DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND

RESEARCH

THE PEDIATRIC SUBCOMMITTEE OF THE ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE (AIDAC)

IN JOINT SESSION WITH

THE PREGNANCY LABELING SUBCOMMITTEE

OF THE ADVISORY COMMISSION FOR REPRODUCTIVE HEALTH

DRUGS

Tuesday, September 12, 2000

1:00 p.m.

Hyatt Regency Bethesda One Metro Center

Bethesda, Maryland

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P. Joan Chesney, M.D., Chairperson
Jayne Peterson, R.Ph, J.D., Executive Secretary

THE ANTI-INFECTIVE DRUGS SUBCOMMITTEE

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Keith Rodvold, Pharm.D. (Consumer Representative)

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Robert Fink, M.D. Susan
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Naomi Luban, M.D.
Robert Nelson, M.D., Ph.D.
Victor Santana, M.D.

GUESTS AND GUEST SPEAKERS

Ralph Kauffman M.D.
Steven Spielberg, M.D., Ph.D.
Robert Ward, M.D., FAAP, FCP

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Michael Greene, M.D. (Chair)
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Elizabeth Andrews, Ph.D., MPH
Elizabeth Ann Conover, M.S.
Patrick Wier, Ph.D.
Katherine L. Wisner, M.D.

GUESTS AND GUEST SPEAKERS

Philip O. Anderson,, Pharm.D., FASHP
Cheston Berlin, M.D.
Jan M. Friedman, M.D., Ph.D.
Gideon Koren, M.D.
Julia Scott, R.N. (Consumer Representative)

FDA

Holli Hamilton, M.D., MPH

Dianne Kennedy, R.Ph., MPH Sandra L. Kweder, M.D. Dianne Murphy, M.D.

C O N T E N T S

P R O C E E D I N G S

Call to Order

DR. CHESNEY: I just wanted to tell you that in the "Science" section of The New York Times this morning there was a full-page article about these meetings and the pediatric initiative at the FDA, including a picture of Dr. Murphy. So, if you haven't bought your New York Times yet, you might want to get a copy of that.

DR. MURPHY: Joan, somebody pointed out to me that they promoted me in this article. So, I wish to deny the promotion -- it is not true.

DR. CHESNEY: I think we are ready for this afternoon's sessions on infants as the recipient of drugs by way of breast milk, another route of delivery, and we will start by having introductions, and I think we will start on the left hand side with Dr. Murphy.

For those of you who haven't been here the last day and a half, the green button on the microphone is what turns it on and off, and please be sure to give your name if you are making a comment or asking a question. So, we will start with the identification first.

DR. MURPHY: I am Dianne Murphy. I am an Associate Director for Pediatric at CDER.

DR. HAMILTON: Holli Hamilton, Pregnancy Labeling Team.

MS. KENNEDY: Dianne Kennedy, Pregnancy Labeling Team.

DR. ANDERSON: Phil Anderson, University of California, San Diego, Drug Information Service.

DR. BERLIN: Cheston Berlin, Pennsylvania State University College of Medicine, at the Hershey Medical Center.

DR. ANDREWS: Elizabeth Andrews, Director of Epidemiology at Glaxo Wellcome.

DR. WIER: I am Patrick Wier. I am a preclinical scientist with SmithKline Beecham Pharmaceuticals.

DR. GREENE: I am Mike Greene. I am the Director of Maternal/Fetal Medicine, Massachusetts General Hospital, Harvard Medical School.

DR. CHESNEY: Joan Chesney, Infectious Diseases at the University of Tennessee Memphis, and also in academic programs at St. Jude.

DR. PETERSON: I am Jayne Peterson. I am the Executive Secretary of both the Pregnancy Labeling Subcommittee and the Pediatric Subcommittee, with FDA.

DR. NELSON: Skip Nelson. I am a pediatric critical care physician at the Children's Hospital of Philadelphia.

