.'

"On the other hand, the announcement appears to be silent on ethical issues involved in exposing and testing drugs in populations in resource-poor countries who might directly benefit from such research but only for the announced purposes of extrapolating results to U.S. populations. Such a plan could only be pursued if, first and foremost, the benefits were secured and committed to the populations where the testing took place. Any plan to initiate such tests in resource-poor countries would have to recognize and resolve in advance the formidable problems associated with paying for and distributing the benefits of the research to the local populations broadly and successfully. Otherwise such testing would be exploitative. During your discussions and further announcements on this initiative, please make sure to include public awareness of the ethical issues involved in

conducting clinical trials in resource-poor countries.

"Thank you."

Dr. Oleske. I think we all know who you are, but maybe you could give just a few sentences of introduction.

DR. OLESKE: I'm Jim Oleske. I'm a pediatrician from Newark, New Jersey. I guess I came to this because I'm the Chair with Gwen Scott of the Pediatric Antiretroviral Treatment Guidelines and an active participant in clinical trials for a number of years.

Interestingly, I just got back from South Africa where we spent a week and a day implementing the MCCT Plus program which is, in fact, trying to get treatment early to both infected women and their family members.

I have some very strong feelings on the need to provide appropriate dosing and experience with drugs that have not been studied in children. I think that we need to, as Lynne very eloquently pointed out, have the responsibility and the obligation to provide reasonable studies on such drugs as they become available in adult populations.

As I told people in the very beginning, infants and children die of this disease much quicker than adults, and access to newer drugs are critical. Now, we're talking

more about in the first 4 weeks of life, and I'd like to address that.

In the outline it says that 300 or so children are born infected. But there's not 300 children born infected. There are 6,000 children who are exposed to antiretroviral drugs possibly, but certainly exposed to the virus every year in the United States. From that 6,000, maybe 300 children become truly infected. But in the first 4 weeks of life, we don't know which one is which. And I don't think even with our best technologies we'll really be able to say someone is absolutely negative or absolutely positive in that critical period of time when in fact treatment started and initiated early may prevent lifelong infection with a uniformly fatal disease. I don't know of anybody who lives through AIDS. I'm always proud to tell people that I have older children. In fact, my happiest moment last week was when one of my patients, who was perinatally infected, said she got accepted to medical school. But the bottom line is that's the exception and certainly not the rule.

So I would just like to say that we need to do PK data in the first 4 weeks of life on HIV-exposed infants. But in general -- and I will admit this -- most of the studies are not going to be begun until infants are 4 to 6 weeks after a presumptive diagnosis of infection can

then be made. We need to study, though, that pool of 6,000 exposed and we need to effectively treat the 300 that remain infected with HIV.

In the United States we do have the advantage of not breastfeeding. That is not available to the rest of the world.

We could all come up with randomized clinical trials, and in my written statement, I included that and what we could do to study this problem. But it starts with having, in selected, small numbers of infants in the first 4 weeks of life, appropriate PK data and safety data on new drugs for antiretroviral use. As resistance develops, we could have other waves of children not sensitive to the drugs that we now feel comfortable in using. So I would make the plea that we need this kind of safety data.

I also feel that the U.S. cohort of exposed infants is certainly not like the exposed cohorts I have seen in the developing world. I think that it's certainly ethical and appropriate to do studies in those children. I don't think that data translates directly back to the United States.

I agree with the last-read statement about the vital importance of doing ethical clinical trials whether it's in the United States or whether we're partnering it in the developing world. We have that obligation to be

ethical no matter where we do our studies.

However, I don't think the studies done in the developing world will be easily transferrable to the U.S., and therefore, I think we are left with the challenge of how do we identify, talk with women so that they are giving their permission in a knowing way, not at the time of labor, to study these drugs. I think if we do a good job, reach out to these women, present them the risks and benefits of studying new drugs, I think they would be included in clinical trials and we could develop enough information to have access in the future to these newer antiretroviral drugs being developed.

Thank you very much.

DR. CHESNEY: Thank you.

I think we'll move on to the questions. Dr. Lewis, did you want to present them to us at this point? You could read them, or I don't know if you have them as an overhead. We all have a copy.

DR. LEWIS: These will just make them a little prettier.

What I'd like to say is the original questions that went out in the committee's backgrounder, as we read over them many, many times, we came to some subtle changes in the wording that we thought really got to the crux of the issues we were trying to bring up a little bit better

than the way we had originally worded them and sent them out to you. The concepts are very similar, but we put them in a little bit different order.

What I'll do is I'll just go through all of these questions and then I'm going to sit down and let you guys hash out what you think the best answers are for some of these. We understand that we may not come to definitive answers today, but the discussion itself may help us a lot in determining where to go next.

So we started with really the biggest question. Given that an estimated 300 to 400 HIV-infected infants are born annually in the U.S., that some of these infants are diagnosed after the first months of life, and that it is difficult to enroll neonates in studies in general, are there too few HIV-infected infants born each year in the U.S. or is there now not enough public health benefit to justify requesting studies in neonates?

The second question. Since neonates born to HIV-infected mothers may be tested for HIV infection in the first 48 hours and again at 4 weeks, HIV-infected infants can be diagnosed within the first month of life. Should only HIV-infected neonates be studied?

If an HIV-exposed population is to be studied, please discuss the risk/benefit assessment for HIV-exposed neonates who might be enrolled in a clinical trial. We

mean the infants whose status is not yet determined with the rates of transmission that are variable in the U.S. and other countries, whether mothers have had prenatal care or not.

The second part of that question. If studies are to be conducted in resource-poor countries where the rate of underlying diseases, malnutrition, infant mortality, and pharmacogenetics may differ substantially from the U.S., can we extrapolate these results from these studies to the U.S. population?

And our last question. Should we continue to request pharmacokinetic and safety studies for every antiretroviral drug under development, which is our current policy? If not, what criteria would you suggest for deciding which drugs should be studied in the neonate? New classes of drugs, different resistance profiles, specific safety issues, or pharmacokinetic parameters?

DR. CHESNEY: Thank you.

So our first question is are there too few HIV-infected infants born each year in the United States or too little public health benefit to justify requesting studies in neonates. And the floor is open for discussion. Dr. Fost.

DR. FOST: Well, I'll start off. First of all, it's not really the province of this committee, but it is

an odd allocation of limited health care resources to be pouring so much into a problem that affects 300 children. Every one of them has a name and a face and Jim Oleske knows them better than I, but for every one of those, there are 3,000 abused children, more of whom will die than these 300 and many of whom will be permanently disabled and so on. And the amount of Federal resources we're putting into research and prevention on that is trivial in comparison. That's not the FDA's responsibility, but it's one reason to be studying this problem, that is the neonatal problem, in the place where it is truly an epidemic where every hour there are 300 children, almost, born with this problem.

But it seems to me there are other compelling reasons for studying this abroad rather than here, and the points have already been made, but just to reiterate them.

The risk/benefit ratio for a child in the third world who has this problem is just much greater. That is, whatever the toxicity of the drugs are, they're nothing compared to the risk of getting nothing, and that is, the potential benefits of getting postnatal treatment are just so much higher. And we haven't heard that the toxicity is likely to be profound enough in frequency or severity to outweigh that potential benefit.

The ethical issues would be the same as here, that is, a satisfactory risk/benefit ratio to that child.

That's at the center of doing ethically responsible drug studies, and it would be much more favorable for those children.

Obviously, the high standards of consent and IRB review and so on should be followed.

Now, whether or not they're extrapolatable to the U.S. I'll leave to the scientists to comment on. Presumably not or for many reasons might not be. But that to me is not a reason not to do them for their own sake.

So it seems to me there's lots to be said from a justice standpoint, but also from an ethical standpoint to be doing these studies where they're needed and where the benefit will be the greatest.

DR. CHESNEY: Dr. Englund.

DR. ENGLUND: Well, I would just like to comment a little on the risk/benefit ratio. By saying that there's an estimated 300 to 400 HIV-infected children born a year really doesn't take into account who these children are being born to. These children are being born to our women who don't have treatment, who never show up to clinic. They're now being born to our teenagers who themselves were perinatally infected -- many of them or some of them. So we're seeing second generation HIV. I think we have a differential risk ratio depending on who the mother is, and I think we need to take that risk ratio

into account when we're talking about risk/benefit.

I also would like to say that I think we can do some extrapolating from some of the foreign studies also, but as a former investigator in ACTG, we have been wrong too many times about the doses to not have to look closer at the doses. But I do think there are subpopulations within the United States that we can try to use but they're very difficult to capture.

DR. CHESNEY: Dr. Nelson.

DR. NELSON: I think we need to start off by being clear about a distinction between HIV-infected infants and HIV-exposed infants, and I think we're bouncing back and forth in the conversation between those two groups. My understanding here is the purpose is to talk about HIV-exposed infants.

If you think about that at-risk population, if you take the data of 2 percent prevention versus what I heard was 10 percent where women would be untreated coming into labor and delivery -- I don't see our statistician around the table. But I took out my chi-square program and spent the time to try and calculate sample sizes. If you even provide for a generous, say, 4 percent difference -- in other words, if you accept a 2 percent increase if you're trying to look in the efficacy arena -- you need 1,200 infants to answer that question. And if you then go

abroad because there are more of them, to go from 10 to 12 percent, you need 4,000. So the sample size for any efficacy study when you're down in the 2 to 10 percent range is considerable regardless of location. But there may, in fact, be enough abroad.

When you then get into the PK data, since that gets down to question 3, I'll wait to comment on what I think are PK and safety data, but as part of this conversation, I think there's some confusion about infected versus exposed. And if we're talking about treating HIV-infected infants and studying them, then the issue gets back to the diagnostic criteria and the ease with which we can make that diagnosis and we shouldn't think that we're treating HIV-infected infants by treating the other 98 at the same time.

DR. CHESNEY: Can I just make a comment? We keep hearing about the 300 to 400 who are infected, but I think we've also heard that you can't make the diagnosis, particularly for those infected intrapartum. You can't know that they're infected in the first 28 days of life. Is that a correct statement? Dr. Mofenson.

DR. MOFENSON: It depends on what test you're using. I'm trying to remember. There was a meta-analysis of DNA PCR, and 20 percent positive at birth and then you end up in the 90 percentage by 3 to 4 weeks. So you can

diagnose most infected children or at least early diagnosis. Ellen?

DR. CHADWICK: And by 2 weeks, you can diagnose well upwards of 70 percent. So if you time your testing appropriately, you can make that diagnosis. It's just a question of how frequently you can get the baby in for repeat blood draws, et cetera.

DR. CHESNEY: Dr. Wilfond.

DR. WILFOND: Even though some people can be identified earlier, as I understand it from hearing the conversation, the clinical question is what do you do for people who are HIV-exposed. The impression I got was that those individuals are continued on therapy for at least 6 weeks before stopping. So regardless of whether somebody is identified with HIV, the clinical question still remains.

The question that I would like to ask -- it's probably more a clarification than a comment. I have the impression that the types of studies that are being described are essentially add-on studies. In other words, somebody is receiving AZT or some other intervention and then an additional drug would be used for a PK study.

But I also heard from Dr. Lewis that in general most people are quite comfortable stipulating efficacy of drugs based upon other information. If that's the case, it

would seem that treating an HIV-exposed individual with a new drug instead of the standard drug would provide efficacy, since that's being stipulated, and then you could still do your PK studies on that population. It seems like that would be a very reasonable way to proceed.

DR. LEWIS: To answer that clarification, there is actually a difference between treatment studies and prophylaxis or prevention of transmission studies. As we've heard, trying to get the numbers available for a study that will prove that a drug prevents perinatal transmission are quite large. Those studies are not part of our requirement. Because they are so large and they are very difficult to conduct, we have not used those as part of these written request mechanisms because clearly not all drug products can be studied in populations of infants that are that large.

The treatment studies -- so an infant is identified as HIV-infected somewhere 2, 3, 6 weeks of age. Then those infants go on a standard treatment regimen, and for those drugs generally we accept efficacy data from adults as correlating with antiviral efficacy data in children.

So efficacy studies are proven differently from perinatal transmission studies. What we really expect the companies to perform as part of their written request is a

PK and safety profile on some subset of the population in that age group.

DR. CHESNEY: Dr. Fink.

DR. FINK: It raises a dilemma that I'm beginning to feel, which is in the United States, if we're talking about prevention of transmission, then in that group of patients, safety becomes a key issue, particularly as Dr. Sever raised the issues of growth development and mental outcome. It is terribly hard to follow those infants for 5 years in the United States with all of the resources we have available. I would think it would be nearly impossible to get long-term safety data from foreign studies.

DR. LEWIS: That is correct. And what we have tried to do is get safety data over a period of at least 6 to 12 months in the population being studied. But remember, in these populations, the length of treatment is generally fairly short, anywhere from a few doses, a couple of weeks; in the longer ones, maybe up to 4 to 6 weeks.

DR. FINK: But in the U.S., it would seem the key issue is potentially the HIV-exposed infants. We want to minimize their exposure to toxic drugs, and we're not going to know that long-term toxicity from foreign studies. Those studies I would think would have to be done in the U.S.

DR. LEWIS: That's correct.

DR. CHESNEY: I think Dr. Chadwick, then Dr. Gorman, and then Dr. Nelson.

DR. CHADWICK: Just sort of a real world look at what we're seeing in the clinics. I'm in a university setting where we have a close relationship with our OB group, and I'm in a freestanding children's hospital. I think a lot of the HIV centers around the country are similar to this.

In those settings, the OB groups that are on top of the women that are providing the prenatal care are, by and large, not delivering infected women. It's the women that come in off the street, the patients that Dr. Mofenson was mentioning, up to 15 percent of women who are not getting prenatal care that are either walking into the university settings or, more worrisomely, in the community that we have to try to find those patients and then among those babies born to the women that are most likely to be delivering infected infants, studying those infants, doing the PK, making sure that we have drugs available that we know the appropriate dose to treat the babies for the time down the road when the current perinatal prophylaxis drugs will no longer be effective because there's widespread resistance. So I think the treatment at hand at this point is to make early identification of the infected babies,

study those babies, and then have that data available for prevention studies in the future.

DR. CHESNEY: Dr. Gorman.

DR. GORMAN: In discussing these questions, are we discussing interruption of transmission or prophylaxis, or are we just discussing the need for pharmacokinetic and safety data on a certain number of neonates?

DR. LEWIS: We're really interested in primarily the pharmacokinetic and safety data on a more limited number of infants.

DR. GORMAN: And is the number that you're requiring the number that is listed on page 3 of the proposed things? So we're talking about 8 neonates?

DR. LEWIS: Yes. We asked our pharmacologists what the minimum number was that they felt they could derive an adequate PK profile in a drug that didn't have extensive variability, and that was their answer, that if they could get 8 babies.

DR. GORMAN: And do you want a potentially larger number for the safety studies?

DR. LEWIS: Yes. This is all dependent on the specifics of the drug being tested. If there's a large amount of variability in pharmacokinetics that we know in adults or older children, we would pretty much anticipate that that might be true in very young infants also, maybe

even more so. So we would need more PK data. If we had particular safety concerns based on the adult or pediatric data, we would want a larger number of infants to be tested.

But again, these are relatively short-term studies. So the real safety data that you see with long-term administration of treatment regimens you may not find. You are certainly unlikely to find it within the neonatal period because by the time the kids get that much treatment, they're no longer neonates. So it's a little bit different safety assessment.

DR. CHESNEY: Dr. Nelson and then Dr. Glode.

DR. NELSON: Some of these questions I think overlap, but let me make my comment and it may also come back up in talking about pharmacokinetic and safety.

But if you are looking specifically at the issue of HIV-exposed infants, one of the problems that you then have to address is what sufficient safety data do you need before you're willing then to expose those infants, which is a very different risk/benefit calculus than if they're proven HIV-infected and then you get the 20 percent versus 70 percent over the first 3-4 weeks.

The other problem you get into is asking what condition are you treating. Even if you limit yourself to pharmacokinetic data, if you're not limiting yourself to

pharmacokinetic data in the infected population, I would assume that you would have to have some reasonable perspective of expecting to use that drug in prevention of transmission to justify doing the pharmacokinetics in that population. So then you'd have to make an argument about resistance and whether that's coming up or about ease of use, which is partly why the nevirapine and other studies have been used.

So there would have to be a justification for that drug. It wouldn't just be a justification to have PK data in that population in order to be able to then use it in a treatment setting if in fact you're studying uninfected infants. I think that made sense.

DR. CHESNEY: Just incredible sense.

Dr. Glode.

DR. GLODE: I was not part of the ethical discussions around 076, but at that point obviously there were exposed infants and 80 percent of those infants were not going to be infected, but 20 percent were. And there the risk/benefit seemed on the whole I guess to favor that study.

So I just wondered if people who were part of that discussion at that time sort of said, well, if it was 95/5, then we wouldn't do it because now, if you have 6,000 to 7,000 exposed infants and you estimate, taking all those

different groups you talked about, the people who do have prenatal care and the people who don't, unless you subdivide that group, it's overall 5 percent. So if 95 percent of the babies are not going to be infected but 5 percent are, then again one has to look at the potential safety issue and ask if that's ethically appropriate.

Did those discussions go on of 80/20 versus 90/10? If it was 90/10, we wouldn't do it, but if it's 80/20, we would. I don't know how one decides what the breakpoint is. I guess it depends on the presumed toxicities.

DR. CHESNEY: Dr. Lewis.

DR. LEWIS: Well, I remember some of those discussions because I worked across the street. I think Lynne was probably involved in some of those discussions also. I don't remember there being a discussion of varying things, but there was discussion that the rates in different countries were different. So the French studies seemed to have a somewhat lower transmission rate than the U.S. seroprevalence data, and it was felt that the 076 study might provide benefit in both of those scenarios.

So, Lynne, do you remember any other specifics along that line? It was a long time ago.

(Laughter.)

DR. MOFENSON: Yes. I guess a comment would

be, what about other conditions that are low in frequency and perinatally transmitted, Chagas' disease, trypanosomes, CMV, HSV? If we say that 2 percent or 10 percent is too low to test drugs for prevention of HIV, what does it mean for prevention of these other diseases that also have low frequency? What it basically means is that you can't prevent transmission of multiple infectious agents, not just HIV, if you decide that there's a percentage below which you're not going to test.

DR. CHESNEY: Dr. Hudak and then Dr. Nelson.

DR. HUDAK: I agree. I've been listening to the discussion about this possible breakpoint in terms of the risk/benefit analysis, and I think possibly back in the 1980s when there was so little information known about the possible toxicities of these agents in newborns and infants, that certainly factored into the equation. We have a lot more information now and are a lot more reassured about, at least in the classes of drugs that have been studied, minimal toxicity in neonates, in children.

From my perspective I think that this is a potentially fatal disease and the difference between a 2 percent versus a 20 percent is the same. I can't personally calculate a different risk/benefit ratio on what we know based on 2 percent or 20 percent. So whether it's a 90/10 or 2/98 or a .1/99.9, I'm not sure that you can set

a set point there on that. Certainly 2 percent is a significant rate.

The other thing that I would like to echo is Dr. Spielberg's comment that this is in fact really a global problem. In this country, as Dr. Fost said, it's really fairly minimal number-wise compared to a lot of different pressing issues we have with child health and neonatal health.

On the other hand, I do think it is important and ethical to get the best information we can get in this country for the dosing among the HIV-exposed babies because that's going to be the basis for doing larger studies in third world countries. I think it's easier to do here, and we have to make sure that the studies we do in other areas are the best studies we can do.

And we haven't even touched on the larger issue in terms of perinatal transmission in several countries where the breastfeeding makes it such a difficult problem and that clearly there would be a need for a lot more different classes of drugs, potentially a lot more drug dosing if breastfeeding continues and can't be abated completely like in this country.

DR. CHESNEY: Thank you. I think we're getting close to maybe being able to vote on this one, but I have Dr. Murphy, Dr. Nelson, and I think Dr. Chadwick had her

hand up.

DR. DIANNE MURPHY: I was saying if one could go back and look at the transcripts of those advisory committee meetings, I do want to reiterate what others have said here is that the safety was really an issue of the long-term safety. I do think we have to then come right back to where we started from which is here you have successful treatments and if you're going to do studies for PK in that risk/benefit ratio, you still have molecules that may be less known that you're going to be putting into this population. The question is, should we be putting it into the uninfected versus only those patients in which we do have a diagnosis?

Thank you.

DR. CHESNEY: Dr. Nelson.

DR. NELSON: Actually my comment I think reinforces Dianne's last comment. I don't think the issue is the 2 percent versus 10 percent versus 20 percent. Now that you have a track record with AZT, with nevirapine, or whatever -- and I'm not sure what PACTG 247 or 316 is necessarily -- what regimen, but whatever regimen is getting you below 2 percent, you've got a track record with that. The risk that needs to be considered is the new drug against that track record, not the 2 percent versus the 15 percent. If there's really no immediate justification for

adding a new drug into the prevention of transmission portfolio, then that's the question in my mind. What evidence do you need to where you think it's justified to enter a new drug into the prevention of transmission portfolio, not entering a new drug into the treatment portfolio, and what safety would have to be established before you'd be willing to do that against the track record of existing agents?

DR. CHESNEY: Dr. Chadwick.

DR. CHADWICK: But I think that comes back to the basic issue which is I think we have to be very clear about who we're testing the drugs in and that we have to start in the infected babies so that we have doses available, we know that they're safe in the infected babies. Clearly those are infants that have a need. We will not be able to do an efficacy study or, I would submit, even a safety study in this country looking specifically at prevention. So we just have to know how to use these drugs to treat. There's no reason to believe that we're going to use them very differently if we come to the point that we will need to use them for prevention. So we start out looking at the infected babies for the new drugs and not try to address prevention issues until we have the data in babies that truly need the drugs.

DR. CHESNEY: I think Dr. Walson's comment

about being able to study it if it's given to the mother in the first couple of days after birth was also an intriguing one.

Dr. Wood?