DR. GORMAN: Richard Gorman, general pediatrician in private practice in suburban Maryland.

DR. O'FALLON: Judith O'Fallon, Biostatistics, Mayo Clinic.

DR. RODVOLD: Keith Rodvold, Professor of Pharmacy Practice, Colleges of Pharmacy and Medicine, University of Illinois at Chicago.

DR. GELLER: Barbara Geller, Professor of Psychiatry, Washington University in St. Louis.

DR. DANFORD: I am Dave Danford, I am a pediatric cardiologist at the University of Nebraska Medical Center and Creighton University Omaha.

DR. FUCHS: Susan Fuchs, pediatric emergency medicine physician, Children's Memorial Hospital, Chicago, Illinois.

DR. HUDAK: Mark Hudak, Neonatology, University of Florida, Jacksonville.

DR. FINK: Bob Fink, pediatric pulmonologist at Children's Hospital, Washington, DC.

DR. LUBAN: Naomi Luban, pediatric hematologist-oncologist, Children's Hospital, Washington, DC.

DR. SPIELBERG: Steven Spielberg, head of pediatric drug development at Johnson & Johnson, representing PhARMA.

DR. KAUFFMAN: Ralph Kauffman, Pediatrics and Pharmacology, University of Missouri, Kansas City and Children's Mercy Hospital.

DR. WARD: Bob Ward, neonatologist, University of Utah and chair of the Academy of Pediatrics committee on drugs.

DR. CHESNEY: Jayne Peterson, the executive secretary, will now read the conflict of interest statement.

Conflict of Interest Statement

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

Based on the submitted agenda for the meeting and all financial interests reported by the committee participants, it has been determined that since the issues to be discussed by the subcommittees will not have a unique impact on any particular firm or product but, rather, may have widespread implications for all similar products, in accordance with 18 USC 208(b), general matter waivers have been granted to each special government employee participating in today's meeting. A copy of this waiver statement may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

With respect to FDA's invited guests and guest speakers, Dr. Philip Anderson, Dr. Cheston Berlin, Dr. Ralph Kauffman, Dr. Gideon Koren, Dr. Steven Spielberg and Dr.

Robert Ward have reported interests which we believe should be made public to allow the participants to objectively evaluate their comments.

Dr. Anderson would like to disclose that he owns stock in Amgen, Ivax, Cell Genesys and Medimmune; and receives consulting fees from TAP Pharmaceuticals and Astra.

Dr. Berlin would like to disclose that he is a researcher through a contract with Medeva; receives consulting fees from Medeva, Pfizer, Merck and Ascent; and receives speaker fees from 3M.

Dr. Kauffman would like to disclose that he has grants with Bristol-Myers Squibb, is involved in research for Bristol-Myers Squibb, Astra, Zeneca, Janssen, Merck, R.W. Johnson and Adventis, and is a scientific adviser for Bristol-Myers Squibb, Johnson & Johnson and Purdue Pharma.

Dr. Koren would like to disclose that he is a researcher for Duchemay Ltd, and receives consulting fees and speaker fees for Duchemay Ltd.

Dr. Spielberg would like to disclose that he is an employee of Johnson & Johnson.

Dr. Ward would like to disclose that he owns stock in Ascent Pediatrics and Viropharma; has grants with Wyeth-Ayerst, Novardis, Ascent Pediatrics, Adventis Pharmaceutical and Sepracor. He receives consulting fees from Janssen Pharmaceutical and is a scientific adviser for McNeil

Consumer Products.

In the event that the discussions involve any other products or firms that are already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

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

DR. CHESNEY: Thank you. Does anyone have anything else to declare?

[No response]

We will move on to our first speaker, Dr. Sandra Kweder, who is the Acting Director of the Office of Drug Evaluation IV, FDA, and is going to provide us with some background information and an overview.

Background Information and Overview

DR. KWEDER: Good afternoon to you all. I don't have any slides. I am just going to try and put a little bit of a framework of why we are here today, and then let us move on to some of the speakers.