DR. WOOD: Just several comments regarding the assessment of risk/benefit because we are dealing with, as Dr. Nelson has highlighted, two distinct populations, those infants who are HIV-exposed and then those infants who are ultimately determined to be HIV-infected. So our assessment I believe is not dependent upon the background transmission rates, but truly the first component of the risk/benefit assessment is whether or not they're exposed. So by definition, all infants who are HIV-exposed have the potential to have direct benefit because they're exposed to a life-threatening illness.

The second component of the risk/benefit is dependent upon whether or not they are truly HIV-infected, and that is dependent upon when you can actually determine their HIV infection status. I actually think that based on the data that Lynne has so elegantly summarized, we clearly know that prepartum, intrapartum, there is clearly evidence that antiretroviral exposure results in a reduction of transmission. And given that that exposure exists and that the infant's status is unknown, that's an acceptable risk/benefit ratio. Once you get to the point where an

infant is born and you don't know their infection status, once that's determined, that would then alter the risk/benefit ratio because if you knew that an infant was truly uninfected, you want to minimize their risks by being exposed to antiretroviral drugs.

And I think that's just an issue that is a gradation of risk/benefit that's dependent upon whether or not you know the infant's HIV infection status. It can be known within the first 4 weeks depending upon the setting, but in other situations it can't be known. And I would believe that as long as the infant's status is not known, if it's not determined whether or not they're infected, then the risk/benefit assessment needs to be based on the fact that they truly are exposed to HIV, which is a life-threatening illness.

The separate issue is regarding the public health benefit of doing PK data and doing these studies in the United States, as well as globally in resource-poor countries. I think everyone has iterated that we clearly have derived critical information from these studies about dosing in neonates. I think there's no question that there is clearly a need to obtain PK data in this neonatal population. I also think that Dr. Spielberg highlighted that the written rule has had the desired effect that we wanted, which was to actually obtain PK data in this

population, and then because of the emerging issues of resistance and heavy treatment experience, as well as those children who are aging out and now having second generation infection, there's a scientific mandate to continue to study these drugs in this country.

DR. CHESNEY: Could I ask, Dr. Chadwick, your suggestion that the new drugs only be studied initially in infected infants would mean that the earliest age they could -- well, that's probably not true. You could find some who were infected at birth, but you said it would be 70 percent at 3 weeks. And then we heard that the metabolism might be different in the newborn compared to an infant over 2 weeks. So does that change your thinking at all, or do you still think we should just study it in infected infants initially?

DR. CHADWICK: Well, I think that's the safest way to proceed. I think the uninfected or the exposed babies -- I should say exposed -- the only ones I would really think would be justified to do intensive PKs on, if that, would be the women who were most likely to be transmitting. In other words, if I had a treated woman who had an undetectable viral load before delivery, that's not a baby I would even think about studying. If I had a woman that came in with perhaps an unable-to-be-controlled virus, then I'd think about that baby. So there's only a small

population of exposed infants I would think about trying to do some of these intensive studies in.

But there are babies out there and there are babies that are intrauterinely infected. 20 percent of infected babies are going to be intrauterinely. 2 weeks is when we have at least 70 percent sensitivity of getting a DNA PCR positive. So there are different time points within that first month that the babies are available. It's just you have to be coordinated and very attentive to find those babies.

DR. CHESNEY: Dr. Mofenson, I don't want to put you on the spot, but I will. Do you agree with that position?

DR. MOFENSON: I'm not exactly sure which position Ellen is discussing because she said two different things. One is test in infected babies, and the other one is, well, but maybe in babies who may be at higher risk, I might test in those children. It comes back to the percentages that we were talking about before. So you end up confused.

If you have a mother come in and she's had no prenatal care and you diagnose her during labor, but you don't have the chance to give her drug, her baby has a 25 percent risk of being infected, maybe more if she has a high viral load because the baby has gotten no pre-exposure

prophylaxis, no post-exposure prophylaxis. That's a very high risk baby. It's just like back when we were doing 076. So I think that, yes, we need to have the data.

I think agree more with the concept that Lauren was coming out with, that you have an HIV-exposed child. That child is at risk as opposed to making percentages different.

Does that kind of answer?

DR. CHESNEY: Dr. Fletcher, I think you've been waiting, and then Dr. Rodvold and then Dr. Spielberg.

DR. FLETCHER: Well, in a word to this question, my answer would be no, and two comments.

Someone from the FDA should correct me if I get this wrong, but my understanding in the application for the antiretroviral agent Kaletra -- that's a combination product of lopinavir/ritonavir -- that the pharmaceutical sponsor provided pediatric pharmacokinetic data from a study in South Africa. And if that's true, if I've got that right, then the company has indicated that they're interested in doing pediatric studies, that they can do them in a foreign country, and that we are willing to accept those data.

And so if that's all true, then I think this question about seeing too few born in the U.S. is probably now narrower than it really is if we're already willing to

accept pediatric data from outside of the United States. Thus, we're probably not talking about 300 infected infants, but a much, much larger group of infected infants if we're just going to constrain it to infected infants.

And then the second comment that I would make. The drugs we may want to study might be ones that are not candidates for looking at prevention of transmission, and the drug that comes to mind here is efavirenz, so a drug that's been deemed to not have a safety profile suitable to be given to pregnant women, but in HIV-infected children has to been shown to be an incredibly efficacious agent. And here is a drug now where we still don't have data in infants that are less than 4 weeks of age. And I think it's one of the real important gaps in knowledge with this drug that has otherwise been shown to be incredibly safe and effective in children.

DR. CHESNEY: Dr. Rodvold.

DR. RODVOLD: With that, I also would make the comment that reading the document that you sent back to the sponsors that this seems awful rigid in the pharmacokinetic design of these studies. You have not really loosened up the design to allow easier sampling. You're kind of looking for full runs at steady state versus using the state of the art population analysis type techniques where you could take someone from a single dose to a second dose,

a fifth dose, a 20th dose, whatever. That way, while you increase your numbers, you increase your number of subjects that have to be studied, you decrease the number of samples that have to be studied, which is a complaint from the industry because you can't collect all these samples. You have a blood limit issue going on. So you then take out those variables that may be inhibiting them from wanting to proceed in these studies.

The other advantage of doing population analysis is that you could do multiple other things. You can account for intra- and inter-patient variability and you could also study continuum. If a patient was coming in and put into a trial, anyplace in the trial -- let's say at 2 weeks of birth -- and they were shown to be infected, they could stay in the trial the whole time because you could sample them at various times and add it into the population analysis versus doing a study only at day 3 or day 4. So thus, those that drop out because they're not infected get studied, but those that are infected get in as well, and they can come in and come out of the study at anytime and anyplace and you can study throughout the continuum in age as well as throughout the continuum of the disease.

The other issue I'd add to that is that then you can mix and match populations. You can take

international data and you can take data from the United States and you could compare them because you could tag them as a variable. But at the end of the day, you'd still have a group of patients that have been PK-studied. Then you could separate from there, and you can continue to build these files to be able to continue to study the pharmacokinetics both within the industry, in the agency, and study groups such as Courtney does.

So I would think that at least the current design that's in this letter is limiting what potentially can really be done that's state of the art today which you do require in a lot of the other studies and were implementing in pregnancy in other types of populations outside of this by FDA sponsors.

DR. LEWIS: Could I respond to that? First to Courtney's comment about the Kaletra study, that was actually not a study done in South Africa alone. It was a multi-site, multi-national study. About 20 percent of the patients in that study came from South Africa. So there was in that study quite a nice mixture of patients from a variety of sites within North America and outside of the U.S. in international sites that had varying levels of sophistication of their infrastructure and general treatment guidelines.

In terms of international studies, the FDA --

and now I think this is passed on from legislation -- accepts any study that is done in an international site as long as it can be shown that that study meets the standards of a study that would have been done in the United States. So it has to meet good research practice standards, and they are subject to audit just like any study that's done within the U.S.

Responding to the comment about the way the written requests are written, these are, as you might consider, somewhat legal documents. We are constrained by the way the law was written in how we can write what we want the companies to do. But what generally happens is that we will get a request from a company saying, okay, we're ready to start our pediatric development program. We know the general guidelines that you want. Basically what we want is PK data in everybody, all ages, safety data in pretty much all ages, and a little more evidence of activity, although not a defined efficacy trial, in infected children.

So we could, in fact, work in other study designs. Population pharmacokinetics have been proposed in some cases, but it's hard to do population pharmacokinetics if you only enroll 7 patients. So we are amenable to those things, but we sort of start from the standard and go from there.

DR. CHESNEY: I have Dr. Spielberg, Dr. Wilfond, and Dr. Englund.

DR. SPIELBERG: A couple of other PK issues following up on that. We've already heard that not all drugs really achieve significant concentrations in the newborn by transplacental routes. So depending on the nature of the drug, taking advantage of that will not necessarily really get us the answer from any drugs.

The second issue is that data at a month really are still not necessarily going to help us with data on how to rationally and safely use the drug at day one. So one way or another, we're going to have to do neonatal studies if we are going to choose to use that medicine in the neonate.

The third issue is -- and I think Dr. Rodvold said it very nicely -- we should really be trying to get as much comparative data as we possibly can among different populations. We already heard from Dr. Mofenson that at least to date for the limited amount of data, we're not seeing huge differences, say, between babes in Africa versus here, despite infestations and protein calorie malnutrition and all the other things. But there may be situations where in fact they are different. And the more data that we're able to accumulate from international studies to be able to say, yes, we can extrapolate here or

no, we can't extrapolate there is going to be important.

And the final issue again gets back to some of the essential differences in the disease internationally. We're dealing with a situation here where primarily, in terms of prophylaxis or treatment, exposure is in utero/intrapartum. In the rest of the world we have ongoing exposure. And to me that changes the whole nature of what we're talking about in terms of prophylaxis and of treatment because we have to, in fact, intervene right at the beginning and we have to continue that intervention or we're running the risk of what? 40 percent? Those numbers are already getting staggering. So we're both in a treatment and in a prophylaxis mode in the rest of the world where breastfeeding is going on.

One can talk about all sorts of other strategies of bottle-feeding or whatever, but basically we're a long way from being able to deal with those issues and we're still going to have to rate babes in whom ongoing exposure is an enormous risk. And you have to start those babes on therapy very early on, and you have to know that the dose is going to be in the neonate as well as at a month. So the disease process, the nature of the disease bespeaks a rather different paradigm in those countries.

If we are, indeed, going to serve those populations, that information, as long as we have the

extrapolation information from one population to another, becomes very applicable. I'd rather have developmental data in newborns from children in the rest of the world to look at potential treatment regimens at day one here than I would children anywhere treated at day 30 because we're going to need those neonatal data.

So basically I think it's an issue of taking advantage in an ethical way of all the differences in disease processes and get those data applied to all children, be it a therapeutic regimen or a prophylactic regimen, and just with the cautionary note that taking advantage of maternal treatment may not be as useful as it really might seem because, again, of some major differences in placental transport of the drugs.

DR. CHESNEY: Thank you for pointing that out.

Dr. Wilfond and then Dr. Englund.

DR. WILFOND: I'd like to sort of take Skip Nelson's comment from earlier on and address it towards how the written request might be written. Skip seemed to make a distinction that I think is very appropriate regarding what the purpose of the study is and the goal of the study and the intention of the study. So if the purpose is to use a drug in HIV-infected individuals, then that's the appropriate group to study. Only if the intention and desire would be to use the drug in HIV-exposed, because of

some of the characteristics such as a better safety profile or better dosing, would it make sense to do that.

The problem, though, is that the written request doesn't distinguish between those two objectives, and so if the written request could somehow distinguish between when it was desired to use it in a prevention setting, then it would make sense to do those PK studies, but it perhaps wouldn't make sense if that wasn't the case.

DR. CHESNEY: Thank you.

Dr. Englund.

DR. ENGLUND: I just wanted to reiterate that I think the international setting is very important, but perhaps to the manufacturers, the international setting is not where they're going to be emphasizing their resources. Certainly these drugs are going to have a limited marketplace in pregnant women and in newborn babies.

But with the increasing development of resistance, which is really changing the total practices of how we deal with our patients, we know in our pregnant women what drugs they are resistant to if they come for care before they ever show up. And we have a need sometimes to use drugs such as tenofavir or some other drugs that aren't approved for kids because it is one of the few drugs or only drug we have available to us, and yet we don't know at all how to use it.

So I think in the context of the U.S., we need to emphasize resistance and put it in the context of some of these children are going to be getting it anyway, and yet they're not going to be getting perhaps the right dose, add that to the population-based pharmacokinetics, and put that into the equation. I think it's very important to think about developing countries, but for the purpose of the FDA, I think it's even more important to think that the drugs are going to be misused in American kids.

DR. CHESNEY: The whole purpose of the Pediatric Drug Advisory Committee.

Does anybody else have anything? Dr. Sever.

DR. SEVER: I think that we've been coming around to a discussion of international settings and U.S. settings and using comparative data from those which seems to be valuable and important. We've not resolved in this discussion so far whether we should limit the studies to children who are infected. Certainly that would be the most desirable, but the reality is if the data is needed in the first few days of life, that would be almost impossible to accomplish. You'd have to limit yourself to those at most 20 percent of children who are infected in utero who themselves might be a slightly different subpopulation. But I think the emphasis should be then on studies done very early within the first few days after birth and

including international and U.S. sites.

DR. CHESNEY: Dr. Mofenson.

DR. MOFENSON: Just a comment about infected children and being able to diagnose them early. We're talking as if the day you draw the test, you get that test result back.

(Laughter.)

DR. MOFENSON: That's not true. You test a child at 2 weeks. You get the result back; it's 3 weeks or 4 weeks. You test a kid at birth; you get the result back in a week. So it doesn't really help you in terms of making decisions during that early time period.

DR. CHESNEY: Maybe Dr. Nelson's comment, and then let's think about voting on this first question.

DR. NELSON: Well, I guess what I've heard from a number of different speakers is whether there's a way that you can enrich the HIV-exposed population to where you're then linking the exposure to a drug whose safety profile may not be as well traveled as AZT and some of the other ones to where there's a justification for using it whether it's picking based on risk factors, based on resistance of the mother's virus or the like. But enrichment might be a way to go rather than just saying HIV-exposed, all comers.

DR. LEWIS: I think that we could perhaps amend

this question to include if you felt there was a smaller subpopulation of exposed infants that could be studied to consider that in your voting.

DR. DIANNE MURPHY: I wanted to make it clear to the committee too that we're asking you to give us what you think would be the best way to go about this, and we can change the written request to reflect that. So you don't need to be limited to what we've done in the past or whatever. As Linda said, if this isn't the way to answer the question, fine, don't answer it that way.

DR. CHESNEY: The question is are there too few HIV-infected infants born each year in the U.S. or too little public health benefit to justify requesting studies in neonates.

We'll start and go around to all the voting members, and please tell us yes or no, and if you feel a need to qualify it, do so. Dr. Glode, we'll start with you.

DR. GLODE: No. I think the studies should be done.

DR. CHESNEY: Dr. Rodvold.

DR. RODVOLD: No. I think the studies should be done.

DR. CHESNEY: Dr. Fletcher.

DR. FLETCHER: No. The studies should be done.

I would certainly accept modification, not just U.S. but international, and I think others probably a little bit better than I could insert language to expand from "infected" to "exposed, high risk."

DR. CHESNEY: Dr. Englund.

DR. ENGLUND: I agree with Dr. Fletcher, with those caveats.

DR. CHESNEY: Dr. Wood.

DR. WOOD: No, and I concur with Courtney.

DR. CHESNEY: Dr. Santana.

DR. SANTANA: No, with the caveat that I think like Dr. Nelson suggested that some strategies should be built into this to allow for enrichment of special populations of subjects that could potentially be identified beforehand like one of the risk categories that I heard across the hall there was a high-risk adolescent who's had no prenatal care who comes in and we know nothing about. That potentially could be a population that because of the history, you suspect that there's a high transmission rate. That would be a population that you could enrich to get the studies done in a very safe way.

DR. CHESNEY: Dr. Nelson.

DR. NELSON: Since I've peaked at 2 and 3 and see that we'll get to deal with HIV-exposed under those two questions, answering this one the way it's worded, "HIV-

infected," I don't see any reason to treat infants in the U.S. differently than abroad apart from some of the feasibility issues in just conducting a trial. But on the face of it, then I would say there should be studies done both in the United States and abroad, conducted according to the same ethical and research standards.

DR. CHESNEY: Chesney agrees with Dr. Nelson and Dr. Fletcher.

Dr. Gorman.

DR. GORMAN: No.

DR. CHESNEY: Dr. Hudak.

DR. HUDAK: I think no, but I'm going to speak up for the 2 percent rather than enriched because if I'm a part of the 2 percent minority, I'd like to be available for that type of study myself.

DR. CHESNEY: Dr. Fink.

DR. FINK: No.

DR. CHESNEY: Dr. Chadwick.

DR. CHADWICK: No, and I agree with Drs. Fletcher and Nelson.

DR. CHESNEY: Dr. Danford.

DR. DANFORD: No, and I agree with the enriched population study notions that have been put forward as maybe a potential way to deal with the problem.

DR. CHESNEY: Dr. Fost.

DR. FOST: Well, emphasizing that this question is just about known HIV-infected infants, no. I mean, that is, studies should be done on known infected infants.

DR. CHESNEY: Oh, I'm sorry. Dr. Sever, I didn't realize you were also a voting member.

DR. SEVER: No. Again, we're either with high risk for infection or infected infants. I'm not sure what the wording is now that we're voting on, but there it says infected, so it would be definitely no.

DR. CHESNEY: I think that we're all under the impression that these are infants known to be infected with this question.

The second question.

DR. LEWIS: The second question actually has another part on the next slide, but we'll get to that a little later.

DR. CHESNEY: Since neonates born to HIV-infected mothers may be tested in the first 48 hours -- but we've heard the result may not be available for a week -- and at 4 weeks, HIV-infected infants can be diagnosed within the first month of life if you have a fast lab.

(Laughter.)

DR. CHESNEY: So the first question is, should only HIV-infected neonates be studied? And the second question, if an HIV-exposed population is to be studied --

so now we get down to Dr. Nelson's differentiation -- discuss the risk/benefit assessment for exposed neonates who might be enrolled. And the third part, if studies are conducted in resource-poor countries, can we extrapolate results from these studies to the U.S. population?

So, the first question, should only HIV-infected neonates be studied? Comments. Dr. Danford.

DR. DANFORD: It would seem clear that the answer to that is no because the information that we need to get is in a time frame during which we would not have the information about whether they're actually infected. I can't see a way around that unless there's more science out there that we haven't heard yet.

DR. LEWIS: I think this question was intended actually to capture that specific population that had already been diagnosed early. So that was really the somewhat different aspect of this particular bullet.

DR. CHESNEY: So what we would vote on is should only HIV-infected neonates picked up early in the first couple of weeks be studied. Any other comments, or do we feel ready to vote on this? Dr. Englund.

DR. ENGLUND: I just want to say one thing. That is going to be a really hard population to get, I mean, really hard.

DR. CHESNEY: I think we're ready to vote.

Shall we start the other way around? Dr. Fost. Should only HIV-infected neonates picked up early in the first month be studied?

DR. FOST: Well, first, I'm not sure we've had enough discussion on this. But if pressured, I'd go back to Dr. Chadwick's comment first, that we're assuming we're talking about drugs that have first been studied in known infected infants for which a safety and efficacy profile has been established, admittedly a little bit older than immediate neonatal.

Given that, I think it's appropriate to study a drug that meets that description in an exposed infant if there was nothing else available, number one, assuming the infant doesn't otherwise have access to known effective treatment and that might be in a third world population or in a non-U.S. population. But for a U.S. child who has access to drugs of known safety, then I would have problems about justifying a new drug in such a child. So to me there's a difference between whether you're talking about a population that already has access to known effective treatment or not.

DR. CHESNEY: Well, that's an important point, a very important point. Any comments? Dr. Mofenson.

DR. MOFENSON: Yes. You can no longer do a study where there's no known effective treatment. If you

go to Africa to do a study, as a baseline you have to be providing some effective prevention regimen. Usually it's single-dose nevirapine. So the studies now all involve single-dose nevirapine versus either something else or something plus.

DR. FOST: No, but at the time the nevirapine studies were done in Africa and in Thailand, there was known effective treatment. There was 076. It just wasn't available.

DR. MOFENSON: No, that's not true. That's true for the Thai study, but the moment that the Thai study became available, the placebo arms in every single trial done across the world dropped the placebo arm. The HIVNET 012 originally had a placebo. It became a comparative trial to short-course AZT.

DR. CHESNEY: So all studies now are comparative and adding on, not replacing.

DR. MOFENSON: Some studies are looking at replacing but most are looking at adding on. Some are looking at different regimens like the SAINT study I talked about compared single-dose nevirapine to intrapartum/postpartum AZT/3TC.

DR. CHESNEY: Dr. Nelson.

DR. NELSON: Just for procedural simplicity, if the answer to question 1 is no, then question 2 needs to be

answered. I'm just wondering if instead of going around and answering 1 and then answering 2 separately, if you'd just prefer each person to answer 1 and 2 together, as Norm effectively I think did.

DR. CHESNEY: Norm, I have one question about your first statement. Did you say if the drugs had been tested in older children, then it would be all right to give these very early diagnosed infants -- or did I make that up?

DR. FOST: Well, it seems to me it's desirable to do it in the sequence that Dr. Chadwick said, that is, to first give drugs to known infected, let's say 1-month-old infants. Presumably we'll know efficacy before that point, but then we'll know safety at least in little babies, admitting that a 1-day-old is not a 4-week-old. But at least we'll know that there's no previously unsuspected toxicity, at least short term to medium term. So that should be a prerequisite to doing a study in an exposed 1-day, less than 1-week infant. Is that your question?

DR. CHESNEY: Yes, because that's not an issue that we've really discussed or that's been put on the table. So I think that's important.

Dr. Fink.

DR. FINK: This may be a stupid question to

some of the people, but we've heard that you can diagnose HIV-infected infants at 2 weeks of age by DNA PCR. How old does an infant have to be testing negative to be sure that they are not HIV-infected?

DR. LEWIS: Lynne, do you want me to handle that or do you want me to dive in?

(Laughter.)

DR. LEWIS: There should be at least one negative test after the age of 4 months? After 1 month and after 4 months.

DR. MOFENSON: Yes. According to the CDC guidelines for PCP prophylaxis, all babies born to HIV-infected women get put on trimethoprim-sulfa at birth. You stop after you have a presumptive uninfection status, which is after two negative tests, one at greater than 1 month and one at greater than 4 months.

It's a good point because you're talking about infection as well, and we usually want a confirmatory test before you definitively call a child infected. So it's not just one test, it's two tests.

DR. FINK: Well, the other thing is where it says in the question should only HIV-infected neonates be studied, I guess I would feel that other neonates who are HIV-exposed would also be eligible for study until such time that they were proved to be uninfected.

DR. CHESNEY: I think that's part 2 of this question.

Could I ask Dr. Lewis, should we work under the assumption that what Norm said is correct, that these drugs would have been studied, or do you want an answer on that before you gave them to 1-week-old infants?

DR. LEWIS: No. These drugs are almost always studied in older children first, and before that, they're studied in adults. So there really is a progression downward of the age group in general practice. I think if a company came in and said we have this great data that we think a drug might be really effective in this setting that would require testing in newborns before fleshing out the other safety profiles, I think we would have to consider that very, very carefully, but in general all of these drugs are studied in adults, older children, younger children, and then in the youngest age group.

DR. CHESNEY: Dr. Nelson.

DR. NELSON: I need to follow up on the testing and make sure I'm not confused. I assume the CDC recommendations are doing HIV RNA not the DNA?

DR. MOFENSON: No. DNA.

DR. NELSON: So the 20 percent sensitivity at birth in these 70 percent at 2 weeks and then the flip false negative. So that would be the false negative

initially or the sensitivity and then at 1 month and 4 months would be I guess the false positive.

DR. LEWIS: It's really more the pathophysiology of being able to identify the infection in that age period more than the sensitivity of the assay itself. If you spike specimens, the assays are sensitive, but depending on the timing of infection of that infant, if the infant was infected in utero, then there is sufficient viremia that you can identify in the neonate at the time of birth. If the infant is infected at the time of delivery from exposure to blood and amniotic fluid and the like, then that infant may not have identifiable viral DNA present until a couple of weeks later.

DR. NELSON: So I guess if you went two different directions, one is if you require test studies in only HIV-infected neonates, you could require it only in DNA PCR positive infants in this 20 percent or 70 percent sensitivity, and is this tail where you have to go long enough just the other 30 percent that you have to follow out? I guess I'm getting a little confused about how you could use this test to see who's in or who's out of that particular population.

DR. MOFENSON: Yes. I understand why you're confused because most of us are confused too. The CDC hasn't yet changed its definition of "uninfection." That's

what you're talking about. How do you define someone who is uninfected? And it's more conservative because there is that tail that may not have a positive DNA PCR until a month or 2 months or 4 months. I know of one child in one of our trials who never had a positive DNA PCR. The only way we picked up their infection was they were persistently antibody positive at 18 months. So they're trying to avoid that tail.

DR. CHESNEY: Dr. Spielberg.

DR. SPIELBERG: Can I ask the question in a little bit different way? We now routinely treat these newborns under the presumption that in fact they are infected. That's why we're using the drug. So in a treatment paradigm, given that we don't fully understand the diagnosis, we are treating them with medicines as we speak. Whether we call it prophylaxis or whether we call it treatment, they are nonetheless being treated under the assumption that they are infected, and that what we're doing with these medicines is either preventing the infection from "taking hold" or that even if the infection does take hold, they are on treatment from the beginning. So they are already getting drug.

The question to me is, if you are already treating the babies either in a prophylactic or in a treatment modality on the assumption that they are at risk

for having been infected in utero or intrapartum, the ethical question then comes, given that we're already treating them, what the ethics of giving a single dose of a medicine for a pharmacokinetic study, which might be used in this patient population subsequently with the development of resistance or in fact might be used in this individual patient for therapeutics later on -- what the ethics of that single-dose PK study, with all the other caveats that Norm talked about in terms of safety in adults, safety in older kids, et cetera -- to be able to get that information in patients who we are already treating.

DR. MOFENSON: No. I think there's a difference because appropriate treatment would be triple therapy usually with a protease inhibitor, and the baseline prophylaxis is AZT alone. So it's very different. If you have a child in whom you have confirmed HIV infection by age 4 months, you change them from AZT to standard combination therapy. So I don't think we can talk that we're providing treatment. That's why I like to use the word "prophylaxis" for that first 6 months and treatment for --

DR. ENGLUND: 6 weeks.

DR. MOFENSON: 6 weeks. Thank you. I'm thinking breastfeeding.

DR. SPIELBERG: But it is nonetheless treatment based on the presumption that the baby has been exposed to virus or we wouldn't treat them at all. Right?

DR. MOFENSON: It's prophylaxis.

DR. SPIELBERG: No. It's prophylaxis but it's based on the assumption that they've been exposed because if we didn't assume that they were exposed, we wouldn't be treating them. And that next baby a year later might be in the same position but, because of changes in resistance in the population, may need a new drug for that same treatment modality, the same prophylactic treatment modality. We're putting them on an agent. Right?

DR. MOFENSON: Yes.

DR. SPIELBERG: So I suppose the question still comes down, given that we're already treating the babes, what is the ethics of adding on a drug for only single-dose PK so that we know the pharmacokinetics of that drug in that patient population. Is it acceptable or not? That's sort of the question.

DR. LEWIS: The trouble is many of our drugs are not amenable to single-dose PK because they don't achieve steady state levels. Maybe Courtney can comment on this a little bit further, but generally, particularly for the protease inhibitors with hepatic metabolism, a single dose does not give us accurate information.

DR. CHESNEY: Dr. Chadwick, did you want to add?

DR. CHADWICK: No.

DR. CHESNEY: Looking at the time and trying to figure out if we can maybe vote on the first two, as Dr. Nelson said, but let's hear from Dr. Fletcher and Dr. Wilfond and then maybe see if we can vote on a combination of the first two.

DR. FLETCHER: I'll try to keep this short. To the point about the single dose versus multiple dose, it seems it's maybe a little bit more question 3.

But I guess I would raise the question as to whether we can do what Dr. Spielberg suggested and have single-dose studies. Do we have to give multiple-dose studies to get to steady state to get useful information in these children? And more and more I'm thinking, no, we don't.

If we were to approach this as if this is a first-time drug in humans and we knew nothing about it, what would we do -- and Dr. Rodvold and I were talking about this -- we'd give a single dose. And perhaps maybe we ought to approach this population somewhat like that, like we don't know what the PK are because every time we studied it, we've been surprised. They've never predicted what we thought they were going to be, and maybe we ought

to think about this in a single-dose context.

And then there are two issues: the long half-life drugs to steady state and the drugs that have their own auto-induction. But maybe I'll just stop and we can talk more about that when we get to question 3.

DR. SPIELBERG: If we already have those data in older kids, we should be able to design things that will give us the key, critical basic information from a single dose.

DR. CHESNEY: Dr. Wilfond.

DR. WILFOND: My question is sort of the analog of Dr. Spielberg's question. Even if we need to do multiple-dose studies, the question is, why consider substituting a new drug for the standard drug as a way of answering that if we believe that efficacy is likely to be present?

DR. CHESNEY: Dr. Fost.

DR. FOST: Is someone going to answer Ben's question, or is that just a comment?

DR. CHESNEY: I thought you were.

DR. FOST: Let me be clear on what this question is about. Are we talking about infants born to mothers who were not treated? Is that the population we're talking about?

DR. MOFENSON: No.

DR. FOST: Not necessarily. We're talking about mothers who were treated.

DR. CHESNEY: May or may not have been.

DR. FOST: And so we're talking about an infant whose mother may have been treated with a presumably effective regimen in which the infant would be scheduled to be continued on a known effective regimen. And we got a new drug that we're considering adding on or replacing the known effective regimen?

DR. SPIELBERG: Single-dose add-on.

DR. FOST: For treatment or just for a PK study? Just for a PK study while the infant is getting the other known effective regimen. All right.

DR. CHESNEY: Dr. Wilfond, did you want an answer to your question?

DR. WILFOND: Yes. Even what Norm asked, that's what's confusing me in the sense that my question was, instead of doing a single-dose add-on PK, if we had presumptive views about efficacy, wouldn't it make sense then just not to do a single-dose PK, but just to substitute this new drug instead of one of the standard drugs.

DR. SPIELBERG: If you got the PK wrong, you wouldn't have that data back and you'd be treating that baby with the wrong dose that whole period of time. That's

the whole rationale in pediatrics of getting that single dose before plunging into the trial.

DR. WOOD: And I'd also like to raise that if you did a substitution and you found out that there wasn't efficacy, then that infant that was exposed was denied an established standard treatment. So I think it would always have to be an add-on whether it's single-dose or multiple-dose based on what we currently know is effective for prophylaxis of exposed infants.

I'd also like to add that when you're looking at the risk/benefit ratio -- and I think this goes again to question 1 and question 2 -- is that everyone agrees that antiretroviral exposure is clearly more than minimal risk. And then if you break it down into what Dr. Sever highlighted during his presentation, it's is there evidence for a direct benefit. Well, the direct benefit applies to all infants whether they are exposed or infected because there is potential for direct benefit to them because they are exposed.

The issue of no direct benefit really is conditional and dependent upon whether or not they truly are infected or only exposed, and that again is dependent upon the time period in which you can make that determination that they truly are infected and, maybe even more importantly, that they truly are not infected.

DR. FOST: Excuse me. If we're talking about a single-dose PK study, we're not talking about any direct medical benefit. So there's no direct benefit for the sort of studies we're talking about. We're talking about a non-therapeutic, single-dose PK study.

DR. FINK: Previously we've held that if a child had a seizure disorder, that a single dose of a new seizure drug to determine PK, even though they would not have that drug available to treat their seizures, had the potential of direct benefit in the future. And I would maintain this is the very same situation.

DR. FOST: Well, if you're talking about what? An intravenous drug to stop a seizure, possibly.

DR. FINK: No, no, no. An oral drug.

DR. FOST: Is there a claim here? I'm confused again. Is there a claim here that a single-dose PK study might have clinical benefit for these infants?

DR. WOOD: That's the thing that's so impressive about the nevirapine data actually particularly in resource-poor countries, that there's reduced transmission even out to 18 months based on a single dose.

DR. FOST: Okay, thank you.

DR. CHESNEY: Dr. Nelson, one more comment and then I'd like to see if we can't vote on it.

DR. NELSON: I can't resist the IRB comment.

Even if you decide to approve this under 5052, which is the prospect of direct benefit, or 5053, which is the minor increase over minimal risk, the prospect of direct benefit still requires that the risks and benefits are commensurate with the other alternatives. And so you still end up in Norm's position that you have to have sufficient safety data to make sure that in fact the new treatment is no different than what you would have been doing in the past, whether it's AZT, whether it's AZT plus single-dose nevirapine. You can't use the benefit to just justify any risk. It needs to be comparable to the alternatives either inside or outside of the trial.

DR. CHESNEY: And presumably there would be safety data from older children.

Maybe we could make another try at these two. I think the real question, leaving out all the assessment for after lunch -- maybe we can vote on the issue of whether people think only known HIV-infected neonates should be studied or should the HIV-exposed population also be studied. Can we try that, Norm?

DR. FOST: With the previous caveat, that we're talking about drugs that are studied in not just older adults and children but known infected infants, it seems to me it would be in the interest of an HIV-exposed infant to be part of a -- or at least there's a prospect of

reasonable benefit that would warrant being in a trial, a single-dose PK trial, with a drug that was of known efficacy and was of known safety admittedly. So it seems to me it's appropriate to study HIV-exposed infants, that it is in the interest of such infants to be in such studies given those caveats.

DR. CHESNEY: Thank you.

Dr. Sever.

DR. SEVER: To answer the first question, should only HIV-infected neonates be studied, I would put that as no.

And for the second question about the risk/benefit, you'd have to have that data from other studies done in older children.

DR. CHESNEY: Dr. Danford.

DR. DANFORD: The first question, should only HIV-infected neonates be studied, the answer is no with the caveat that should the time come when instant diagnosis is available right at birth, then I reserve the right to change my mind about that.

I think that a rational mother, informed to the issues that we were informed of today, would be capable making a decision saying that yes, I would enroll my exposed but not definitely infected infant in the sorts of studies we're talking about, and so I think risk/benefit

would be favorable for going forward with these trials in the exposed population.

DR. CHESNEY: Tom is wondering if that's a yes or a no or a fence-straddle?

(Laughter.)

DR. DANFORD: Question 1, no. Question 2 was a please discuss. That's what it says up there, so I discussed it.

(Laughter.)

DR. DANFORD: Yes, go ahead with the studies in the exposed population.

DR. CHESNEY: I probably wasn't very clear, but I thought maybe we could review the risk/benefit assessment when we came back from lunch. I realize that might influence your vote.

Dr. Chadwick.

DR. CHADWICK: I think that the answer to the first question should be no.

And in the second question, I think that we can justify studying exposed infants if they are considered to be high-risk exposed children in this country. In developing countries, that's a different issue.

DR. CHESNEY: Dr. Fink.

DR. FINK: I guess I would have to say I think no to the first question, but I would probably fudge that a

little bit by saying multi-dose trials should only be in HIV-infected infants.

And that would sort of be my answer to the second, that a single-dose trial would be ethical in HIV-exposed infants but not a multi-dose trial so that an HIV-infected infant could be either in a single-dose or multi-dose PK trial. An HIV-exposed infant could only be in a single-dose trial.

DR. CHESNEY: This is good. We're getting some of the risk/benefit assessment we can do after lunch.

Dr. Hudak.

DR. HUDAK: I would say the answer to the first question is no, and with respect to the second question, I think that given adequate efficacy and safety data in older populations, I would say all HIV-exposed infants should be offered the opportunity to participate rather than a high-risk group.

DR. CHESNEY: Dr. Gorman.

DR. GORMAN: The answer to the first question is no, and I will echo some of the other comments that there are hopefully ethical researchers and well-peopled and intentioned IRBs that will make sure that the design of those studies will continue to be ethically as well as clinically efficacious.

In terms of the second question, if the HIV-

exposed population is studied, I would think that anything that increased the risk of transmission would therefore increase the benefit of the infant in the study. So the presence or absence of maternal therapy, the mode of delivery, and the choice of postpartum feeding mechanisms would all be issues that would be in that particular risk/benefit.

And a second issue that I would want to raise is if the mother's infective agent is known, whether or not it is resistant to known therapies would also be a thing that would significantly influence my risk/benefit assessment.

DR. CHESNEY: Dr. Chesney agrees with Dr. Gorman.

Dr. Nelson.

DR. NELSON: The answer to the first question is no.

In answering the second question, I want to just make sure that people don't use the fact that a neonate who is exposed may become infected to justify exposure to risk that would only be acceptable if you're infected, and that's where I find this logic very important to keep separate. Someone may be infected, but it then needs to consider that risk against known prevention strategies at this point, which gets into whether that

single-dose nevirapine or AZT or the like, with the caveat that there may then be enriched exposed populations, whether that's based on maternal known resistance or other factors that are determined, where you might justify a higher risk of drug exposure because of those factors that have led that population to be defined at an increased risk of becoming infected.

DR. CHESNEY: Dr. Santana.

DR. SANTANA: No to the first one and concur with Skip. I think a major issue here is knowing what the alternatives are and clearly having as much information in other age groups that could help guide the decision of how to apply that to this neonatal group.

DR. CHESNEY: Dr. Wood.

DR. WOOD: No to the first question.

Yes to the second question regarding HIV-exposed infants with the caveats that have already been mentioned.

However, I would also like to raise the issue in terms of assessment of transmission risk. While clearly there are correlations between treatment and viral load with risk of transmission, we all know and are aware of the fact that there are women with undetectable viral loads who transmit to their children who have been extensively on highly active antiretroviral treatment for many years. So

I put that out because from a neonate's perspective, there's no such thing a percentage of transmission risk. Either I get infected as a neonate or I don't. And as a neonate, I would like to be given the maximum benefit to prevent getting infected. So that's my caveat.

DR. CHESNEY: Dr. Englund.

DR. ENGLUND: The first question is no.

And the second question is yes, we should study the HIV-exposed infants, and I think we need to have our clinicians design studies that are going to be acceptable in the different populations in which you do the studies.

DR. CHESNEY: Dr. Fletcher.

DR. FLETCHER: To the first question, no.

To the second, yes, exposed should be studied with the caveats of Drs. Gorman, Nelson, and Wood.

(Laughter.)

DR. CHESNEY: Dr. Rodvold.

DR. RODVOLD: No to the first question, and yes to the second question, just like what Courtney stated.

DR. CHESNEY: We're now referring back to about five people.

(Laughter.)

DR. CHESNEY: Dr. Glode.

DR. GLODE: No to the first question.

And yes, I think the HIV-exposed population

should be studied. I'm not so enthusiastic about enriching population studies myself because it looks to me like if you do it perfectly, you still have a 2 percent risk. So you enrich it to what? Enrich it to a 5 percent risk and then it's okay? So it depends on how toxic you think these medications are or what the evidence is that they're highly toxic. That's what I would use to sway that, but right now I would think all HIV-exposed babies should be eligible to be studied.

DR. CHESNEY: Dr. Fost, the first part of your answer was no. Is that correct?

DR. FOST: Correct.

DR. CHESNEY: Thank you.

We were originally scheduled to have an hour for lunch, but if you wouldn't mind, could we still come back at 1 o'clock? I think for those of us at the table, they are bringing sandwiches, for which we're very grateful, but we also all have planes to catch. So if you don't mind, let's start again at 1 o'clock. Thank you.

(Whereupon, at 12:20 p.m., the subcommittee was recessed, to reconvene at 1:00 p.m., this same day.)

AFTERNOON SESSION

(1:05 p.m.)

DR. CHESNEY: When we finished before lunch, it was unanimous that everybody agreed that not just HIV-infected neonates should be studied.

And then we got to the second part, and I think most people agreed that the HIV-exposed population should be studied, but everybody had different caveats in terms of risk/benefit assessment. I thought maybe we could give them a little bit more guidance.

What I wrote down from what you all said was that the drugs had to have been previously studied in older children and demonstrated to be safe. We were talking potentially about single-dose only pharmacokinetic studies.

We had to have some estimate of the resistance I don't know if in the mother or the area. I don't know if there is such a thing as area resistance.

Then there was a lot of talk about whether to single out some children as being at higher risk for transmission, and people talked about the maternal history of having received drug or not having received it and the maternal viral load.

Do we want to expand on that in any way? Do we want to suggest single-dose only, or just having raised the issue, that was enough? And do we want to talk more about

narrowing down a population that would be at higher risk for transmission, after Dr. Wood made the point that you can have a negative viral load and have been on long-term therapy and still transmit to your infant? Any comments in terms of this? Dr. Englund and then Dr. Nelson.

DR. ENGLUND: I want to suggest not just single-dose only. Of course, it depends on the agent, and there are some agents that will be perfectly appropriate as a single dose, but we know there are others of our antivirals that you have to give multiple times and that there's accumulation like the protease inhibitors. A single dose will tell you basically not much at all. So I think we have to be a little careful here because it really might depend on the agent.

DR. CHESNEY: Dr. Nelson.

DR. NELSON: In many ways the answer to the question would depend upon the details of the particular drug, the particular protocol, the safety profile, and the population and how that population has been defined.

But I think the general principle is that the risk and benefit, if you're going to argue benefit, has to be comparable to the alternatives, which are existing treatments. And if you're in a no-benefit situation, you're in a minor increase over minimal risk which places you back into having sufficient data to establish safety to

where you're confident in that risk estimate, which gets you almost in the same place as the other approach. I think being able to specify that in any more detail would probably require much more specification that we have available here.

DR. CHESNEY: Norm.

DR. FOST: Dr. Mofenson, could you just clarify for me something you said before lunch, that some kind of treatment you think is available everywhere in the world today? Are there populations where no treatment is available?

DR. MOFENSON: No. I was talking about doing clinical research. There are resource-limited countries where prophylaxis is not available, but if you go into that country to do a study of prevention of transmission, it's felt that you need to provide the minimum effective care, the minimum effective care being single-dose nevirapine.

What's actually happened in the places that we're doing clinical trials is that there's been a large effort to bring nongovernmental organizations in to provide that level of single-dose nevirapine. So in many of the countries, it's then upped the standard of care, the standard of care being single-dose nevirapine, which wouldn't necessarily be the standard of care here.

So I don't think that you would be able to do a

study where you don't offer at least single-dose nevirapine, at least in the clinical trials groups that I've worked with.

DR. FOST: Politically you mean.

DR. MOFENSON: Ethically.

DR. FOST: I would argue ethically. If there's a country or an area where presently no treatment exists and doing a trial presents the offer of treatment to hundreds or thousands or however many infants are in the trial, assuming that it's a well-designed trial and the drug is plausibly safe and so on, that's a potential benefit to that population, apart from whether you offer it to the whole population of the country.

And secondly, the agencies or the sponsors that are doing the studies are not typically ones that either have the resources or are responsible for providing care to the whole country. So that oft-stated premise that you shouldn't do a study in a place where you're not going to offer treatment I think can and should be questioned.

So, again, given that risk/benefit ratio matters, if you're going into a place where there's presently no potential treatment, then the benefit of being in the study, even for just exposed infants, is much higher because the alternative is zero.

DR. CHESNEY: Dr. Lewis, could I ask a

procedural issue? Do you want a more definitive statement about the risk/benefit assessment? In other words, do you want a vote with respect to what population might be at high risk or have you heard enough just in the discussion to provide an answer to this section?