Let me start with telling you a little bit, for those of you who don't know, about how we actually came to

organizing this meeting. We have two initiatives at FDA that converge at this issue. One is our pediatrics initiative, which those of you on this side of the room are very familiar with. The purpose of that initiative is to change the way we do business and try to facilitate and encourage the study of safety and efficacy of drugs in children.

We have another initiative, our pregnancy labeling initiative, that the people on this side of the table are familiar with. Through that initiative we have been dedicated to improving the information available in product labels on appropriate use of drugs in pregnancy.

Interestingly, for those of you who don't know that, these two initiatives that have their own independent staffing both happen to be housed in the Office of Drug Evaluation IV, of which Dr. Murphy is the Office Director and I am the Deputy Director. So, it has been very convenient.

But, historically, lactation has always been an issue at the FDA that has run sort of pari passu or in keeping with the pregnancy section of labels. If you pick up a package insert for any given product, the lactation section follows the pregnancy use section. That makes some sense. You know, the focus on the pregnant woman and her use of a particular medicine and its effect on her

developing fetus could change at any moment to a lactating woman taking the same medicine and possible risk to her now newborn.

Well, as we have gotten involved in trying to frame what the pregnancy section of labeling ought to look like, we have rolled up our sleeves and tried to develop a new framework for that. Holli Hamilton will give you a little later, for those of you who aren't familiar with it, an overview of what we are thinking in that area. So, I won't dwell on it.

But, we held a meeting with the Pregnancy Labeling Advisory Committee on this framework about a year ago to just get some general concepts on the table. Following that meeting, we had a very thoughtful letter sent to us by Dr. Phil Anderson, who is here today, that said, "wait a minute, folks. You know, you're talking about revising this section of the label, well, this section of the label has always included lactation and things are pretty much in a woeful state and you're going to have to confront this. How can I help?" So, that is why we are here today, to try to get your help on this.

Before we can address what lactation sections of product labels should look like, we need to examine what exists now a little bit. We won't dwell on that, although Holli is going to provide you with some examples that will

probably be familiar to most of you. More importantly, we need a sense from you, as clinicians out there seeing patients and teaching, what is important in this section of the label; what is the science that is important; and, what clinically is important. So, we are seeking your guidance on the needs of practicing clinicians and, most importantly for now, what are the scientific issues underlying that that we need to begin to address.

I would like to emphasize one point. The purpose of this meeting today is not to ask you whether FDA should require studies of drugs in lactation under the Pediatric Rule or as part of a requirement for marketing exclusivity. That is a question that people have asked me and I just want to put it right on the table -- that is not what we are here to talk about today.

Those of you around the table are mostly clinicians and scientists of other types. This is only the beginning. Ultimately, we are going to need to hear from other groups, particularly patient groups or women who often feel very much alone in making decisions about medicines and breastfeeding. So, as we move forward in thinking about what that section of the label will look like, we are going to have to seek input from those groups as well, particularly in the areas of language.

So, unless there are any questions, I am going to

thank you again for being here. I really look forward to your discussion. I know it is a big group which tends to make things a little difficult but we have two very capable chairs. I think we should be covered.

DR. CHESNEY: Thank you, Dr. Kweder. I wonder if we could ask everybody on this side of the table that wasn't here before to introduce themselves, and I think Dr. Berlin was the last person to introduce himself and Dr. Andrews started it up again. So, if everybody else, in order, could tell us who you are and where you are from?

MS. SCOTT: Julia Scott, president of National Black Women's Health Project, and I am the consumer representative guest.

DR. FRIEDMAN: I am January Friedman. I am Professor of Medical Genetics at the University of British Columbia, currently on sabbatical at CDC.

DR. KOREN: I am Gideon Koren. I am Professor of Pediatrics Pharmacology and Medicine at the University of Toronto.

DR. DATTEL: Bonnie Dattel, Professor of Obstetrics and Gynecology, Maternal-Fetal Medicine, Eastern Virginia Medical School.

DR. WISNER: Kathy Wisner, from Cleveland. I am Professor of Psychiatry and Reproductive Biology at Case Western Reserve.

DR. CHESNEY: Thank you very much. Our second speaker is Dr. Cheston Berlin, who is at the Hershey Medical Center, the Penn State University College of Medicine, and he is going to provide us with a perspective on breastfeeding from the American Academy of Pediatrics.

American Academy of Pediatrics Perspective on Breastfeeding

DR. BERLIN: The interest of the American Academy of Pediatrics in this whole topic arose in the early '80s, and culminated in the preparation of the initial statement in 1983 of the transfer of drugs and chemicals in human milk. This statement was revised in 1989 and in 1994. The current revision was submitted to the Committee on Drugs in May of 1999, and Dr. Robert Ward, who is here, is currently shepherding that through the rather increasingly complicated processes of the Academy. These statements require a lot of review effort by different organizations within the Academy, and we are hopeful that this will see the light of day soon.

The reason for the statement encompassed two issues and I want to be sure that I mention these both to you. One is to inform the clinician of the possible risk to the nursing infant but of equal importance, I think, is to permit the necessary treatment of maternal illness without necessarily the interruption of breastfeeding.

The initial statements and revisions, particularly the revisions, were intended to be as comprehensive as

possible and to rely on published primary data. The first statement, in 1983, if reviewed, will show a substantial number of references to two things, one, the Physician's Desk Reference and, secondly, "personal communication." These references have been omitted in subsequent statements because it was not felt by the committee that this represents a primary data source.

We continue to recognize that most current reports of the excretion of drugs in human milk rely exclusively on either single case reports or an N of a very small number. In addition, some of these reports lack drug measurement in body fluids in either the infant of the mother and rely on anecdotal evidence of clinical effect.

The statements in labeling are not helpful. Just to give you an example, "the clinical should exercise caution." I don't know what that means. The other one that I see a lot is that "this drug should not be given to nursing mothers, or mothers who take this drug should not nurse." The alternative which we like to push is that this drug is, we think, safe for nursing mothers and both maternal therapy and nursing can continue together.

Some recommendations for acquiring data for more precise labeling of drug therapy would include the following, and this is not intended to be an inclusive list but just some of the ideas that we have discussed in the

Committee on Drugs of the American Academy of Pediatrics:

The measurement of drug disposition in the mother and, when possible, in the infant in both acute and chronic therapy -- I want to emphasize the importance of chronic therapy. It is one thing to be concerned about the transfer of drugs for the treatment of a headache or an acute attack or asthma as opposed to a mother who may be taking a drug for months and, indeed, for years for a hormonal condition or increasingly for a psychiatric indication.

It should be assumed that any drug that can be used in women can and may be taken during lactation and should have necessary labeling.

Consider all routes of administration, including dermal, respiratory routes and transmucosal. Some of these so-called non-traditional routes are becoming very popular routes for drug administration, and we have yet to learn completely whether or not these routes may transmit into excretion into milk.

Consider the possible effects of excipients, that is, the non-active drug ingredients in any formulation, whether it be solid or liquid.

Single-study subjects should be avoided. A series which would provide statistical significance with longitudinal studies involving the same mother should be used to acquire data of the possible changes in drug

excretion over the entire period of lactation.

Issues of the mode of collection are also important. Do you take individual samples? Do you have to pump an entire nursing supply, so to speak? Emptying the breast with a mechanical device is extremely artificial, and possibly the best physiological way to study particularly quantitative aspects of drug administration is to use what is called test weighings, that is, weigh the infant before and after nursing and then take a sample of milk at multiple times during the nursing period.

It is very possible that maternal drug metabolism may change during the lactation period. We have very little data on this -- whether or not a mother who nurses for 6 months or 12 months may have different aspects than the mother who nurses just a short period of time. With the recent emphasis of the American Academy of Pediatrics for human milk being the sole milk for the first 12 months of life, this is an increasingly important piece of information to get.