DR. LEWIS: I think all of these ideas are very useful. I don't know that we need to vote on each one of them, but just getting sort of the general feeling of the group of what things could be done or how we might alter study designs or whatever that might get to the data that we're interested in, which is how to use the drugs in the very young population, is really what we're after.

DR. CHESNEY: Dr. Chadwick.

DR. CHADWICK: I just want to make sure we're very clear about single-dose versus multiple-dose studies. I think single-dose will get us started for most drugs. Nevirapine is an exception because it has such a long half-life and it did have the benefit of providing antiviral coverage for several days. Most of our drugs don't do that. So single-dose studies will get us in the ball park of what sort of dosing range we would use to then base a multiple-drug study. I think that when we're talking about these things, these are important differences that we need to be clear about what we're using these medications for.

DR. CHESNEY: Dr. Mofenson.

DR. MOFENSON: Just a comment that single-dose studies are not going to help us with the major problem in developing countries which is breastfeeding, and there infant prophylaxis requires multiple doses. So, for example, one of the studies that we're doing looking at 6 months of nevirapine in the infant required us going back and doing a phase I study in infants to look at different doses to be able to determine what the appropriate dose would be for a phase III study. So it wouldn't help a large part of the problem to only do a single dose.

DR. CHESNEY: Could we go on to the third part of that question, which is, if studies are conducted in resource-poor countries, can we extrapolate results from these studies to the U.S. population? Comments? Dr. Nelson.

DR. NELSON: To comment on this, let me just try to expand Norm's comment. I think if one goes into a setting where there may not be care provided at this point for HIV-positive women and infants, I would hope, Norm, you would agree that the intervention being tested should be one that could, in fact, be provided in that setting maybe not to everyone but it ultimately could be sustainable past the end of the trial. We could discuss that.

But if you take that as the minimum principle that at least what we're testing ought to be applicable in

that population, if then you wanted to extrapolate to the U.S., by extension then if we would not allow a control group other than a comparative study here, you sort of end up in a position where you're going to be testing against a sustainable control group there and an intervention group that could be applicable here. Now, that's separate from PK studies and the like. Anything more specific than that I think would be mainly a scientific question about extrapolation.

DR. FOST: Well, no, I wouldn't agree with your premise. Obviously, it's desirable when it's sustainable and of benefit to the population, but again, if you're an infant or a mother in a country where there's no treatment and, let's say, Engulf and Devour comes in and wants to do a study just because it's easy and convenient and cheap to do and then they're going to get out and you're never going to see them again, but you're one of the 300 or 500, or whatever the number is, kids in that trial and you have a 50 percent or a 100 percent chance of getting something that could of substantial benefit to you, I don't understand why it's not in your interest to be in that study and why it's not in the interest of people in that country who otherwise would have nothing, as a study that at least offers potential benefit to a small number is better than nothing. So this whole idea that it must be

sustainable I don't think is coherent.

DR. CHESNEY: Dr. Fink.

DR. FINK: I'm not sure that it has to be sustainable, but I think the United States has signed on to the Helsinki Protocol which very specifically states you can't have a placebo group if there's a generally accepted therapy. And I think we would be on really soft international grounds or bad international grounds if we advocated doing research that didn't comply with that.

DR. FOST: Time does not allow us to discuss all the elements of the Helsinki doctrine that are violated every day by almost every FDA-approved study in the U.S. The Helsinki doctrine is a wonderful aspirational document, but there are a half a dozen requirements in it that are violated on a regular basis by just routine studies in the U.S. and elsewhere. So it's hardly a standard for rigorous ethical thinking about clinical research. I think that will get us afield.

DR. CHESNEY: Dr. Gorman.

DR. GORMAN: Never being afraid to tread into dangerous water, I think -- I'm going to try to paraphrase Skip and your comments, Norm -- we wouldn't be able to extrapolate data that we felt were unethically obtained. We have sort of taken that as a standard we've applied in the past. We may choose to change that in the future, but

in the past we've chosen not to extrapolate from data that had been unethically obtained.

But if they are ethically obtained in a resource-poor country, then the extrapolation issues then become scientific. Can we really generalize those data or not? But if they are generalizable, then we can do it.

And just because I love the Helsinki report so much, I always use the example of hair loss when they come up with we can't do a study with a placebo control. There's a disease where placebo-controlled trials would be very acceptable at the IRB I sit on.

DR. FOST: Well, obviously, the results in the developing country would be extrapolatable to that country or countries like that or populations like that. But the question here is whether they would be applicable to a U.S. population. That's complicated and would depend on the case.

DR. CHESNEY: Dr. Santana.

DR. SANTANA: I understood the question very differently, not that this discussion is not important. I think it's very important, but I understood this question very differently. I think they're asking are there patient-related variables that are so different across populations that would lead us to not or, yes, accept the data as it exists. I guess here, as it's always said, the

devil is in the details. How different, how concordant, how discordant are the populations in these patient-specific variables that would lead you to conclude that the data is valid or not? I could add more variables here that have nothing to do with patients. They may have to do with compliance, issues of the environment that would lead you to believe that the data is valid or not valid.

So maybe the FDA can help us clarify this question. Are they specifically asking us to comment whether these patient-specific variables are things that they should be looking for when they look at data from other countries to see how concordant or discordant they are to the U.S. population.

DR. DIANNE MURPHY: I think that it is a science question, and it has to do with a general question having to do with experience in other trials. Have we seen differences? If we have, your input as to how you would stratify for that or think about it. But really that would be for larger studies. I think that is a question you'd use as a background, if you will, that type of information because really we're asking, though we're not going to be doing efficacy trials, if you had that kind of information, then how would use it or not use it, or do we have to. Would we exclude all malnourished children? Clearly there would be a level at which you would even in a PK study I

would think. So that would be my take.

Linda, did you have anything else that you wanted to add to that?

DR. SANTANA: But that's what I was getting at. If this is a science question, then the details are very protocol-specific driven because if you have a population that's malnourished, you're clearly going to have as entry criteria a level of albumin or a level of something that helps you control for that. If you control it, then the populations are the same whether they're in the U.S. or whether they're in another country. So I think the specifics of the detail is protocol driven, and as long as those details are valid, I think the data can be extrapolated and can be used.

DR. DIANNE MURPHY: I think that that's part of the question. The other part of it is if you say yes, then it's the other issues that are going to be around the table I think actually in question 3.

DR. CHESNEY: Dr. Spielberg, Dr. Fost, and Dr. Fink.

DR. SPIELBERG: I think there are a couple of things. The really precise, I suppose, aspect of this question is whether ontogeny dominates over other aspects of variability in the population and therefore understanding neonates in one setting is extrapolatable to

the changes in clearance, the changes in distribution we'd expect in another population.

If you look at a lot of the experience with ICH-E5 and the variability among ethnic and racial groups, yes, there are often differences, although when you look at the variability within a population, that variability often is as great as the variability between or among populations. And as such, if you understand the mechanisms of clearance of the drug -- and remember, these are drugs that we're going to be taking into the newborn with adult experience, understanding of its metabolism, understanding of its renal handling, we should be able to make some kinds of general judgments about whether we'd expect, for example, malnutrition to have a dominant effect.

Having said all that, again we're always surprised by data that we actually get, and one of the opportunities that does exist here, because we probably will, in fact, be doing studies in several different populations, is to really begin to develop a better database so that we understand the effects of immaturity and of ontogeny of clearance processes vis-a-vis all those other variables.

My guess is for a lot of processes, when we get down to newborns, if you look at renal clearance -- and your average neonate has a clearance of what -- I don't

know -- 30, 40 mls or so. For an adult, that would be overt renal failure. Right? So you're looking at the extremes there in terms of where the neonate is in terms of what an adult population would be.

My guess is ontogeny is going to be the more important variable, and to be sure that we get the dosage right with age and development. But we are obliged to prove that, and the more data we have for each individual process and groups of compounds as we go through, we really should try to iteratively get that information into everybody's hands.

DR. CHESNEY: Dr. Fost, Dr. Fink.

DR. FINK: Well, I think the other thing is obviously we can only extrapolate that data to the U.S. population to the extent that what data is available in the U.S. population allows us to make comparisons. So extrapolation with no data in the United States really, I wouldn't think, is feasible or advisable. So it's really dependent on how much data we have here to reinforce the extrapolation.

DR. LEWIS: So this comes back to that multinational, multi-site study would give us the best survey of all of these things. We don't know probably all of the scientific variables that might be different between a population in Thailand or India or South Africa or Omaha,

but we do know that they exist and if we can control for them in some way, then we feel like we get a better handle on the population PK.

DR. CHESNEY: Dr. Fost.

DR. FOST: I take it then you're just asking about whether the PK data can be extrapolated because if you gave --

DR. BAYLOR: PK and safety. They're not efficacy trials.

DR. FOST: Okay. But if a single-dose agent might have some efficacy and you showed this efficacy in a third world population, that would be very interesting and relevant. So at least that part of it is extrapolatable.

DR. LEWIS: Just one sort of example that has come up is in some of the studies done in sites outside of the U.S. where malaria is a major pathogen, we have to change the way we think about anemia and whether that's a side effect or sort of a baseline condition. Levels of hemoglobin that we would not tolerate in U.S. infants might be really pretty normal in a population where malaria is quite prevalent. So these are the things that we try to balance, but sometimes it becomes very difficult.

DR. CHESNEY: Do you want a vote on this, or have you had enough discussion? Move on to the next question?

DR. DIANNE MURPHY: I think this is an important enough question. We're asking fundamentally a science question here. I think that we would like to have individual comment around the table.

DR. CHESNEY: So we will start with Dr. Glode.

DR. GLODE: I would go back to a comment made earlier. I think you can't extrapolate until you have some directly comparative data from U.S. populations giving the same drug under the same conditions, and then you can enlarge those studies presumably. But I think you have to have direct comparative data to know if you can extrapolate.

DR. CHESNEY: Dr. Rodvold.

DR. RODVOLD: Yes. I would somewhat agree. I think the study design in needing both sets of populations -- there's not much you can, even in pharmacokinetics, say a group from South Africa versus a group from the United States -- are they that much different or not coming into it. I think that as you take certain compounds through by having both groups to compare, you'll be able to tell whether or not you can extrapolate data and whether or not you even need to do a study in all populations. So I think in the beginning you can't say you can extrapolate, but you need to do studies so that you can decide whether or not you can extrapolate it. Then that may answer the question

of which direction you go in the future.

DR. CHESNEY: Dr. Fletcher.

DR. FLETCHER: I will agree with Dr. Rodvold. I think you can. I think the degree to which you have, as Dr. Lewis mentioned, multi-site international/U.S. protocols that have, the degree to which you can, some standardized entry criteria such as for albumin and those type of things, I think those studies, well-done, should be able to be extrapolated. You would probably want to do some confirmatory testing after that, but I think the answer is yes.

DR. CHESNEY: Dr. Englund.

DR. ENGLUND: Well, I do agree with Dr. Fletcher, but I would say if we're talking about HIV-infected neonates, are we going back to the HIV-infected neonates or not? Because I think it's going to be hard to get much confirmatory evidence on infected neonates. It depends if you're looking at the beginning of the question or not. How much you can directly extrapolate with infected neonates in this country is going to be very difficult because we don't have many infected neonates. If we're talking about exposed neonates, yes, we can extrapolate. So it's a little bit of a difficult question.

DR. CHESNEY: Dr. Wood.

DR. WOOD: I think I would have to concur with

the comments raised by not only Jan but Courtney and Keith as well, and that is that initially early on, there are going to have to be trials conducted relevant to the design of the specific drug that's being studied so that you can really see whether or not the data is extrapolatable. I think the comments from earlier this morning, in terms of designing those trials to take advantage of the population pharmacokinetics that would allow for inter-population, within-population, and even inter-individual variability would be very useful.

DR. SANTANA: I think from the scientific point of view, when you go into these multinational trials or groups, you know a priori a little bit about the mechanism of action of the drug, its metabolism, potentially what pathways are affected by that drug, and you clearly relate your study design to those, understanding that for those you can control, and then the data is comparable or can be extrapolated, and then there will be many others that will come as a surprise because you cannot anticipate.

But the latter I think makes the trial more interesting because if these drugs are going to be used across different populations around the world, that data is very important too. It just doesn't only reflect the U.S. population, but reflects other populations that could benefit from benefit from these drugs.

The point is that when you go into the study design, you already know a priori some information about what potential variables you need to control for, and you control for those as best as you can. Then in that setting then, I think that data is valid across many different ethnic groups and cultural populations in which the study may be conducted.

One of the issues that did not come up in this is the issue of compliance. I advise the group to read a recent article in the Journal of Clinical Oncology, published either in December or January, in the last few months, that actually criticizes a lot of issues of compliance in oncology trials even within the United States and how we think that doing multi-hospital trials gives you the same data. Uh-uh. Even issues of compliance are critical to extrapolating data. I know you wanted to address the scientific questions, but I throw out the issue that compliance also has to be clearly regulated when you start extrapolating data.

DR. DIANNE MURPHY: We think compliance is a science question because it impacts it so tremendously.

DR. CHESNEY: Dr. Nelson.

DR. NELSON: I guess just to point out I don't think I have much to add on the science other than to identify what I hear everyone arguing, that from a

scientific point of view we should treat the populations similarly unless we have already demonstrated or in the process of trying to demonstrate relevant differences. To the extent that you want to assume you should treat those populations differently for other reasons, then you'll get back into some of the ethical issues that Norm and I are going to simply finesse at this point in time. But I finesse it indicating that there could be considerable discussion on the points that were raised earlier, meaning the standard of care that should be applied for that population.

DR. CHESNEY: I think they could be extrapolated under all of the conditions that have been mentioned already.

Dr. Gorman.

DR. GORMAN: I think Dr. Santana raised the issue that I think is most crucial. If you can identify issues and then identify them and control for their severity in extrapolation, I think you'll do fine. And the question that will be unanswerable before the studies are done is how diversified will the pharmacogenetics and the ontogeny of those pharmacogenetics be from population to population. And those questions cannot be answered until the studies are done.

DR. CHESNEY: Dr. Hudak.

DR. HUDAK: I think that the answer has to be a cautious yes with conditions, as everyone has said. I think the PK data and so forth are more likely to be more easily extrapolatable. I think given the differences in biology and the biological complexity of the systems, that as you move up to safety issues and then to efficacy issues, you're going to have a lot more difficulty extrapolating to our population without having some similar type studies in this country.

And I also think, at least in the way that I look at some of the studies that might be done in the third world, study designs that are put together there may be very radically different in their approach to either the transmission prevention or to actual treatment, that it might not really, in terms of study design, be exactly applicable to what we need to do in this country. So I think that's another complicating issue.

DR. CHESNEY: Dr. Fink.

DR. FINK: I guess I would recommend cautious extrapolation with two comments. One, a well-designed and well-done multinational trial may be preferable to a trial performed in the United States because my second comment would be even studies performed in the United States have been notoriously poor in reflecting some of the pharmacogenetics of our large minority groups, and I'm not

sure you can routinely extrapolate trials performed in the United States to the U.S. population. And we probably have some unique pharmacogenetic mixes in the United States that exist nowhere else in the world.

DR. CHESNEY: Dr. Chadwick.

DR. CHADWICK: I would agree with that and just say that I think the possibility that we can extrapolate exists, but we have to collect the data to be certain about that.

DR. CHESNEY: Dr. Danford.

DR. DANFORD: I would say, sure, you can extrapolate results from a study such as that. The question is how much confidence are you going to have in them. It's a question that has an answer in terms of a continuum, not a yes or no. We would have more confidence extrapolating studies of neonates in resource-poor countries to our own population in question than we would have extrapolating results from studies done on elderly individuals. We would have a great deal more confidence if we could do the study on the kid's twin brother. I think the resource-poor countries where we would study neonates probably fall intermediate. So you have to extrapolate carefully.

DR. CHESNEY: Dr. Sever.

DR. SEVER: Well, I would join the group for

extrapolation with, as everyone has said, the involvement of multi-site, multinational studies, including patients in the United States, and then to standardize entry on the key factors which are known about the metabolism and the excretion of the drug so as to try to keep that as close as possible, and then obviously evaluate the data and see if you do end up with comparable populations.

DR. CHESNEY: Dr. Fost.

DR. FOST: Well, it gets easier as you get to the end. But I think the word "extrapolate" and the word "results" oversimplify.

First, results. I mean, as I've said, there are things you can learn from studies in another population that would definitely be useful to a U.S. population, not immediately translatable but extremely useful for telling you whether you'd want to go ahead and, for example, repeat the study.

Extrapolate. I was going to make Dr. Fink's point, that is, doing a PK study on 8 children in the U.S. with different gender, race, genetics, and other variables doesn't tell you that every child who is going to get that drug is going to behave in the same way. So any PK study always gets you in a ball park of roughly how this drug works in this age group or, at least, in these 8 children that you happen to study. And in general, that will be

pretty predictive of most other children, but I don't think the big cut there is going to be third world versus U.S. It will be various genetic and other variables, socioeconomic and nutritional and racial and gender and so on. So, yes, we'll learn something about the pharmacokinetics of a drug in that population, but what population it will be applicable to in the U.S. you'll have to think about carefully.

DR. CHESNEY: Thank you.

So we'll go on to question 3. Should we continue to request pharmacokinetic and safety studies for every antiretroviral drug under development? And if not, what criteria could be used to decide which drug should be studied in the neonate?

Dr. Wood.

DR. WOOD: I think the first comment that I'd like to raise is the issue, as Jan and I were discussing, about every antiretroviral drug under development. I think the caveat to that would be based on known safety data. If there are clearly preclinical and animal model data or adult data that would suggest that there is toxicity of this new agent that would be particularly relevant for neonates, no, you would not want to study it or to have them exposed to it.

I think that if we looked at the greater

historical issue of just approach regarding the principle of requiring it, the principle and the desire is so that we would have adequate, sufficient data in populations that we know are potentially going to be exposed to these agents.

My major concern is that if we did not continue to request pharmacokinetic data, that we would not get the pharmacokinetic data on these antiretroviral agents. And we know that these children potentially ultimately might be exposed to these same drugs because they would ultimately potentially be licensed and their mothers would be taking them for their own health. And I think that's another ethical consideration that we have to keep in mind.

DR. CHESNEY: Dr. Fletcher.

DR. FLETCHER: I agree with Dr. Wood about the drugs for which we should request pharmacokinetic and safety data.

Here maybe I'd just add some comments about, now, what do we request? What might actually be required? My sense currently is -- I'm not sure if it's what the FDA is actually asking the companies to do or whether it's the companies' interpretation of what they should do. Sometimes those things are very different.

At least what I see right now from both the Pediatric AIDS Clinical Trials Group and the industry are multiple-dose studies to steady state, trying to look at

both safety and efficacy. So in a sense they're trying to do everything when they go into this population. And I think that means there becomes a very limited number of children that can enroll in these studies. They are very difficult to do. They take an incredibly long time to enroll. At least so far every one -- I hate to make generalities because I'm sure I'll be proven wrong quickly, but at least every one I can think of, the initial starting dose that we used to go into neonates was wrong. In other words, it was suboptimal in terms of achieving the systemic exposure that was shown to be safe and efficacious in adults.

So increasingly I've been thinking about maybe we need some alternatives in terms of what do we really ask for. This now gets to this issue of single-dose studies. Should that perhaps become a requirement? So just a few points here.

It seems to me what a single-dose PK study would do would really be establish basic pharmacokinetic characteristics for the drug in that age group. Some of these drugs do present some challenges for single-dose studies. They have long half-lives. So a first dose, a single dose is not going to tell you what concentrations look like at steady state, but if pharmacokinetic principles hold, you should be able to extrapolate to

steady state really with a high degree of confidence.

Now, if you have drugs that are auto-inducing, which we do in these antiretroviral agents -- so, in other words, the first dose is not going to predict steady state. The half-life will get shorter the longer you dose it. If we know something about the time course of that auto-induction in adults and in older children, it seems to me that again we can have some confidence in extrapolating that to neonates if we know what the PK are initially from a single-dose study in neonates.

So if we can do that, then these studies are clearly easier. The designs lend themselves to both international and U.S. sites. They probably allow themselves a broader patient inclusion criteria, so not only HIV-infected but probably HIV-exposed.

And then I will just come back to where I started. They do, however, just become starting points. I think it's information needed just like if you were going first dose of a brand new drug in humans. It's a starting point to design a multiple-dose dosing regimen that's going to be given in HIV-infected infants that then would need some type of confirmation. Now, you're not going to have to learn everything. You're just going to have to confirm that this multiple-dose regimen now is achieving the types of exposures that you thought it would and those type of

things, and don't require intensive in-patient types of pharmacokinetic studies.

DR. CHESNEY: Dr. Spielberg and then, Dr. Rodvold, did you have your hand up?

DR. SPIELBERG: A couple of thoughts. When you start out, even if you have several drugs in a class, often we have no idea which will ultimately be an optimal drug to give to neonates. It can come down to something as simple as which of those is going to be formulatable. So if you start off with three drugs in a class, if you only ask it of the drug that it turns out is unformulatable, then you're going to have to ask it of the next drug, et cetera. So that's one thing to consider.

And some drugs will have more favorable pharmacokinetics or metabolic profiles vis-a-vis the relative maturity or immaturity of a given pathway in the newborn and may be more suitable for certain disease states than other disease states.

Having said that, there are some analogies to oncology because we've got a serious, life-threatening disease, with very limited numbers of patients, and we know that we can't, for example, take every drug in a class into a COG protocol.

Victor, can you comment at all from the oncology experience how some of the decision making about

doing all drugs, doing some drugs, et cetera is done?

DR. SANTANA: Well, I think from the experience of phase I studies in pediatric oncology, we always request some PK data even if it's a me-too drug or something like that because minor differences in structure potentially could lead to differences in some excretion pattern or things like that, and you only find that out if you study it. But it's a graded system so that for a brand new class of drugs in oncology we would request a lot of pharmacokinetic data or we would want a lot of pharmacokinetic data before we moved that drug forward, whereas if it's a drug that's another me-too drug or another derivative, we may ask for more limited studies. So it's graded based on the class of drugs, how much more information you had ahead of time, but the basic principle is that before we move any phase I oncology drug to the phase II or phase III setting, we want some pediatric data.

Does that answer your question?

DR. SPIELBERG: Well, do you know how the review division at FDA deals with issuing written requests on the multiplicity of compounds out there?

DR. SANTANA: I think they're better suited to answer that than I am.

DR. SPIELBERG: Some of the same analogies apply, given patient supply and number of investigators and

difficulties of doing the study and that it's a life-threatening disease.

DR. DIANNE MURPHY: With the written request, in the beginning of this process, we had to take the position that it's a voluntary program. You issue it. You don't know who's going to respond. We did not feel that our mandate was to wait and see if this company responded, then start all over. So we did issue written requests to basically every player in the field and have done that unless there were reasons to do otherwise. So the position is that you do issue a written request unless there is a reason not to do so, such as a safety issue, such as some concern in pharmacokinetics that you want worked out before you issue a broader written request because the need is in a bigger area and you think that there's something else that needs to be done.

Or you may issue a written request -- and we've done this -- where we say we want you to do this. You have to solve this problem first, then come back and give us the information. Then you'll go to the second part of the written request, and then you have to complete the whole written request before you can get exclusivity. We have done it that way also.

But the crux of the question is that we have taken the stance that children deserve as many options as

adults.

DR. CHESNEY: Dr. Rodvold and then Dr. Fink.

DR. RODVOLD: Well, with that, again I'd encourage that the design of these studies move up more to the state of the art of the science a little bit. I think traditionally people are looking at these as more traditional single-dose studies. I think you're going to have to really look at a prior knowledge of each of these compounds and decide whether or not a single dose or multi-dose and using optimal sampling windows and maximum likelihoods and be able to use that data to be able to design the study as best you can, as well as analyze it the best you can. I think it needs to be encouraged here. The industry I think is equipped to do it. There are no doubts about that in my mind. And I think the people at CDER know how to do this really well, as well as the evaluators.

I just think that that's missing over here on this side of the table of the pediatrics, and particularly in this area, I think it will really lend itself to be able to sort out variables. That I think hasn't traditionally been thought of. So I'd encourage that be brought here because you have it in your other statement papers for the FDA guidance papers of how to do other studies, mainly up on the adult side. It easily can come down to here. There are plenty of people who can do it.

DR. CHESNEY: Dr. Fink and then Dr. Nelson.

DR. FINK: I guess as this discussion goes on, I'm getting more and more uncomfortable with the concept of pharmacokinetics and would just like to point out that particularly if we're talking about the neonate, the marrow response in the neonate is very different from the child, and when we're talking about drugs that work in an intracellular level, I'm not sure we couldn't be led badly astray by saying that similar pharmacokinetic levels in the blood will lead to similar intracellular efficacy. The infant, particularly the neonate, has a very polymorphonuclear response from his marrow and many of the lymphocytes are undetectably committed in the neonatal period as to what kind of cellular markers they're going to express. And I don't know how to interpret all of that, other than to say it makes me very uncomfortable in the neonatal period that pharmacokinetic data alone on blood levels is actually going to predict biologic response.

DR. LEWIS: Just as a response to that, there has been a lot of debate, particularly with the nucleoside analog drugs, about exactly what is the most useful pharmacokinetic parameter. Is it a serum level or a plasma level or is it an intracellular level, which gets to your question. We still don't have excellent technology for determining those things. So the best estimates that we

can make that correlate are target AUCs and Cmax for plasma and serum levels in many cases. We're getting a little better at some of the intracellular levels, but again, those are even different compared to the plasma and the serum levels.

I would love to hear a comment from the pharmacologists about that.

DR. RODVOLD: Well, I think you'd have a tough time getting the answer to your question until we have the PK answer because the next thing that comes hand in hand is to model the PK with the PD. So if we don't get the PK answered to a beginning degree -- and I don't think Courtney or I are saying definitive studies here -- you can't even go on to the next step and link it to toxicity or efficacy, which is what we would ultimately want to do.

So I keep coming back to we need to turn this back to let's pretend we almost don't have any information. What would you do the first time in man? A single-dose study or a really well-designed study, get some information and get you comfortable to move up the next step and be assured into some dosing level and then move on to collect that next piece which is the link of efficacy and safety. But I don't want to give up on that knowledge I know too. So I want to use some of that in here at this point. But that's going to have to be done.

DR. FLETCHER: I absolutely agree with Keith. I should probably preface at least all my comments in the context in which we're discussing this in which the question has been raised. Should we require these data at all? And so if that's the question on the table, my answer is yes, we should require it, but I think there are some things we could do to perhaps obtain this information in an easier way, in a quicker way than what we've done before. But Keith is right. The PK really just become the starting point for then I think the whole continuum of antiretroviral drug development in neonates, infants, and children.

Just a final comment on the point about phosphorylation of the nucleosides. Right now zidovudine, AZT, really remains the drug about which we know the most. What has really struck me from the studies principally conducted at St. Jude in children -- granted phosphorylation data are really quite limited, but when you look at the phosphorylation of this drug to its active triphosphate form in children and you compare those with adults, there are just no striking differences. There are different dosing regimens that we use now because of differences in pharmacokinetics, in absorption, distribution, and metabolism. But when that is done, the intracellular triphosphate levels look very, very

comparable.

DR. CHESNEY: Dr. Nelson and Dr. Hudak.

DR. NELSON: As we were discussing questions 1 and 2, there were a number of different criteria that we brought out for when we thought a trial might be indicated in either HIV-infected or HIV-exposed infants. The form of the question bothers me a little bit because the way that I would want to ask it initially every antiretroviral under development sort of implies that it's a drug-related request as opposed to a population and study-related request.

One could look at this as just a question of whether you can extrapolate scientifically, but I would want to bring into this all of the various conditions that have previously been discussed as to whether a trial is appropriate in the first place. And I personally would hope that one would never request, as part of a written request, a study unless you could imagine that it could be done ethically.

I'm assuming that's true, but the question is just worded from a scientific extrapolation point of view and I just want to make sure -- that's what's been bothering me -- that we're not going to ask for studies just because we want the data as opposed to we think that this study ought to be done and we need the data in order

to do the second study after we have that data.

DR. DIANNE MURPHY: I think I just have to respond to that.

(Laughter.)

DR. DIANNE MURPHY: This committee and certainly the members of it know that we always consider the ethical issues or hope we do. And if we have any concern, we frequently bring it to this committee and certainly would not go forward with a study if we were concerned. Again, our mandate is that it has to have a public health benefit, and certainly an unethical study would not be a public health benefit.

DR. CHESNEY: Dr. Hudak.

DR. HUDAK: I'd just like to probably state the obvious that maybe everyone is thinking about. Some disproportionate percentage of these babies are born preterm. And we're talking about pharmacokinetics and so forth, and there have to be provisions made obviously to study some adequate number of the very preterm babies to get good information because we sort of fly by the seat of our pants many times with these kids. And I don't know how this population pharmacokinetics works with preterm babies who are clearly very different or can be very different many times.

To anyone who has any doubts about how many

babies might have to be studied for these things, one can just think that every three years we have different recommendations in vogue for the dosing of gentamicin and vancomycin in preterm babies based on gestational age and postnatal age. It really changes every three years, and clearly these are very well-studied drugs.

DR. CHESNEY: Dr. Englund.

DR. ENGLUND: I think that's a very, very good point.

One thing I would like to say that might influence the FDA advisors is whether the drug is an oral or intravenous formulation. In fact, we have a paucity of intravenous formulations for these preterms because in fact many of them have more oral formulations and that might be more applicable to third world countries. But because there's such a potential need for the intravenous formulation, that should be viewed by the FDA as -- you know, a drug that would have different formulations would be an advantage to those of us practicing clinical medicine and we would encourage multiple routes of development depending on the formulation of the drug.

DR. CHESNEY: With respect to the first part of this question, can anybody give specifics as to when we would not request pharmacokinetic and safety studies for a new antiretroviral drug, given that it was safe, everything

was being done ethically, and it had been looked at in older children? Can you think of any me-too drug or new drug that you don't think should be tested in children? Dr. Gorman.

DR. GORMAN: My answer to this question would be no. Every antiretroviral drug should not be tested. The question that you just asked is the answer. One is if there's an emerging resistance pattern that makes that antiretroviral drug worthless, or two, if there's emerging toxicity data that shows that other drugs in that class have a toxicity which is unacceptable.

DR. CHESNEY: Dr. Wilfond.

DR. WILFOND: I can think of a second reason. Again, this gets back to the distinction between use for treatment versus use for prevention. If there was a drug where the intended goal was only to be used for treatment of HIV-infected individuals, then it would make no sense to do any studies in HIV-exposed and not infected individuals.

DR. CHESNEY: Are there existing examples of that kind of a drug, Dr. Mofenson?

DR. MOFENSON: Linda?

DR. LEWIS: I don't know that we've found one yet, but there could be with some of our future drugs.

DR. CHESNEY: Dr. Fink.

DR. FINK: I was just, I guess, puzzling over

that issue of if we were looking at what kind of drugs -- it seems like usage for most drugs is going to, first of all, occur in the pregnant female, and if it doesn't have bad effects on the fetus, how much comfort or not can we take in that. Particularly if it crosses the placenta, you're going to see a large number of infants born with in utero exposure well before we probably ever undertake clinical trials in that age group.

DR. LEWIS: Yes, certainly pregnant women are now being treated much more aggressively than they were when I was coming through training. So they are treated with multi-drug regimens. Some of the drugs we know are mutagenic or carcinogenic at least in animal studies, and we accept that risk in the pregnant woman both for her treatment and health and well-being and hopefully for prevention of perinatal transmission.

I think there are still physicians who are a little hesitant to use very new antiretrovirals for which there's not a great deal of data available in pregnant women, but that's more a clinical management issue.

We have very little data on these drugs actually in pregnant women, and some of the studies that are being done now, as I said, enroll the women during the second or third trimester and follow them very closely and then follow the infants after delivery. So we have

gathered some data but not very much specifically in pregnant women.

DR. FINK: It raises a question since pregnant females are a large part of this discussion if we're dealing with neonates. What is the FDA's stance on asking companies to do pharmacokinetic studies on the pregnant female? When your blood volume increases by 50 to 75 percent and there are large circulatory changes in renal function, are we treating pregnant females with the right doses?

DR. DIANNE MURPHY: Sandy Kweeder should be here. We have a group of individuals at the FDA who basically have taken on the activity of making sure that pregnant women do have those sort of questions addressed and wherever possible, with all the usual caveats that something you know would clearly be teratogenic, you would not. Talk about the preemie having changes. We're still trying to find out how to use some very old drugs in pregnant women and finding out that we are achieving the right doses.

So the answer to that is that there's a group of people at FDA who are very much focused on trying to make sure that these products are appropriately studied in this population.

DR. CHESNEY: Can I ask a question of those of

you who are caring for these children all the time and very much a part of studies? Are there toxicities that you would accept in a new drug that was very potent to treat an infected child but would not accept to use in an exposure prophylaxis setting? In other words, a child who had a very resistant organism and this drug was going to do exactly what you wanted, but it had some renal toxicity. Would you accept that in that child as opposed to an exposure prophylaxis setting? Which I think goes back to what Dr. Wilfond was saying that you might accept a drug in one setting and not another. Maybe there's no precedent for that.

DR. MOFENSON: Just a comment. The use of drugs for prophylaxis is different than chronic use for treatment. So when you're talking about prophylaxis, you're talking somewhere between 1 dose and 6 weeks to the baby. So you may have a drug that has a chronic toxicity, but that chronic toxicity may not be seen with a shorter course. So your question is I think more complicated than you thought it was.

DR. CHESNEY: That doesn't surprise me.

(Laughter.)

DR. CHESNEY: But I think it does pertain to the second part of this question, which drugs might you study and which ones might you not.

DR. CHADWICK: Dr. Chesney, just as a treating physician, I think that most of us would accept more toxicity in the treatment setting than we would in the prophylaxis setting. Certainly Lynne's point, if it's something that is reversible when you take away the medication, then we'd be more likely to accept the toxicity in prophylaxis as long as we knew we're going to stop it.

DR. CHESNEY: Thank you.

Dr. Mofenson.

DR. MOFENSON: But take nevirapine. When we tested that in pregnant women and newborns, we knew that it rarely caused Stevens-Johnson syndrome which was occasionally fatal. It was a small percentage, but we took that risk when we tested that drug. So yes, that's true, but yes, it isn't true too.

DR. CHADWICK: But, again, you're talking about a very small percentage of the time it's toxic as opposed to a more routinely toxic problem.

DR. CHESNEY: Dr. Nelson.

DR. NELSON: This morning when pharmacokinetics was discussed, the term "fade-out PK" was used, and my question, for those who have the scientific background, is how much mileage would you get from identifying pregnant women who are on medications that cross the placenta and then do fade-out pharmacokinetics to get the kind of

information you may want to know about the neonate. And how applicable would that be to prospective dosing of that neonate, or at least of other neonates like that neonate?

DR. FLETCHER: I think potentially you could get a lot of mileage out of that. It was brought up earlier that if one were to do a PK study at 3 weeks of age, that may not be as informative as you would like if you were going to use that drug for treatment in a newborn beginning at 24-48 hours of age because of some of these changes in metabolism. It would seem to me, as you described, if the drug did cross and you were able to then in the newborn, without giving a dose, follow that decay of drug in the body, that that half-life would probably much more closely mimic that half-life at birth than might a half-life determined at 3 or 4 weeks of age.

In a sense that's really the first study that was done with AZT. It was following the decay in infants that had been exposed, and it was I think quite informative in terms of how then to begin designing that initial dosing regimen for the first 6 weeks of life.

DR. NELSON: As a follow-up, since the pregnant women who are infected would be likely or ideally on highly active treatment with some of the medications that we might be uncomfortable just starting off giving to the neonate, if there is placental transfer, doing initially a fade-out

PK would give you data without making the choice to expose the neonate to the drug after birth. So it may be a nice way to perhaps have your cake and eat it too in some of these difficult classes of drugs to study.

DR. FLETCHER: Again, I agree. Dr. Sever talked about some of the analytical developments that have gone on. They're not in every lab now, but certain tandem mass SPECTs that have higher degrees of sensitivity so you can quantitate much, much lower concentrations than you could before. They're reasonably available, which I think makes these washout studies feasible for a larger number of drugs than might have been five years ago.

DR. SPIELBERG: It is indeed a great way of looking at clearance. What it doesn't tell you is the performance of a pharmaceutical product. And the neonatal gut is a pretty finicky organ that sometimes simply rejects molecules for reasons we never know. You can give oral phenytoin till the cows come home and you don't achieve levels. So one way or another, you're going to have to go back and actually look at the pharmaceutical product, the specific formulation, and the way that formulation is bioavailable in the patient population of concern.

So you still are going to have to do the studies. But as a starting point for looking at clearance and getting an idea of half-life and of metabolism, et

cetera, sure, we should take advantage of those things.

DR. CHESNEY: Dr. Rodvold.

DR. RODVOLD: Yes. You'd probably get half-life very accurately. You probably won't even get clearance because you don't have the dose you gave, and so you don't know how much was coming. You don't know the starting spot. Mom sent something, but you don't what it was that she sent. So you're missing dose, the amount that's coming, and that's the critical parameter to calculate clearance and volume. And you would never have volume. So you're missing the physiological parameters.

DR. SPIELBERG: You're not going to get Cmax.

DR. RODVOLD: But I mean, it gives you some information. I would still encourage, just like what Courtney said, to do some studies in certain selected drugs. The more toxic the drug was, you'd up it. You'd probably do it that way. But like what Steve is saying, you still have to come back to the issue to be able to sort out dose and dosing interval with better science eventually. So in certain cases it would work. Probably the higher the toxicity rate was on the compound or concern to give the neonate the compound, that might be then the first step you would do to be able to minimize that on the back side. So there's some application.

DR. CHESNEY: What I think I have heard is that

we would encourage every new antiretroviral drug under development to be looked at in infants except a drug that had unacceptable safety in older children and a drug that, for whatever reason, didn't have potential use for HIV exposure prophylaxis.

Were there other suggestions as to when we would not recommend that a new antiretroviral drug be looked at?

(No response.)

DR. CHESNEY: Do you want an official vote on that? Is that enough information?

Dr. Englund has thought of a reason.

DR. ENGLUND: This is an addition. I do think that we are not going to encourage breastfeeding in our country, but it's something to consider to evaluate if the drug is going to be used in other countries as to how much of the drug is actually transmitted in the breast milk. But, of course, we're not going to do it here. So you can say that's only for non-U.S.-based things. But it's something to think about. We could get toxicity of an agent potentially if we're dosing the baby and the mother is transmitting it too.

DR. CHESNEY: If this is acceptable, I think Dr. Oleske had something additional he wanted to add. It is our choice outside of the official public hearing. So

it is our choice to hear from you again.

(Laughter.)

DR. OLESKE: I'm sorry, and I appreciate the privilege.

I've been biting my tongue in the back, obviously. There are a lot of things I had wanted to say. But I just wanted to make one point, and that is the reason that many of us who have been taking care of patients are anxious to see studies go on -- I just remind everyone, in '83, '84, '85, when we started thinking about AZT, it was 10 years or almost 8-9 years before we showed it dropped transmission, and then the transmission rate dropped very rapidly. So a delay of a few years can mean a lot in pediatrics.

So if there's some anxiousness in some of the people maybe behind you, as well as at the front of the table, it's that we want drugs appropriately and ethically studied in infants and children as soon as possible, and if you don't start with infants, they get delayed in being studied in children and there's linkage between going from pregnant women to infants to children that you have to sort of understand.

DR. CHESNEY: Thank you.

Do you want any more input from the committee on your questions before we move along?

DR. DIANNE MURPHY: No. I think what you've heard from the division is that they're clearly getting one side of the discussion from others. They felt it very important to get input from a variety of other perspectives.

I'm whispering on the side here to make sure the division doesn't have anything else that it would like to ask you today. It would be unfair, but we would take advantage of it if we could. Linda?

DR. LEWIS: No. I think this discussion has been very helpful. As I said earlier, the issuing of written requests for pediatric studies is a collaboration between a pharmaceutical company and our division. We are always happy, if the sponsor feels that a particular study design might not be able to be done or if they feel there is some other study that they can do better, to evaluate that in the context of now this additional information we've gotten. I think this has been a very helpful discussion.

DR. CHESNEY: Given that we've only been sitting here for an hour and 5 minutes, could we bypass the break and go on to at least hear Dr. Murphy? Well, wait a minute. There's an objection.

DR. DIANNE MURPHY: I think they can release some of these individuals who may wish to be released.

(Laughter.)

DR. CHESNEY: That was the objection. So I guess it is best if we take a 5-minute break and then reconvene just the members of the committee. Sorry about that.

DR. DIANNE MURPHY: Thank you all very much. It really has been very productive and helpful input.

(Recess.)

DR. CHESNEY: I think we're ready to get started for the second part of the program, if people can take their seats.

So our next issue on the agenda is an overview of the Division of Pediatric Drug Development, the Office of Pediatric Therapeutics by Dr. Murphy, and I think we're all very eager to hear the picture from on top. I don't think Dr. Murphy needs any introduction, although I can do that if you would like, Dianne.

DR. DIANNE MURPHY: No. I'll keep my past sins quiet. Thank you, Joan.

Thank you all. This is the overview of alphabet soup. At the end of the session, I hope you'll know the difference between OPT and OCTAP and a variety of other acronyms.

This is what will happen through the rest of this afternoon. I'm going to provide a quick overview, as

much as my Irish background can allow me to anything succinctly, of the pediatric organization and the new Office of Pediatric Therapeutics.

Then we're going to move into an arena, in which you will be involved in the future, which is receiving updates on the safety reports that we have on products that have been granted exclusivity. As you know, the legislation mandates that we report this to this committee and you advise us if we need to do anything further than what we're already doing. You will hear about how we obtain reports and how we plan to implement this new program and get the preliminary assessment of the first product that we're able to provide this information on. This is a product that was granted exclusivity and which has been out there almost long enough for us to provide you data. So we're going to provide it to you in a preliminary manner. Dr. Solomon Iyasu will do that for us.

Then finally, you're going to get to meet Dr. Shirley Murphy, who is our new Division Director. And we don't just hire by name.

(Laughter.)

DR. DIANNE MURPHY: We try to stay out of jail. It just happened to be the best qualified candidate. So what can I say?

We're just delighted to have her here, and she

will be presenting to you the tremendous range, the broad range of activities that are going on in this division and the types of consults and types of activities that we are involved with. She's described as the marriage made by Congress, our collaboration with NIH and NICHD that is becoming quite intense.

At the end here, Terrie Crescenzi will provide you with our latest update on all the activities which have been ongoing, including the now 50 new labels that we have. It's sort of a new marker for us.

Also, before I move any further into this, I wanted to say Rosemary Roberts says hello to everybody. She's sorry she cannot be here. This would usually be something she would be doing, and I probably won't do nearly as good a job. Rosemary, the deputy in OCTAP, which you're about to hear about, is on detail down to the Department working on a counter-terrorism issue for us for bioshields. So she is well utilized at the moment but did wish to send her greetings to you.

At one time we were simply an activity within the FDA, a lot of pediatricians advocating for children, and with the help of many other people, were able to develop a number of groups and teams. You've heard pediatric team. You've heard the pediatric committees. You've heard of PDIT, pediatric implementation team.

They finally made us an office about two years ago which was the Office of Pediatric Drug Development Program Initiatives. And within those program initiatives, as you'll remember, we had pregnancy labeling. We had pediatric drug development. We had drug shortages. We had antibiotic resistance and we had counter-terrorism, just because we didn't have enough to do I guess. So those were all the initiatives that were in this office.