Infant sampling should be very strongly considered in the evaluation of any labeling issue. Very minimal amount of blood is now necessary for multiple analyses. The collection of urine does give some data concerning drug exposure but may not provide pharmacodynamic data.

Special consideration needs to be given to the

issue of psychotropic drugs. These drugs characteristically have a very long half-life and their metabolites may have an even longer half-life. It may be necessary to observe infants for a prolonged period of time, perhaps years, to determine whether or not there has been any neurodevelopment that will have an effect on the infant by the transfer of psychotropic drugs during lactation and, indeed, also during pregnancy.

Many drugs taken by the nursing mother are over-the-counter drugs and/of off-patent drugs. A consideration should be given to labeling this group of drugs, as well as drugs under patent and currently being developed.

A special comment about environmental compounds, these are frequently very lipophilic, with very small or undetectable plasma concentrations in the mother. Pregnancy and lactation may be the only two ways that these drugs are mobilized from lipid tissue. This may not be a frequent concern in drug labeling, but there are potentially some compounds which could be transferred in minute quantities and stored for a prolonged period of time in the infant's lipid tissues. Some of these compounds have been studied using pooled samples of maternal milk, and this should be avoided. It is also important to recognize that these environmental compounds may have regional differences in distribution within the United States.

I think with the emphasis on the collection of data on drug concentration in both mother and child, observation of possible clinical effect, prolonged follow up, it is possible to improve under current labeling status of drugs during lactation. It is important to protect the infant from the untoward effects of maternal ingestion of drugs, but it also is important not to deprive lactating mothers of necessary drug treatments.

Thank you for this opportunity to make this presentation.

DR. CHESNEY: Thank you, Dr. Berlin. I think we are going to have time for questions after we hear from the next two speakers. Dr. Philip Anderson is speaking next. He is Director of the Drug Information Service for the UCSD Medical Center, and he is going to speak to us about counseling nursing mothers.

Counseling Nursing Mothers

DR. ANDERSON: Well, part of my role as Director of the Drug Information Service -- having been identified as somewhat of an expert in this area, I get a lot of calls on drugs and breastfeeding, about a thousand a year and 20 percent of those are from health professionals, about 80 percent are from nursing mothers.

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After having done this for 20-plus years, I would

have to say that I would agree with Dr. Scialli that the label at this point is one of the biggest impediments to giving good information, and causing the most confusion among both prescribers and nursing mothers. So, I would like to talk a little bit about the impact of this poor quality of information.

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With the Health People Initiative, as probably most of you know, sponsored by a number of federal agencies and non-governmental organizations, the goals for breastfeeding were first put forth in 1990, and you can see that by 1998 we still haven't reached the 1990 goals, and the 2010 goals are, you know, beyond this.

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The use of drugs during lactation I think is one of the reasons why we are not meeting these goals. It is certainly not the only one, and maybe not the largest one but it does have an impact. You can see that several studies that have been done -- none in the United States so far but in many other countries, almost every mother gets a medication during the first month. In Norway, it was found that at 4 months postpartum 17 percent of mothers had taken a drug in the last 2 weeks, and in 2 very different countries it was found that 5 percent of nursing mothers are taking medications chronically.

[Slide]

I didn't know Dr. Koren would be here but I have a number of slides from his group. They looked at two groups of mothers. One group essentially was taking medications and one group was not. They were nursing mothers. And, you can see that by one year there was a tremendously different rate of dropout from nursing among the mothers who were taking medication and those who were not. The main reason that was stated by the mothers was the lack of reassurance by prescribers of this being a safe practice.

[Slide]

Dr. Ruth Lawrence has done a review of 60 anti-hypertensive drugs, looking at various sources -- the American Academy of Pediatrics lists, Briggs' textbook, Hale's textbook, a local database at Rochester, and the Physician's Desk Reference.