As of 9/11, they decided they really needed to reorganize us once again and very gratefully infuse more resources into this office. The OPDDPI, which was unpronounceable even as an alphabet, morphed into OCTAP, which is the Office of Counter-Terrorism and Pediatric Drug Development. We now actually have, besides teams -- this is the big news -- real divisions, which is an important step from a structural and organizational point of view because you get more FTEs, you get basically more recognition.

We now have two divisions. One division is dedicated to pediatric drug development. That does not mean, as you will hear, that we are doing all the pediatric drug development within FDA, but we are basically coordinating the activities across the Center for Drugs. Also within this office is the Division of Counter-Terrorism which handles drug development for the Center for

Drugs for antidotes for counter-terrorism.

Now, that was before BPCA. What you see up here now is we have also after BPCA the Office of Pediatric Therapeutics. Everyone knows Best Pharmaceuticals for Children Act, BPCA. The Office of Pediatric Therapeutics is placed in the Commissioner's Office and reports to Dr. Mack Lumpkin who has been an advocate for children for many years within the agency, and he heads up the Office of International Activities and Strategic Initiatives so that the Office of Pediatric Therapeutics is basically reporting to Mack up here, and all of this is within the Office of the Commissioner, versus OCTAP which goes up through the Center for Drugs, which is CDER. The Center Director is Janet Woodcock who reports up to the Commissioner.

As I said, this office was established under section 6. Again, because there might not be enough for us to do, this new office is supposed to coordinate and facilitate all activities at FDA that may have any effect on the pediatric population or the practice of pediatric medicine or may in any way invoke pediatric issues. They got carried away at Congress when they wrote this one up. So that's our job description.

Now, knowing that job description, they decided we needed an ethicist and a safety person. So within the legislation, they only identified two positions that we'd

actually really have to have, and then they left it up to FDA to try to take care of all these tasks in the way it saw best.

We have the ad running for the ethicist in the New England Journal of Medicine, and we have one or more experts in pediatrics, particularly safety issues, with Dr. Solomon Iyasu. I am not going to read through everybody's credentials but just say Solomon comes to us from CDC with a tremendous background and experience working with NIH in epidemiology, and we're very glad to have him on board.

Now, the impact for this committee, as far as the Office of Therapeutics is concerned, is that we see subpart D and adverse event reporting as two activities this committee will be progressively involved in, in addition to the usual stuff that we've been bringing to you.

I have to preface this by saying the organizational structure for how we're going to handle the referrals to FDA under the subpart D section in which an IRB sends a referral to FDA, because it's a regulated product, is not completely defined. I should say this is my perspective on it right now. We want these discussions of any referrals that come to us from IRBs to be in the public domain. So we anticipate that if we don't utilize this committee, we will utilize parts of this committee.

Plus, the ethicist people who have helped us on previous ethical issues would be asked to participate in a panel that would be involved in addressing any of these issues that come to us under -- I can never remember all the numbers. What is it? 5054. Because you saw, it's more the minimal risk and it's not direct benefit and they're having to decide and they want additional input.

This does not usurp anything that would go to HHS that would be a federally funded program. If it's federally funded and regulated, then we have a joint committee. But what I'm talking about the people in this room may be involved with more in the future would be where it's a regulated product only, not federally funded, and that there are issues that an IRB is sending to us. So we would need to put together an expert panel, and we anticipate that the future process would involve many members of this committee plus others.

The adverse event reporting is pretty well described within the legislation fairly succinctly. You're going to hear more about that, so I'm not going to talk much about that, how we're planning to do that and the role we think you will play in that.

This summarizes basically the fact that we're supposed to report to you on a yearly basis.

As I said, in developing the written requests

for the off-patent products, we have now developed a very delineated, focused relationship with NIH, NICHD, in how we put together written requests that are going to be going out for contract. Well, the same thing has happened internally for us when developing this program of adverse event reporting on products that have been granted exclusivity in working with our own Office of Drug Safety. As I said, I'm going to ask Dr. Iyasu to explain more to you about how we see that this program will move forward.

How to avoid overlap and duplication? You've got this Office of Pediatric Therapeutics at the Commissioner's Office. You've got OCTAP, which is an office that's overseeing pediatric drug development, and you've got a Division of Pediatrics. So this is how we do it. We all hold up our sign when we answer the phone.

(Laughter.)

DR. DIANNE MURPHY: This is truly trying to avoid creating multiple layers. So in a true government way, we all get multiple jobs instead. It helps in the efficiency of the communication activities, needless to say, in that most everybody is involved at all levels. And that's Rosemary down there holding the OCTAP. She's the deputy in that office.

And the big news is -- we got this last week, folks -- we have an e-mail address, opt@fda.gov, for the

Office of Pediatric Therapeutics. We have a phone, the one we were all answering, and we also have a fax number. We would be glad to entertain questions that people have. Terrie Crescenzi, whom you'll hear from, is the lady who is in charge of making sure all of your questions are addressed and answered. That was another job she got too in all of this.

That is really all I had to say about the alphabet soup, and I will let others give you more meat and details as to how we're really going to do this.

So, Min Chen. Was I supposed to do her background introduction? Do you want to do it, Joan? Do you have it? I'd appreciate it. Thank you.

DR. CHESNEY: So Min Chen is the Associate Director of the Division of Drug Risk Evaluation in CDER's Office of Drug Safety. She's been with the FDA's Postmarketing Safety Office for 13 years. Prior to that, she was a project manager for a CDER New Drug Division and a practicing clinical pharmacist for many years.

She graduated from the University of Missouri and National Taiwan University with a masters in pharmacology, has special expertise in the FDA's program for postmarketing safety evaluation and pharmacovigilance practice and in the agency's postmarketing safety reporting regulations and guidance.

She's going to be giving an overview of the FDA postmarketing safety surveillance practice for drugs and biologics.

MS. CHEN: Good afternoon. This overview provides some introduction to Dr. Iyasu's presentation later regarding how the Office of Drug Safety supports the Office of Pediatric Therapeutics as far as drug monitoring in the pediatric population. After Dr. Iyasu's presentation, if you have any questions about our system, I'll be happy to answer them.

I'll go over some of the following: Office of Drug Safety organization, postmarketing reporting regulations, the Adverse Event Reporting System, often called AERS, and how we evaluate a case report and assess the safety issues in CDER, some of the regulatory actions and the risk management programs that can be proposed for some safety issues.

The Office of Drug Safety is in CDER under Dr. Janet Woodcock. We're with the Office of Pharmacoepidemiology and Statistical Science headed by Dr. Paul Seligman. The Office of Drug Safety is headed by Dr. Victor Raczkowski. In the Office of Drug Safety, there are three divisions: the Division of Drug Risk Evaluation, Division of Medication Errors and Technical Support, and the Division of Surveillance, Research and Communication

Support.

Overall, the Office of Drug Safety has about 95 staff members, supports 15 Office of New Drugs reviewing divisions who have all the regulatory authority. They review all the new drugs. We have safety evaluators, epidemiologists, some social scientists and project managers as a functional pool with different expertise.

I want to talk a little bit about postmarketing regulations, and I think everybody is very familiar with this. Why do we need postmarketing monitoring? Because there are limitations of premarketing clinical trials such as the size of the patient population studied during clinical trials. Usually it's limited about 3,000 or 4,000 people. And a narrow population because the elderly, children, women may not be included in a study. Narrow indications, certain disease states will not be included in a study, and finally, there's a short duration, only about a few months to a year maybe at most to study this. So it's not reflective of the drug's potential chronic use problem.

Beyond approval, hopefully in the postmarketing arena, we can monitor and detect low frequency reactions that have not been identified in clinical trials. We can see some high risk populations that experience some problem with the drugs, long-term effects or drug-drug and drug-

food interactions that have not been studied before and now we're seeing them happening. Finally, a very important function we have here, we hope to monitor the increased severity or increased frequency of some recognized or known reactions identified during clinical trials.

The regulations started back in 1962, the Harris-Kefauver amendments to the Food, Drug and Cosmetic Act. It mandates for the manufacturer not just to prove there's efficacy from the drug, also they have to report all the adverse events when they submit the information to the FDA.

Now, current regulations on safety reporting follow. There are quite a few of them. It includes IND safety reporting and pre-1938. We call them the grandfathered drugs reporting. Postmarketing prescription drugs under the NDA, generic drugs, biologics, OTC drugs, and dietary supplements. The most important one relevant to this initiative is 314.80. Most of the drugs have no reporting requirement unless the drug was approved under the NDA. They follow the NDA requirement. Dietary supplement and food is voluntary reporting now.

Source of the reports. We all know that it's voluntary from health care professionals, consumers, patients, or others like lawyers. We've often heard about the spontaneous reporting, and that's the same thing,

voluntary reporting.

The manufacturers are required for postmarketing reporting, and actually more than 90 percent of the reports come from manufacturers.

This is the MedWatch form as a vehicle of reporting. In your package, you see a yellow sheet that's an example of a form.

The manufacturers should report the commercial marketing experience, postmarketing studies, scientific literature that has any adverse event. That means that all domestic spontaneous reports should be reported. Foreign and literature reports, only serious unlabeled events should be reported. For study reports, in addition to serious unlabeled criteria, there should be a causality assessment in place, that if there is a reasonable possibility that an event is related to the drug, then a report should be submitted to the agency in an expedited manner. That means within 15 days.

Well, it would probably be useful to list all the regulatory definitions of "serious" in order to understand what kind of reports would be qualified to be sent in to the agency in an expedited manner. Death. Life-threatening. Hospitalization includes initial hospitalization or prolonged hospitalization due to the adverse event experienced. Persistent or significant

disability, birth defects, congenital anomaly, or any important medical events that may require medical or surgical intervention to prevent one of the above outcomes. So this is an outcome-based definition of serious.

There are many factors affecting reporting: nature of the adverse event. As we know, more serious ones will get reported more. And type of drug product and indication. More widely prescribed drugs will be reported more than the orphan drug indications. And prescription OTC status. Length of time on market or public or media attention such as this one will probably stimulate more reporting. Sometimes the manufacturer's surveillance system will give more reporting and probably a better quality of information than we have received.

However, we all know there are plenty of limitations of this system, this kind of reporting. It's a passive system, so we don't get all the reports. We don't know the exact incidence out there. Reporting bias may exist. Quality of the reports definitely are very variable and most often they are incomplete. That's a major problem. Also, we cannot reliably estimate the rates of the adverse event that we are interested in because the numerator is uncertain and the denominator can only be projected.

This is just a reporting trend in the last 10-

12 years. As you can see, it's been increasing due to many, many factors. We have more drugs and public interest, so we get more reports. On average nowadays, we get 270,000 reports a year. The yellow part is the 15-day reports. Those are the ones that are serious unlabeled events that got reported in a timely manner within 15 days, and that has been increasing too.

This system is a database of spontaneous reports established in 1969 and restructured in 1997 with greater capacity to accommodate internationally accepted reporting standards such as E2B data element for each safety case report and MedDRA coding terminology. That is a medical dictionary for drug regulatory authority. So we use that to code adverse events and the indications for retrieval of the case reports from the system. It allows the electronic submission transmission standard using the internationally established standard.

The process flow here for the paper MedWatch form you have sent. Some of you have personally filled out a form and sent it to us. We appreciate that. The form received by the FDA will be sent to the contractors to scan every report into images for retrieval, and then each report will be text data entered in E2B format. Adverse events and indications are coded in MedDRA.

The safety evaluators -- and those are the

reviewers in FDA in the Office of Drug Safety -- will review this report in our electronic in-box you will see on the next slide. For all the 15-day reports and direct reports sent to the FDA, we screen and monitor any potential signals from the reports.

The 15 reviewing division medical officers also have access to this data through AERS Datamart. It's a database very similar to AERS.

The electronic submission allows some companies already in place to send these case reports electronically directly into our database via a gateway. That's very cool. We can get our reports right away.

As I said before, the safety evaluators will try to identify and assess previously unrecognized new serious adverse events. We do hands-on review of all these reports. Most intensive monitoring actually occurs over the first several years of some new drugs, but it's continued over the drug's lifetime.

This is a typical in-box of a safety evaluator. We'll have the line listing of the case reports sent in to our office. Each person will review each of the reports, and we can highlight each report in a line listing, review a little more on this screen. This captures some of the MedWatch information like patient information and reporter information, manufacturer information, product information,

reactions, and MedDRA codes. The most important part is the event narrative, a description of the adverse event. We review and read each of these and try to establish the temporal relationship between a drug event based on the information here. You probably know a lot of times the information is not complete. We have to do a lot of follow-up with the reporter to get more detailed clinical information to establish the relationship.

We're all looking for some good reports to help us out to evaluate these safety issues to see whether there are really safety signals. What are the elements of a good report? Hopefully it will contain complete data about suspect drug therapy dates, concomitant drug therapy dates, and patient medical history. Hopefully the patient's baseline status has been documented, and there is confirmed diagnosis of the disease. It's not he says/she says, but we have medical information to document that. Trying to establish the temporal relationship between a drug event by using dechallenge/rechallenge information.

How do we generate a signal? If there is no threshold, how do we define the signal? One good case with a new drug a very serious event may constitute a signal. Of course, many times we need more good case reports from the system or from literature publication -- usually they have better information -- or other sources like public

interest can trigger further evaluation of any potential safety signal.

From our database, if we find that there is a high number of reporting for certain events coded as PT or other higher level grouping case counts, that can trigger us to go into more investigation of potential safety signals.

Evaluation of the reports. Hopefully we have one very good case or good case series to review collectively to find out whether there is something that we need to go further. We try to establish the temporal relationship at the case level and we try to establish a case definition, if possible, to give us a better criteria or better cases to evaluate the safety issue. We look for trends and patterns of events like age and gender, time to onset, dose severity, and outcome. We try to identify risk factors among the case series and then we try to evaluate strength of the evidence for a causal relationship between the drug and event, and finally to assess the clinical significance of this issue.

We have a big staff of epidemiologists. They will help us out to calculate the reporting rate, if appropriate, using the drug utilization database such as IMS, such as PCS, to find out a background incidence rate of a certain adverse event by using the literature sources,

the knowledge to see how big the background rate is for that event, to help us understand what is the reporting rate we have in our system.

If we don't have a good idea, we can always query large databases outside the FDA via cooperative agreements such as the Medicaid or large health plans' databases. We can initiate a feasibility study to see whether we can answer some questions from those searches, investigations.

We're trying to develop some active surveillance methods to look for drug-related adverse events in a more prospective fashion.

The drug safety assessment in the Office of Drug Safety does not just provide signal generation. We also try to address many safety issues outside of CDER, FDA, such as the Congress, the Government Auditing Office, HHS, FBI, Consumer Product Safety Commission, and foreign regulatory authorities. There are constant requests from all different interested parties. We're trying to develop risk management programs, and we're trying to be involved in advisory committee meetings such as this one. In the past we have participated in PPA, COX-2 inhibitors, and non-sedating antihistamines, just a few of the examples.

Communication within the FDA is very frequent. We maintain informal communication with the reviewing

divisions all the time. We have safety evaluators collocated in the different buildings with a reviewing division so they can talk to the medical officers all the time. We have pre-approval safety conferences, that means those conferences right before the drug is approved. We talk to the reviewing division about any safety concerns trying to develop some strategy for postmarketing monitoring. There are also regular safety conferences with the reviewing division to go over the pending safety issues. We have written communications to summarize the analysis and assessment of any specific safety issues, or sometimes we do overall safety review of a drug. And we have advisory committee meetings as a communicating vehicle too.

What are the possible regulatory actions or risk management programs once the safety issues are identified? There are labeling changes in the ADR sections, adverse drug reaction sections, precautions, warnings sections. If needed where the risk is high, working with the reviewing division, it's proposed to restrict the use of the drug, a registry, or special monitoring being put in place. We try to evaluate the effectiveness of any of the risk management programs and revisit this to see whether it works, and if it does not work, what can we do. Of course, if everything fails,

there is the withdrawal from the market option there.

Just to touch a little bit on risk communication, there is a physician package insert everybody is familiar with. There's a patient labeling the company put together to give to the patient, and there's a MedGuide for high risk drugs that's dispensed every time the drug is dispensed so a patient has information in hand to read. There are "Dear Doctor" letters sent out by the company every time there is some specific warnings needed to be communicated right away to the doctor. FDA will issue talk papers, public health advisories, and then some peer-reviewed journals, publications to inform the public about this safety information. FDA has a MedWatch website posting all the FDA published safety information that is public, actually worldwide. Interested people can visit that to get the information.

That's it. Thank you.

(Applause.)

DR. DIANNE MURPHY: Joan, because we're going to move on, if people have questions, maybe we could take them after each speaker.

DR. CHESNEY: Any questions? Yes, Dr. Glode.

DR. GLODE: I have a question. So if you have 270,000 a year, that's about 1,000 a day that are being reviewed. Does the reviewer review the same drug? Are all

the reports on fosamax sent to the same person or on any given day, might different people review those?

MS. CHEN: First, I'd like to clarify that. We receive 270,000 reports. There is no way anybody in the world can review all these reports. So in practicality, we only review all those 15-day types, which is those serious unlabeled event reports and direct reports sent to the FDA. That's why we have about 20-23 people reviewing this by therapeutic categories. So one person will monitor one drug, all the reports sent in to the FDA.

DR. GLODE: Okay, that's what I was wondering because I just wondered about sort of automatic red flags as opposed to supposing that the person is going to use their own judgment in that regard. I mean, life-threatening or death. I assume all of those are.

MS. CHEN: Yes. Based on the reviewer's clinical skills and knowledge of the drug, every time they look at the reports, hands-on review of the reports that are received in our in-box, they have to make a judgment whether there is a safety issue there they should work on further, such as retrieving other similar reports in our database to see is it 1 case of aplastic anemia or 10. That can help us out to see whether we need to follow up and get more information to work on that issue right away.

DR. CHESNEY: Dr. Nelson.

DR. NELSON: I guess let me ask a clarification of your answer to that other question before I ask my question. When you say serious unlabeled, do you mean that the adverse event you're reviewing is not listed on the label?

MS. CHEN: Right. Each case report can have a lot of adverse events happening. As long as there is one adverse event described there that's not labeled and the outcome is a serious outcome there, that whole case report constitutes a serious unlabeled event report to be submitted within 15 days of the company's receipt. So not every adverse event is unlabeled, but at least one of them.

DR. NELSON: My question. Whether you look at the full 270,000 or whether you look at the ones that you review hands on, could you give a relative percentage of those that would be an adverse event that occurs when it's used within the label, meaning either for the population or the indication, and those adverse events that occur because it's being used off-label either in a different population or at a different dose or indication?

MS. CHEN: When we look at a hands-on review of each report, whatever the event that is very serious, we kind of prioritize all the different kinds of events we have received. Of course, for those very serious ones, death, life-threatening, liver transplant, or whatever

procedure needs to be in place, those are the ones that we will concentrate or focus on first.

From that case series, if we find any risk factors such as off-label use in pediatric population, we find out there's a high percentage use of that, it certainly is a signal for us to look into that. If there's a possibility of higher risk in a population, we need to address that if it's not being addressed in the labeling.

So there are many, many issues in these reports that we can look into. However, as you say, we have to look at something that is very serious and something brand new and something that has more of a public health impact.

DR. NELSON: If you had to describe the whole universe of adverse events, can you say what percentage is related to on-label use where it's a rare adverse event that occurs and it's just an extension postmarketing of the same population or how many occur because it's being used outside of the indications, in other words, off-label use?

MS. CHEN: We have not done any statistics like that in the past about off-label use because the indication field is not usually very reliablly captured by our database. Only since 1997 did we capture that field, indication. Before that, it's not there. So it's hard to know the exact proportion of off-label use.

But every time we look at any safety issue, we

retrieve all the reports, we do a hands-on review of each one of them, 20 or 100 or 200. We do a hands-on review. Then we'll look at that data field to see what's the possible off-label use. But for all the drugs, there's always some off-label use. I just can't tell you what's the proportion of it.

DR. DIANNE MURPHY: Let me see if I can help with this. In their review, they will try to obtain as much information as they can, calling the physician, calling whomever they need to call. They will try to obtain the information about was this used in a different way, in other words, for a disease that wasn't listed as an indication, or even in a different dosing way which would be off-label also. So they do try to obtain that information.

I don't know, though, if anybody can give you a percentage of how many times. We have certain drugs which have literally come off market because, even though they were labeled for that, the dosing and the way they were being used were incorrect. So it does occur, Skip. I don't think anybody can give you an absolute percentage.

DR. CHESNEY: Dr. Gorman.

DR. GORMAN: Since all of this reporting is passive, whether voluntary by individuals or mandatory by the companies, can you answer two questions? One is the

active surveillance that you mentioned. What strategies and implementations are on the horizon, and are the obstacles to active surveillance regulatory or resource?

MS. CHEN: I think that's a very good question. I don't have a lot of answers. I think our office is trying to develop active surveillance from different sources out there such as the child health agency and then the AIDS population and I think Boston women's health, certain populations that we can go in there and define what we want and hopefully to find the information during a certain period of time of our interest. I don't think we have gone very far yet. We're still using spontaneous reports to identify some signals and then trying to go from there, but I think that definitely that's a very important part of our function in the Office of Drug Safety to develop that. If you have any good ideas, also let us know.

DR. GORMAN: I guess do you have the regulatory authority to go to active surveillance is the question I'd like an answer to.

MS. CHEN: That I don't know. I don't think we have it in writing.

DR. DIANNE MURPHY: Well, I guess what we could say is that certainly under PDUFA III we've been given more authority. It's one of the emphasis areas with more

resources to become more aggressive postmarketing. As part of the PDUFA III negotiations, the agency asked for more resources and ability to do that. So it is an area which we are actively looking at, as was described, as trying to develop a more aggressive approach to what happens to a product after it gets on the market.

I don't mean this in a negative way. I think the industry has realized that it's really to their benefit for us to have better data and information once a product goes out, or sometimes it may get blamed for everything that happens to a person. So there has been a much more structured process now going into place for trying to develop this postmarketing surveillance in a very active way. Certainly if it's a subpart H product or any of those under accelerated approval, they have mandatory postmarketing activities.

But now I think what you're hearing -- as you heard earlier this morning for some of the phase IV, the agency has been directed to become more aggressive in how we follow up on our phase IV commitments. As I said with PDUFA III, now we have more direction to become more active in postmarketing follow-up when a product is marketed.

DR. CHESNEY: Thank you very much.

Dr. Solomon Iyasu is a lead medical officer in the Division of Pediatric Drug Development and joined the

FDA in November. Among his chief responsibilities are monitoring postmarketing adverse events of pediatric drugs, providing consults to other divisions within the FDA and serving as the clinical contact point for the Office of Pediatric Therapeutics and developing projection methodologies for inpatient pediatric drug use.

Prior to coming to the FDA, he worked for 13 years as a perinatal epidemiologist at CDC and most recently led the Infant Health Research Program in the Division of Reproductive Health. He's a nationally recognized expert in perinatal and pediatric epidemiology and has served on the American Academy of Pediatrics' Committee on Fetus and Newborn, the Global Task Force on SIDS, and the National Children's Study, Pregnancy and Infant Work Group.

He received his doctorate in medicine from the University of Delhi, his masters of public health from Johns Hopkins, and is trained in both pediatrics and epidemiology.

He's going to be speaking to us about adverse event reporting.

DR. IYASU: Good afternoon. I first would like to acknowledge Min and Julie for their contribution to this presentation. They have been a very supportive group for this presentation.

Min has provided you with an overview of FDA's postmarketing adverse event surveillance system. I will be talking to you about one specific surveillance activity, namely, adverse event tracking as mandated by the Best Pharmaceuticals for Children Act. I will describe to you the relevant section of the Best Pharmaceuticals for Children Act and also will describe the FDA plan to carry out the mandate, including the proposed adverse event report review template and finally give you an example of a preliminary review of one of the drugs that has been given exclusivity.

Section 17 of the Best Pharmaceuticals for Children Act, or BPCA, enacted January 1, 2002, requires that FDA review adverse event reports for a period of one year after a drug has been granted pediatric exclusivity. It also mandates FDA to report to the Pediatric Advisory Subcommittee for their review.

To comply with section 17 of the BPCA, we developed an adverse event review plan and defined the roles and responsibilities of relevant FDA competence. As Dr. Murphy mentioned before, the Office of Pediatric Therapeutics will coordinate and facilitate all FDA activities that affect the pediatric population or the practice of pediatrics. It's a very broad definition, but its other main function is to receive post-pediatric

exclusivity adverse event reports and provide for the review of the subcommittee.

The roles of this different FDA conference are described below. The Office of Counter-Terrorism and Pediatric Drug Development, where I sit now, will notify the Office of Drug Safety of drugs granted exclusivity for the purpose of tracking adverse event reports. Although BPCA does not specifically require us to track pediatric adverse events for the drugs denied exclusivity, we will track them as they are also used in children off-label. OCTAP will also serve as a clinical contact point for the Office of Pediatric Therapeutics related to adverse event reports.

And then the Office of Drug Safety will review all adverse event reports for a one-year period after the date of granting exclusivity, and it will complete their review within 90 days of the one-year post-exclusivity date. However, when there are serious, unexpected events, including deaths, the Office of Drug Safety will discuss them with the Office of Pediatric Therapeutics immediately. An additional role of the Office of Drug Safety is to share the adverse event reports with the Office of New Drugs and, of course, with the Office of Pediatric Therapeutics and OCTAP.

In collaboration with the Office of Drug

Safety, an adverse event report review template was developed. The proposed template identifies the various components of the review. A copy of the proposed template is in your handout which was handed out a few minutes ago. The template contains an executive summary that must contain the important findings and conclusions. It also contains the usage information for the drug to help provide a national estimate of the extent to which a drug is used in adult and pediatric patients. Use data is generated for two years prior and one year after exclusivity is granted so as to provide some trend data.

The next section pertains to the AERS search, or the Adverse Event Reporting System search, and the search will be done for two time periods. One will focus on the period from the drug approval date to the present date, and the second search will focus on the one-year post pediatric exclusivity. This search will generate counts of adverse events for adults and pediatric age patients and also count the most frequently adverse events and finally a count of unexpected or previously not described events.

This is followed by a detailed review of post-exclusivity pediatric event reports, which includes a description of the demographic characteristics which mostly includes age and gender, and a description of the serious outcomes, indications or conditions for which the drug was

used, and the dose ranges that may have been used, unexpected events or events that are unique to pediatric patients or those occurring at increased frequency more than expected are also described separately. All pediatric deaths are reviewed, summarized, and evaluated to determine if they are related to the drug in question. And finally, an adverse event pattern or profile is developed based on the analysis of all the available adverse event information, including the use data for the drug so that we can at least have some preliminary estimate of some reporting rates for each of those important adverse events.

To illustrate what the review looks like in real life, I will provide you with an example of a review of sertraline, brand name Zoloft, the first drug granted exclusivity after the law was enacted on January 4. It's only 10 months' worth of data and the review is based on incomplete data and is very preliminary. So I just want to stress that. No final conclusions can be drawn at this time. This was just done to provide you with an example of how the system works so that you can give us some feedback on the template. We plan to present to you a complete analysis of the adverse events for this drug in the future and a few additional drugs that will come due.

As shown on this slide, sertraline has several indications for use in adult patients and recently was

approved for use in children 6 years and older for the treatment of obsessive-compulsive disorder. Sertraline is a selective serotonin reuptake inhibitor and the first of March marks the one-year post-exclusivity date for sertraline.

This table shows numbers of adverse event reports for sertraline from international and domestic sources. The U.S. or domestic reports are shown in parentheses on this table. When looking at this table, the numbers are not going to add for two reasons. First, the total in the first row includes reports with unknown age. Second, these counts may include duplicate reports as well. Fortunately, duplicates are usually easier to sort out by a very careful review.

Therefore, the AERS search for the 10 months since granting exclusivity for sertraline generated about 892 adverse event reports domestic as well as international, of which 577 were from the U.S. alone. Among pediatric age patients, there were 41 adverse event reports, of which 30 we're serious and 4 were reports of death. One of the pediatric deaths is a duplicate, so the number of unduplicated pediatric deaths will be 3.

Adverse event reports are categorized according to preferred terms and a frequency distribution is generated. These are ranked in decreasing order of

frequency.

This slide presents the top 10 most frequently reported adult and pediatric adverse events for sertraline. Note that adverse events not previously described or not on the label are marked by an asterisk. This includes maternal drug affecting the fetus, complications of maternal exposure, and memory impairment. Sertraline, as you know, has a pregnancy category C. There are no adequate and well-controlled studies for pregnant women, so use of sertraline is only indicated if the potential benefit justifies the risk to the fetus. And the other one, memory impairment, may be synonymous with concentration impaired which is an expected adverse event.

Now, I'd like to turn my attention to the demographics of the 40 unduplicated reports for the 10-month period. Looking at the age distribution, there were 7 reports among infants less than 1-month old. All these that were less than 1 month, fall loosely under the category of maternal exposure to the fetus. The rest of the age distribution is really unremarkable. 23 of the 40 adverse event reports occurred among females.

An examination of the serious pediatric outcomes revealed 3 pediatric deaths. 15 were hospitalized, and 21 were life-threatening or required some intervention or were medically important events. Please

note that these numbers are not mutually exclusive as each patient may have experienced more than one of the outcomes.

Now, let's turn to the clinical condition for which sertraline was used. The most common indication for which it was used was depression in children in pediatric age groups. We also have several for which the indication for use was unknown or accidental. Just as an aside, the accidental use was in 3 cases where a 15-month baby and a 13-month baby had accidentally ingested sertraline, and another one was a dispensing error.

Now, let me turn to the 3 patients for which death was reported. Patient number 1 was a 7-year-old male prescribed sertraline for depression, also using amitriptyline and clonidine. Dose and duration was unknown, so this shows some of the quality issues that Min mentioned before in terms of MedWatch reports being sometimes incomplete. Also the drug levels were two to three times higher in the liver than the prescribed amount. Again, the MedWatch report doesn't say what kind of assay they did in this case, so it's not clear. The possible conclusion, though, is death probably is due to chronic multiple drug toxicity as there were multiple drugs being used in this case.

Patient number 2 was a premature male child born to an HIV-positive mother. The mother was using

sertraline for depression, also using multiple other medications during the last 3 months of pregnancy, including L-dopa and antiretroviral drugs also. The baby died 15 days after birth secondary to pneumothorax and septic shock. The possible conclusion is death probably is unrelated to sertraline in this case.

The last case, patient number 3, was a 13-year-old male who committed suicide following 1-week of trial of 50 milligrams a day of sertraline therapy for depression. The patient remained significantly depressed during therapy, according to the mother. The parents did not notice any agitation or mood changes. Again, this is based on parents reporting. The exact event, however, is not know, but the initial report was really in 1997. So this technically doesn't fall within the one-year post-exclusivity, but there were multiple updates to the report. Suicide ideation is labeled but is a rare event. So the possible conclusion is we're not really certain whether there is a relationship between the sertraline use and this event. This case was being treated for depression and suicide ideation is a risk there.

Now, in summary, therefore we developed a plan and process for tracking adverse events as mandated by BPCA. We've defined the roles and responsibilities of the Office of Drug Safety, Office of Counter-Terrorism and

Pediatric Drug Development, and also the Office of Pediatric Therapeutics. We discussed the proposed adverse event review template and finally I presented an example of a preliminary review.

What would we like you to do? Today we would like for you to provide feedback on the review template and plan that we have just presented. And starting with the next advisory committee meeting, we will be presenting to you reviews of adverse event reports for each drug that has completed 12 months post granting of exclusivity and the 3 months it takes to complete the review.

At these future meetings, we are hoping that you will help us review the adverse event reports that we'll present to you and also give us insights, which are very important, and your feedback, which will be critical in helping us reach valid conclusions.

And last but not least, if warranted, your recommendations regarding further investigations or actions would be also equally important.

Thank you very much. If there are any questions, I'll be happy to answer them.

(Applause.)

DR. CHESNEY: Thank you.

Dr. Spielberg.

DR. SPIELBERG: Thank you, Solomon. Obviously

one of the real concerns we all have is how we're going to go about both postmarket follow-up and long-term follow-up on kids, and I think everybody is delighted that things are beginning to happen within the pediatric office towards those ends.

A question, though, and it really relates to time frame. If part of what our interest is is evaluating the impact of new data generating under the Best Pharmaceuticals for Children Act on potential outcomes, a 1-year follow-up after exclusivity ain't the right time to do it. We won't even have labeling done. If we do have labeling done, it certainly won't be reflected by that time in the current labeling.

So if one of the questions that we're asking ourselves and that Congress may ask us and the public may well ask us is what is really the impact of all of these studies and of the labeling process on pediatric outcomes, we are going to have to look rather longer after. So clearly we're going to need to collect data before and collect data afterwards, but we're going to have to go well beyond that year after exclusivity at a time that most of the labeling negotiations aren't even done.

DR. IYASU: I think that's a very critical point and I completely agree with you. Today's presentation was just really restricted to what the law

says and what we're doing towards complying with the law.

But clearly there's a need for long-term follow-up for all pediatric drugs really and some of them more important than others. Right now besides maybe having some phase IV commitments for certain drugs, we don't really have a program that is implemented that looks at long-term. So that is a discussion that is ongoing. I think there are a lot of people who are interested, including Bill, who when he recruited me and Shirley and Dianne, said this will be one of the areas that we need to work on. So I think it's an important area and I do agree with you completely.

DR. SPIELBERG: We also do have to be a little bit careful, though, because if in a couple years Congress comes back and asks us -- people get hung up on what happens during that one year afterwards. We're going to have to be very careful how we explain those numbers so that they're not misinterpreted in context. Something that isn't disseminated can't possibly have an impact until those data are out there.

DR. CHESNEY: Dr. Nelson.

DR. NELSON: It's difficult to interpret the importance of some of these events without knowing the denominator. How hard would it be to work with, hopefully, cooperative dispensers, national pharmacies or either large

HMOs to actually have an ability to say, well, how much is this drug actually being used in the population at what ages so that when you see an adverse event, you have some idea of what the incidence might be.

DR. IYASU: I think you're absolutely right. Interpreting this data is dependent on what the reporting rate is, and I think Min touched upon this issue before in terms of what kind of data systems are available to FDA to try to estimate the use data among the pediatric population, the IMS data.

We'll also try to work on inpatient use data to try to project from data systems that are out there from vendors so that we can have a pretty good estimate of what the projected use is in the inpatient pediatric population.

So I really agree with what you're saying. It's just that there aren't really that many good data sets except the IMS system which we've been working with. But we're trying to work with groups to try to find good data systems outside FDA.

DR. NELSON: But if you do find them, I assume then that will show up in the template?

DR. IYASU: Oh, absolutely. In fact, it's one of the things that would be included in the future reports that we'll provide to you. We'll try to give you an estimate of what the background rate is, at least from the

literature, compared to a reporting rate based on estimates of the numerator and the denominator.

DR. NELSON: I guess not just background rate of the event itself, but the prescribing patterns.

DR. IYASU: Absolutely.

DR. DIANNE MURPHY: Yes. We're going to provide that to you for what we have.

DR. NELSON: I didn't see that in the current template.

DR. DIANNE MURPHY: Yes. And the thing is, as you know and I think this committee knows, we usually use IMS for outpatient and we now have these children's hospital inpatient data that Solomon was referring to, which unfortunately right now is the best we have. It's 24 hospitals, and they're spread throughout the country, but it doesn't have a projection methodology. That's what we're working on, is trying to get a national projection methodology validated so that you could use that inpatient data for national use. Because as you know, you can't get the use data from every pharmacy, so you have to have some sort of projection methodology for it. So that we will be providing to you.

Then the next question I think would be if we bring something to you and there are still questions, we can go out and, assuming we have the funds, we can purchase

additional information if we have to from other databases looking at adverse events, I mean, different databases that do different things. So that might be something the committee might want if there's a question that needed further development.

DR. CHESNEY: Dr. Gorman.

DR. GORMAN: This is somewhat tangential but in some of the labeling that is approved under exclusivity, there are concerns raised about use in pediatrics, but the drug is approved and labeled in children. One of the other selective serotonin reuptake inhibitors seems to have some impact on growth in adolescence. Is that going to be captured under your system, or is there another pathway in which those potential adverse events will be pursued?

DR. IYASU: This system, the Adverse Events Reports System, doesn't really do a good job on that. It doesn't capture it very well. So the best alternative there is for a phase IV commitment from manufacturers, the drug sponsors, for some of those drugs. In fact, there is one out for Prozac which is one of the SRIs. So unless we can increase the number of willing participants who would do this phase IV commitment, we'll just have to be creative and come up with other ways to track growth and development.

DR. CHESNEY: Dr. Spielberg and then Dr.

Santana.

DR. SPIELBERG: Just one potential recommendation for some denominator data. There's a group, the Pediatric Pharmacy Advocacy Group, PPAG, which is a group of national pediatric pharmacists. We've used them in the past when we've been interested in changes in utilization trends of various medicines and they have fairly good data and certainly could be encouraged to continue to collect data. They have both inpatient and outpatient data from their pharmacies. It doesn't necessarily reflect what's going on in the community pharmacy base, but for a lot of medicines, I think they could be of some help and would probably be delighted to help in that regard.

DR. IYASU: Thank you very much for that suggestion.

DR. SANTANA: So I'm going to try to address this differently. I'm going to ask the question if you come to me with some data to look at and the two issues central to this whole discussion is the safety of children and getting more information about how these drugs can be applied in children and what is their safety profile, the two issues to me are, is the frequency of the adverse events different from what we already know in different populations like adults. And for that, the adult data set

should be as vigorous as the pediatric data set. If not, it will be misleading potentially. And then the other endpoint is, are there unique adverse events in the pediatric population, unique to that population, and how do we capture those? How do we identify the greater percentage of those so we can identify those in a quick manner and do correct labeling, so on and so forth?

So knowing that those are the goals, establishing the frequency in comparison to something that we already know that we trust, which is the adult data, and on the other hand, identifying the uniqueness of the pediatric population and the uniqueness of those events, I would go back to the points that have been discussed around the table that I think we really need a very vigorous data set and we need to tap into the sponsors to provide as much data on patients in which the exclusivity medications are being used so we can develop that. Because if not, what I fear is that we will be presented or you will be presented with data sets that potentially will lead to the wrong conclusions. So I think the numerators, denominators, the usage patterns, are they being used for the indication like Skip suggested, that is, what the label says, I think would be very important information.

And I have a fear, just like I have a fear with the MedWatch, that that's a voluntary system and you're

only capturing a set of the data and it's not a universe of data that potentially is going to lead us to the wrong conclusions if you come to us to seek advice. So it's just a general comment of precautionary notes, as you come to us and present this data and seek our advice, of the limitations that I will have if the data is not clearly coming from sources that are very trustworthy or represent the universe at large. And the universe at large is not very big. We're talking about pediatrics. We're not talking about a big universe. So we should make a major effort to try to get as much as possible.

DR. DIANNE MURPHY: Well, let me see if I understand what you're saying then. What you're saying is that you think that for these products that we're going to be tracking the adverse event reporting and bringing this back to you, that we need to have a formal follow-up mechanism in place. Is that what you're suggesting? Because that would become a very different situation. Or are you suggesting that we have additional databases that you think we would automatically survey besides the IMS and the CHC data?

DR. SANTANA: Let me try it again. So the whole issue here is that we need to improve on the safety information so that the label says the correct things in regard to pediatric use. That's the goal.

DR. DIANNE MURPHY: Right.

DR. SANTANA: There are two ways of getting at that. One is comparing the frequency of adverse events in children as they relate to what is known in adults. Just to be very simplistic, I know a lot about oncology. Nausea and vomiting occurs in the same frequency in this population as it occurs in this other population. So it's not an issue. It's the same adverse event profile in adults as it is in kids, and the label reflects that. How do we capture that information? How do we have the comparator numbers to say that the side effect profile is equivalent or is the same? That's one issue. Right?

DR. DIANNE MURPHY: Okay. So we would have the use data, which will give you the denominator of how many people are using it so you'd have a comparison of those numbers. You could do it percentage-wise. But then you're asking for is the reporting for adults and kids on adverse events somehow going to be different. That's your question.

DR. SANTANA: Right.

DR. DIANNE MURPHY: And how can we ascertain that, how it would be different.

DR. SANTANA: Yes, because if not, the label is not going to adequately reflect what's happening in the pediatric population or the uniqueness of the pediatric

population, which is what the intent is. Right? The uniqueness of this population as it relates to adverse events. If it's all the same, it doesn't matter.

DR. DIANNE MURPHY: Right.

DR. SANTANA: But if it's unique, how do you get that information correctly?

DR. IYASU: Let me comment. One of the things that we will be doing is looking at the adverse event profile for adults and for children, and one of the comparisons that we'll do, at least from the raw data, is trying to identify pediatric adverse events that are unique and not seen in adults. So bear in mind this is a limitation of the AERS system, but it gives us some idea of some of the adverse events that are just unique to pediatrics and not seen in adults. There's a longer history for the adult use. So that will I think give us some idea. It's not probably the best, but at least it will give us some flags.

And the other thing is, also looking at having the denominator data for both adults and also the pediatric population, and then comparing maybe the reporting rate for events that we expect, whether they're occurring more commonly in pediatric patients than in adults, although they are both expected. So if they have an increased frequency more than the expected, that may also raise some

flags.

So there are ways of tweaking the data, but it's still not the best approach probably. We may have to do more, and that is a question that we all have to discuss.

DR. SANTANA: Does the agency know if there's a natural tendency for more reporting of pediatric events than there are of adult counterpart events? Are people more sensitive to reporting pediatric events than they are adults?

DR. IYASU: I don't know. Julie, can you answer that question? I think there's more sense in terms of reporting at the earlier time a drug is approved than later, but I don't know whether there is more pediatric than adult.

MS. CHEN: In a special population, either pediatric or elderly, as far as I know, they have similar proportions. They're all being reported, especially for the high-risk situations. We have seen them. Yes, I would say people tend to report more if they experience more rare and serious events for those in the extreme population.

Recently we also look at the antipsychotic drugs in pediatrics and found out there is also some use there. They're all off-label, but we found out that's a typical class of drugs that's being used in the pediatric

population and we got similar reports in our system too. So that's consistent as far as reporting and the use.

DR. BEITZ: This is Julie Beitz. I just wanted to say that there are many, many reporting biases to the AERS database, some of which we know about and many of which we don't know about. There could be a new publication that comes out about children that could cause a spike in reporting for children relative to adults. So that may be very obvious, but there may be media attention and so forth. So it's going to be crude. The best we can do is to give you numbers of reports in the system for adults versus children. Bear in mind that it's noisy data.

DR. DIANNE MURPHY: So I think what she's trying to say is that there are biases and there are many and this is just one of them, and we probably have about as good a handle on this bias as we do any other. You will have the baseline comparisons for use. You will have the percentages to look at, and that's going to be the best. So actually I have seen them give reports where they will show a recent article, like she said, came out and we had a spike or we had a change in a label or there was an advisory committee meeting and we'll have a spike. So they do actually go back and try to look at some of that that clearly might impact the reporting.

But other than that, we'd have to come up with

a hypothesis and test the system that there's a differential between adults and pediatrics, and we have not anticipated that at this point.

DR. CHESNEY: Dr. Gorman.

DR. GORMAN: I think we all have the same opinion that we have a database that has more than a few flaws, and for 10 years as the medical director of a poison center, which has a report system -- it's another voluntary reporting system -- the data is poorly reported, not complete. The flaws are obvious I think even on short-sighted review.

It probably brings us back as a committee to ask for a renewed look at the active surveillance system where I think a lot of the questions that we're concerned about in terms of reporting kind of disappear if you're seeking out the answers rather than waiting for them to bubble up to you even though those systems are going to be very different. And you'll have no trend data in those systems because they'll be new.