You can see that most of the specialty sources recommend that many of these are okay to use during breastfeeding, and the PDR is overwhelmingly to stop nursing and the other ones are this vague cautious warning, which almost leaves the impression that it is really not a safe thing to do but if you want to do it, go ahead anyway. So, there is really a big disconnect between the labeling currently and more expert opinion.

[Slide]

I thought one way to kind of get a handle on this is to look at all of the published literature on adverse reactions during breastfeeding. We looked at published studies, and this part is not quite done yet so there may be a few more here, but there are only 14 controlled studies that we could find.

Six of them were on oral contraceptives, and the primary finding there was that estrogen-containing contraceptives tend to suppress lactation and cause a dropout rate from nursing.

Three are on narcotics, mostly comparing two different narcotics, showing that malperidine is a problem.

There are three on povidone iodine, as well as a number of case reports showing that it can cause thyroid suppression; one on fluoxetine that we did at UCSD, showing that the infants of mothers who are nursing, while taking fluoxetine, didn't gain weight at the same rate during the first six months as a control group; and one on mesalamine which found no difference between placebo in terms of side effects. There were also three observational studies, and I will talk about one of those in a moment.

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The case reports were probably the most interesting part of this. We only found 79 publications worldwide in all languages. Most were published since 1950.

These 79 studies reported 88 infants, and there were only 2 very questionable deaths, a methadone which was a postmortem analysis that found methadone in the serum but there was really no cause and effect relationship reported, and an overlying death, the mother was taking phenytoin and phenobarbital and it was thought that perhaps the baby was sedated enough that it didn't struggle when the parent rolled over on it.

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The most striking finding was the age of the infants reported. You can see that the vast majority of babies were under 2 months of age that had side effects reported. In fact, after 6 months, it is very unlikely that a baby will have a side effect from a drug and breastfeeding.

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Now, the classes of drugs that were most commonly reported are here, and you can see that half of the drugs are drugs that cause central nervous system depression. Of course, this is primarily in the first month. So, that seems to be a high risk time that needs to be looked at closely.

The next 25 percent were drugs that primarily caused gastrointestinal upset, nothing really very serious, and then the rest were just one or two case reports here and

there.

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This is fairly consistent with what was found by Motherisk. In a telephone follow-up of 838 infants, they found no major adverse reactions, defined as having to seek medical advice. There were minor reactions in 11 percent, but this probably represents some over-reporting because they basically took what the mother said. If they reported that there was diarrhea, they took it as such and as being drug related. So, there was no control group. So, this is probably higher than really happens.

With antimicrobials there were side effects in 19 percent of the infants, with diarrhea being the most prominent, but it is about 12 percent. Similarly, down the list, analgesics and narcotics, about 11 percent of the time there were side effects reported; antihistamines, 9 percent; and CNS depressants cause drowsiness.

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One thing that people have been trying to do is come up with some standard scheme for assessing the exposure of the infant, looking at the pharmacologic side effects, and there are two or three systems that have been reported. The most commonly used one is the weight-adjusted percentage of the maternal dosage. It is fairly simple, the dose of the infant would get during 24 hours of breastfeeding on a

milligram per kilogram basis, divided by the mother's daily dosage times 100.

This was prominently brought forth by the World Health Organization group that was put together to come up with a treatise on this topic. They felt that drugs that are less than 10 percent of the maternal dosage that the infant would get are acceptable, with a caution range of 10-25 percent of the maternal dosage, and it was unacceptable drug if it was 25 percent of the maternal dosage or greater; if there was some inherent toxicity such as a cancer chemotherapy agent, or that there were credible reports of toxicity in nursing infants.

Well, Dr. Bennett went through this book after it had been published, in the second edition, and looked at 205 drugs in this book and found that 87 percent of the drugs were below 10 percent. Another 10 percent were in the cautious range of 10-25 percent, and only 3 percent were greater than 25 percent. Now, it is interesting that in the book the reported side effects increased as the percentage increased so that in this 3 percent of drugs, each of them had at least one reported side effect. It doesn't mean that every time you give it there is a side effect, but there was a reported side effect. So, there seems to be a correlation there.