DR. DIANNE MURPHY: One of the things that could possibly happen is that we bring to you -- again, I don't think the unique things, the things that we've seen learning difficulties in school -- we'll be able to pick up those. It's going to be is this really a higher incidence than what you're seeing in adults or is it just a reporting

artifact.

We'll bring something to you all, and I think that because the legislation was clearly vague in that it didn't tell us how we're supposed to do this, we're going to be developing this process as we go along. We are trying to put together a report that we think is the best we can do at this point. And it may be that we find, as I said, the questions are basically more and that we have to go out and develop different databases or different approaches or for a certain type of product, we may need to bring the divisions in and have a combined advisory committee with a subspecialty group to talk about a better way to approach labeling. That gets back to some of the activities with labeling.

But I don't know right now that we can really promise you anything better than the data systems that we've tried to put together knowing that they are flawed at this point and ask certain questions. Are there known reasons something would be different?

DR. CHESNEY: Thank you very, very much.

Our next speaker for the afternoon is Dr. Shirley Murphy. Dr. Murphy, many of you may know, is a pulmonologist who was on the faculty at New Mexico in the School of Medicine and College of Pharmacy and also chair of the department there for a period of time. She was Vice

President of the Neuro-health Specialty Division at Glaxo Smith-Kline Pharmaceutical Company before coming here to the FDA a few months ago?

DR. SHIRLEY MURPHY: Five months ago, but who's counting?

(Laughter.)

DR. CHESNEY: Many other qualifications, including serving as chair of the NHLBI's Asthma Expert Panel which produced the national guidelines for the diagnosis and management of asthma and chair of the FDA's Pulmonary and Allergy Committee.

Now Dr. Murphy is the Division Director for the new Division of Pediatric Drug Development.

DR. SHIRLEY MURPHY: Thank you very much. It's a pleasure to be here. I'm the other Murphy.

First of all, I'd like to really thank the committee for giving up Sunday and Monday and coming here and to warn you that we have a lot of work ahead for you. We really value your input. If I could call you together every day, I would at 5 o'clock for a little conference call, but I can't. Please mark your calendars because we have a lot of issues to bring to you.

What I would like to do today is to provide an overview of the Division of Pediatric Drug Development and to update you on some of the activities that we've been

doing this past year, particularly in the months since I've come.

First of all, we were a glimmer in Dianne Murphy's eye just a year ago, but being the recruiter she is, she started up the division even before I got here, and we have gone from 0 to 16 in the last few months. We have nine medical officers with two more on their way. This is really a fantastic group, a very intellectual group, a very diverse group, ranging from pediatricians who are experienced in practice to pediatricians who have FDA experience to subspecialists to people with pediatric boards and also M.P.H.s. So we have a very diverse group.

We also have three project managers, a couple of whom were stolen from Capitol Hill, and they are extremely capable and keep us on track.

And then we have three support staff for the glue that keeps us all together and makes it all work.

Just to show you the dedication of this division, this is the day after the big snowstorm, and this is over half the division, through rain and sleet and 26 inches of snow, who made it in.

DR. DIANNE MURPHY: Post 2 feet of snow, for those who weren't here.

(Laughter.)

DR. SHIRLEY MURPHY: But these are the people

who got in to come to work at the FDA.

What's the role of our division? What do we do? Well, we're the champions of pediatrics throughout the FDA. Just like you have to have champions of pediatrics in hospitals and in organizations, you have to have it in the FDA. Dianne Murphy certainly was the champion of getting this division up and going, and now we are able to champion pediatrics throughout the FDA.

One of our most important roles is our partnership with the National Institute of Child Health and Human Development that I'll be talking about in a little bit.

We also provide a consultative service to all the centers within the FDA. So that's Biologics, that's Devices, that's Foods, as well as Drugs.

We conduct detailed reviews of proposed pediatric trials for the on-patent drugs. We're often the referees. We put on our striped shirts and we contribute to the resolution of scientific and ethical issues, and we disseminate new pediatric labeling information both through the website and also through giving external talks.

Now, I'd first like to turn to one of our most important roles, and this is our partnership, which is mandated by BPCA. This is not my quote. This is George Giacoia's quote from NICHD that we're a marriage made in

Congress, and I think it really does sum it up. We've been married about a year. We're back from the honeymoon.

(Laughter.)

DR. SHIRLEY MURPHY: We know each other's relatives. We're getting to know each other's cultures. We are just doing some terrific things together, and that's what I'd like to talk about, is some of the things that we're doing together. It is a work in progress, just like a new marriage, and we're really happy for all your input on the things that we're doing.

Our first task was to develop a list of drugs for which pediatric studies are needed. This is mandated by BPCA and it is mandated for NIH to do this and publish it in the Federal Register. This is a very long, involved, iterative process which you all participated in the last advisory committee and this has been led very capably by Bill Rodriguez from the FDA and George Giacoia from NICHD. Input was obtained from a whole lot of sources to produce this list.

Now, there are three criteria that were laid out in the law that the list should consider and that's the availability of information, whether additional information on children is needed, and whether new pediatric studies will produce a health benefit for pediatric patients.

I want to show you this process a little up

close and personal in some detail. This is a work in progress, and we're already talking about how we might do this differently.

Every year FDA published a list under FDAMA of 426 drugs where further pediatric studies were needed. There was a list published in 2001, but it wasn't as detailed with information as the one in 2000. So the 2000 was picked. You gave input at the advisory committee, and some drugs were presented to you. NIH was given this list of 426 drugs and they gave it to the United States Pharmacopeia which removed some of the on-patent drugs and also produced some references of what was existing in the literature.

The NIH then sent this list back to the FDA with now 284 drugs on it. Terrie Crescenzi spent a lot of time on this researching all these drugs and basically cleaning this up, and then it was grouped by drugs and their indications and the divisions at the FDA.

We then sent this dwindling list back, now 180 drugs, to NIH. NIH -- and this is NICHD when I speak of NIH here -- ranked the 180 drugs with input from their institutes, the AAP, and outside subspecialty experts.

This list was then further whittled down to 34 high priority drugs. That was sent back to the FDA, and with Bill and Terrie leading the charge, the review

divisions then ranked the drugs on what they thought the public health benefit was, whether there were other approved drugs in the class or other therapeutic options available. And then the use data that we were talking about, outpatient from IMS and inpatient from the children's hospitals database, was added to this list.

We sent this 34-drug list back with the information to NIH, and then they sent this out to one to two experts in each field that reviewed each one of these drugs. And then these reviews were actually typed reviews, just like a grant review, and were sent back to NIH.

NIH convened an expert panel. Some of the members on this committee were on that that looked at each drug and really scored each drug of the 34 from 100 being a good priority to 500 being a low priority. These scores were totaled, and then FDA and NIH met, and we took the top 16 and then selected 12 drugs from that, and the list was published in the Federal Register on the 21st of January.

This is the list of drugs for 2003, and this process will be updated every year and may be updated in the middle of the year. We are looking for input into how to improve this process, so maybe during the discussion period -- several of the people from NICHD are here -- we could talk a little bit about that.

Now, what happens to these drugs when they're

on the list? Well, there's a mechanism ready to receive these drugs, and that's the BPCA process to study off-patent drugs in which the FDA again collaborates with NIH. In this process, the Division of Pediatric Drug Development performs a label review and a very, very extensive literature review of everything that's out there in the literature, and we hope to be publishing these reviews in the future.

And then, working with NIH and the reviewing divisions at the FDA, the Division of Pediatric Drug Development writes a detailed plan for the studies, and that's called a written request. This is sent out to the sponsors and if there's no company that wants to do this, then this is referred to NICHD to be let as a contract.

This is a diagram of the process in which industry has 30 days to respond if they don't want to conduct the studies, and it would be very unexpectedly that they would want to do it on an off-patent drug. Then it is referred to NIH.

Now, where do we stand in this process right now? The RFC has been published in the Federal Business Opportunities. There are three more RFCs that will be published soon, and that's nitroprusside and then lorazepam for two different indications. There are five other off-patent drugs in process that currently the Division of

Pediatric Drug Development is working on. So that's the off-patent drug process.

Another very important role that the NIH and the FDA have had for a long time has been collaborating on scientific issues and on ethical issues. This newborn drug development initiative is really the brain child of George Giacoia from NICHD and Debbie Birenbaum from the FDA. Debbie was on the phone to me as soon as I took this job, pushing this initiative. It is really such an important initiative. Really BPCA looks at neonates as a special subpopulation. And as Debbie would say, if she were speaking up here, the orphans of the orphans, and we need to develop passion around these babies and study medications in them. And that's a gaol, to really foster the development of safe and effective drug therapies for this population.

We are marching down the road towards a workshop that will be held in early 2004 that will look at the state of the art and will define the research priorities for pain control, cardiac disease, neurologic disease, and pulmonary disease, the four topics that were picked for this. We had a planning meeting in which 50 experts came from around the country, and working groups are established, and we are moving forward.

Now, Dianne spoke a few moments ago about

another role we play and that is being the consultative service to all the centers within FDA, and this is really one of the most interesting things that we do. Just like when you get a consult in the hospital of subspecialists, these are usually the patients that everybody else has given their best guess at, and then they call you in for the tough cases. And these are usually the tough cases.

Most of the information about what we do is proprietary, and Dianne Murphy will personally shoot me -- or at least fire me -- if I talk too much in depth about this. So I want to give you a little bit of feel for some of the diverse things that we are doing.

We've been involved with the Division of Devices in several areas. First of all, you probably read about the potential association of cochlear implants with meningitis, and Hari Sachs has been working on that. Hari is a pediatrician and came to us from her practice and really has lent a lot of practical information to that. She's also involved in silicone breast implants and what the effect on the infant might be if it is breastfed from a silicone breast transplant.

Lisa Mathis, a pediatrician who came to us from the Dermatology Division, has gotten steeped in GI devices and there's a lot new exciting devices coming out.

The other area is the Center for Food Safety

and Nutrition, or CFSAN. Formula companies want to add everything into formulas, and Lisa Mathis has been taking a look to make sure that these are appropriate.

We're very fortunate to have Susan Cummins join us with all her environmental expertise, and she's been looking at safety issues regarding exposure from phthalates that soften plastics in medical devices and what the effect can be on children.

We also have a formal consulting process with Counter-Terrorism to make sure that children are in all those labels that are countermeasures to all the horrible things that we read about in the newspapers. Lisa Mathis has been spearheading this.

I'll show you one label. This is Prussian blue. This is a chelator in the gut for the treatment of contamination of both radioactive and non-radioactive cesium or thallium. We would have had to just extrapolate from adult data, but there was a very unfortunate exposure in Brazil, which is a subject of a recent Nova program, in which adults and children were going into the dump piles in Brazil and looking for waste to recycle, metals, and they got into medical waste that had cesium in it. These patients, the adults and the children, received Prussian blue after this exposure and a lot of data was gained from that. I have to say that all the children lived except for

one who went home and ate a peanut butter sandwich with their hands and got another exposure instead of going to the hospital. Just like in adults, the half-life was reduced by the Prussian blue by about 46 percent in adolescents and 43 percent in children. So this is an example of the labeling that we're doing in Counter-Terrorism.

I'm happy to report to you that we have 15 new labeled products for children since you last met, and I don't want to go through each one of them, but I would like to highlight a few of these products for you.

First of all is montelukast which, as a person who takes care of asthma, is near and dear to my heart. This is for the prophylaxis and chronic treatment of asthma. It's a leukotriene receptor antagonist. It was only approved to 6 years of age. Now it's approved in ages 12 to 23 months using a new formulation which was developed, an oral granule packet, and it's also approved for 2 to 5 years using the granules or the chewable tablets.

Next is Elocon, which is a very popular, mid-potency steroid that's used in corticosteroid responsive dermatoses. New safety information was obtained on this looking at HPA axis suppression using the cosyntropin test. In the cream, there was 16 percent of the patients ages 6

to 23 months that had suppression. In the ointment, there were 27 percent of the patients. So we did discover that there was HPA axis suppression in these patients. It was reversible in all, I think, but one of the patients that were followed up. Skin atrophy was found, but only in 1 patient and it was very, very mild.

All of the corticosteroids that are mid-potency are now labeled that they shouldn't be used for the treatment of diaper dermatitis because that's an occlusive dressing and it just causes more absorption.

Tamoxifen is a drug that is used for the treatment of breast cancer in women, not a drug that's usually thought of as a pediatric drug, but here's a very unique indication. This was 27 female patients, I think all the patients in the United States with McCune-Albright syndrome which has an associated precocious puberty with it. They were treated with tamoxifen for up to 12 months, and they found a 50 percent reduction in the frequency of vaginal bleeding, reduction in the mean increase of bone age, and the linear growth rate was reduced in these patients. There was a safety concern in that the mean uterine volume increased after 6 months and doubled at the end of 1 year. This is all now laid out very, very nicely in the label.

Three statins were approved for use in children

for familial hypercholesterolemia in sort of late childhood and adolescence.

Vinorelbine, or Navelbine, is very interesting. In the spirit of trying to identify active cancer compounds earlier, Navelbine was tested in a phase II trial in children who had refractory or relapsed solid tumors. There was a lack of activity noted, and this will be going into the label. I use this as an opportunity to advertise tomorrow's advisory committee, which is the Oncology Pediatric Subcommittee, and they're going to be talking about labeling of oncology drugs.

Atomoxetine, or Strattera, is a very exciting new compound. It's the first non-stimulant, non-scheduled drug for ADHD. It's labeled down to 6 years of age. It's a selective norepinephrine reuptake inhibitor. The caveat is we really don't know what the effect is on final height, and in the label it actually says that consideration should be given to interrupting the therapy if a growth problem is seen.

We talked a little bit about fluoxetine, or Prozac, which is approved now for major depressive disorder and obsessive-compulsive disorder. I think the worrisome thing that is now in the label that has been reported in several case reports is the decrease in height. In a 19-week study, the patients treated with fluoxetine gained an

average of 1.1 centimeter less in height, and I think the Washington Post translated that into a half an inch. So the label says that height and weight should be monitored periodically and there is a phase IV commitment for a long-term growth study.

Also the other side effect that was seen is what is seen with other SSRIs, and when used for depression in bipolar patients, it will often unmask the bipolar state and flip the patients into mania. And that occurred in the children in this study and it has been reported before in adults.

I close with my former boss' quote to me when I called her up and asked her -- when I saw Dianne's ad in the New England Journal, I called her up and I said, you know, Jane, what do you think? Is this a good job? Is this a good fit for me? And she said the FDA is the most fun and interesting place you could ever work, and I have to say that that's very, very true. And I would like for you to send me the CVs of all your friends, yourselves, and any burned-out colleagues that you have because this is really a place to reenergize yourself. And there's no night call and no weekend call.

(Laughter.)

DR. SHIRLEY MURPHY: Thank you very much.

(Applause.)

DR. SHIRLEY MURPHY: I'd like to turn it over now to Terrie Crescenzi.

DR. CHESNEY: Terrie Crescenzi is the Associate Director for Regulatory Affairs in the Office of Counter-Terrorism and Pediatric Drug Development and assists the Office of Pediatric Therapeutics on issues related to subpart D. She has been involved in pediatrics at the FDA since June of 1999, and before that, she was a project manager in the Division of Antiviral Drugs. Before coming to the FDA in 1997, she served as the Director of Pharmacy Services in the United States Air Force at various hospitals throughout the country, and she's going to give us an update on pediatric statistics.

MS. CRESCENZI: Good afternoon, and thank you very much for sticking around. I will try to keep this somewhat brief since it is late and I know people have planes to catch and whatnot.

The first thing I would like to talk about and direct your attention to is our pediatric drug development page. This page was recently updated. I think we finally got it live around the January time frame. We tried to revise it, make it a little bit more user friendly. We do have new information on the page, and we recommend that you definitely take a look at it.

With regard to some numbers, as far as the

proposed pediatric studies request, so far, since section 111 of FDAMA was passed, we've had 324 proposals come into the agency, and to date we've actually issued 264 written requests. The number of determinations is now up to 82 determinations, and we've granted exclusivity to 73 drugs. As far as new labeling goes, we're actually up to 50 new labels and that is since the beginning of exclusivity.

As far as studies breakdown goes, there's not really anything new and earth-shattering here. We still remain at about a third of the studies asked for are efficacy and safety and a third are PK and safety. We're actually up to asking for 616 studies so far, and that could potentially involve over 36,000 patients. Remember too, all the studies that we ask for -- we don't always have the exact number of patients listed in those studies, so we think it will be quite large.

This is another web page that we've developed. It is brand new. We actually just got it up on the Web on Friday. This is part of the mandate in BPCA under section 9 where we have to have dissemination of information. With regard to this, any pediatric studies that are submitted in response to a written request have to be reviewed in 180 days if it's submitted as a supplement. In addition to that, we also must post on the Web medical and clinical pharmacology summary reviews. This is actually the first

summary that we've posted, and as I said, we just did this on Friday. We hope to have the next one either today or tomorrow, so this page will be growing.

One other point to make with this as well is BPCA did give us a mandate where we can disseminate a lot more information that we could not in the past. With regard to this page, we can actually now put up summaries for actions that are taken. That includes approval actions, non-approvals, and approvables, where in the past, you never heard about those. The only thing you ever saw were approval actions. You never actually received the information for the non-approvable or the NAs. So those summaries will get posted.

With regard to the pediatric rule, we still are posting numbers on the rule even though the rule was struck down last year. There is a lot of activity on the Hill with regard to codifying the rule. FDA is certainly working with the folks on the Hill to hopefully get the rule codified. We believe that the rule and pediatric exclusivity work hand in hand and we'd like to see both of them.

So with regard to our numbers, these numbers actually date back to April 1st of '99 when the pediatric rule became a regulation. At that time, up until December of last year, we had 517 applications that triggered the

pediatric rule.

The biggest numbers that I really want to point out at this point are the applications with completed studies. Out of the 517, there are 130 that have pediatric information. Now, what we've done is we've actually subtracted out any of those that were studies submitted in response to a written request and received exclusivity. So, needless to say, we have a bottom line number of 54 applications that now have new pediatric information in the labels that we can attribute to the rule.

Another new page that we have up -- and this in regards to the rule -- we're trying to get the labeling up similar to what we do for exclusivity. We have gone through a number of the labels. Right now the first posting -- we only got 12 labels up, but the labels are there. You can't see them all obviously from here, but if you take a look at the site, you will see them. We are in the process of looking at an additional 30 and eventually hope to have all 54 of them up there so that you can see some of the pediatric studies that were done and the new indications that were attributed to the pediatric rule.

Some of the reasons for concern with regards to the rule. What we've seen in our office previously, when the rule was still in effect, the number of cases where we deferred pediatric studies under the rule, sponsors are now

coming in and asking for waivers. We think that is a concern because it may indicate that they actually are not going to bother doing the pediatric studies. Technically they really don't have to ask for a waiver at this point since the rule is not in effect and we really can't waive or defer something that we have no authority to do. But we are getting those questions.

And last but not least is discussion of pediatrics early in drug development. The pediatric rule clearly outlined some of the areas, and this was with regard to some of the key meetings where pediatric drug development was to be discussed. We'd like to see the rule codified to help bring these back.

With regard to contacting us, I do want to point out we have a lot of new information. We have a lot of new phone numbers, and we're actually going to have an additional pediatric website. It will be the Office of Pediatric Therapeutics website which will be accessible from the FDA home page. The page we hope to have up within a couple weeks and that page will contain some of the information and issues that the Office of Pediatric Therapeutics is addressing.

As Dianne said earlier, we do have an e-mail account for the Office of Pediatric Therapeutics, and thanks to her, I will be taking those e-mails.

(Laughter.)

MS. CRESCENZI: She wanted to share the dual hats.

That's really all I have at this time. Thank you.

DR. CHESNEY: Thank you very much.

(Applause.)

DR. DIANNE MURPHY: Before everybody starts asking questions, Terrie pointed out to you the fact that we are now posting up on the Web the reports that are coming in. If a company conducts the trials that we ask and they submit them to us, we will have them up on the Web within the 6-month deadline. That is such a wonderful, new piece of information. You know, tell all your friends not only to send their CVs, but also tell them to go to our website because that information, if it was approvable but we want more information or not approvable, that wasn't public before, and this is one of the good things that the legislation has done so that pediatricians now, even for products that didn't make it, can access that information. I think that that's really critical that that is out there.

We would like feedback from you about how to make it more useful. There are some things that we can control and some we can't. We can't really put up our own format. It has to be in the format in which these reports

are written. But if there's anything else that we could do to make the information more useful, we would really like to know or link it with something else. Please let us know because I think this is going to be very important information for pediatricians.

Thank you.

DR. CHESNEY: Very impressive. Comments for Dr. Murphy and Terrie? Dr. Santana.

DR. SANTANA: Dianne, one thing that I found, for example, in oncology that's been very useful is that ASCO, the American Society of Clinical Oncology, communicates to all their members periodically all FDA actions regarding oncology products. I think that's a good example of how your office, instead of waiting for people to hit your web page, proactively can communicate that kind of information through the current pediatric organizations, AAEP and some others, if they give you access to that. I find those summaries, at least from the oncology side, very useful. They are very succinct and they go to the point and it keeps everybody in the oncology community updated with what ODAC has been doing. So I think that may be another vehicle proactively to provide the information rather than having people download.

DR. CHESNEY: Well, I don't see any other comments or questions, but I really, on behalf of everybody

sitting here, would like to thank the FDA for just always very professional presentations and a very, very impressive amount of work and how much you've accomplished since we last met.

Does anybody have any other last-minute comments?

(No response.)

DR. CHESNEY: Well, thank you very, very much.

We're meeting again in June for three days.

DR. DIANNE MURPHY: Yes. Please do try to make it. We've got some very interesting topics and some that I think will be quite controversial, and we're going to need your input. We always appreciate it. Do block it off. Thank you again, everybody.

(Whereupon, at 4:34 p.m., the subcommittee was adjourned.)