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Taking this one step further, people have tried to make a correlation between infant plasma levels and maternal plasma levels. That is a little bit more direct, and maybe one step close to what you would like to know. Essentially, the definition is weight-adjusted for percentage of maternal dose divided by some measure of the clearance.

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Begg et al., from Australia, have put together a classification system that is quite similar. If it is less than 10 percent of the maternal plasma level it is probably considered safe. The risk here is a wider range, 10-50 percent, and it is not advisable if it is greater than 50 percent, and it is contraindicated if there is a potential toxicity and, again, cancer chemotherapy is the best example, on in G-6-PD-deficient infants for those drugs that cause hemolysis.

[Slide]

Although I like this system for two reasons, because it is a little bit more pharmacokinetically appealing and it also breaks groups down by infant age, the problem is that clearances haven't been measured on most drugs for all these different age groups. So, they somewhat arbitrarily just divided the adult clearance by a factor to come up with the estimated infant clearance. So, it kind of throws another variable into the whole thing. It kind of

adds pluses and minuses to the system.

[Slide]

Again, the Motherisk people have come up with a system called the exposure index, and actually it is based not on measurements of infants but just on the physical chemical properties of the drug. That is one way to measure the dose, and then just use the adult clearance. If you look at their paper for 86 drugs, they again found, somewhat coincidentally, 87 percent of drugs were less than 10 percent for the exposure index. It also provides basis for a nice screening method because they found that no drug that had a clearance faster than 5 ml/minute/kg ever fell in the greater than 10 percent range -- so, high clearance; low exposure for the infant.

[Slide]

This is the graph that shows how the 5 and the 10 clearance came out there.

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Another feature that is rarely discussed is drugs that actually interfere with lactation, and that is an important part of the label that needs to be included.

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Of course, all dopaminergic agents, such as bromocriptine can inhibit prolactin release and have an impact on lactation that is negative.

Estrogens and antigens used to be used in combination for mothers who didn't want to breastfeeding. That was injected immediately postpartum to dry up the milk supply.

A group of drugs that is not well appreciated by most people is the sympathomimetic vasoconstrictors, and there is essentially no human data that has studied this, but we see it clinically all the time. Mothers who are taking Sudafed or other cold products really have a drop-off in their breast milk in a short period of time. It is not entirely clear whether this is due to decreased blood flow to the breast from the vasoconstriction or CNS effects that can inhibit prolactin and oxytocin secretion. Nevertheless, it does have that effect.

Diuretics in high doses have been used in some studies to suppress lactation. Narcotics have been shown in animal studies to inhibit oxytocin release but it is not clear what the human impact of that is. It may not be great.

Again, central anticholinergics appear to decrease prolactin secretion, and the problem there is that older antihistamines and combination cold products are fairly anticholinergic and when combined with the vasoconstrictors the two really have quite an impact.

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So, my idea of what we need for labeling follows: First, I think we have to not discourage breastfeeding unnecessarily. All too often, the statements in the package insert, if they don't come right out and say not to breastfeed, they are quite fear-inducing statements, kind of vague statements that indicate that perhaps this is really not a good thing but go ahead and do it if you think you ought to.

I think, number one, we have to have the age of the infant considered. As all of you know as pediatric practitioners, a one-month old is not the same as a one-year old, and I get calls from mothers who are nursing one time a day with three-year olds who are just deadly afraid of taking a medication because of what they read in the package insert. Even the difference between a one-month old and a six-month old is fairly evident.

I think there should be some element or some way of expressing the infant exposure, and it should be based on human data, perhaps even in vitro data with some of the newer techniques that we have, but animal data are useless. In fact, they are misleading because the differences in the amount of protein and the amount of fat in milk varies considerably from species to species and really skews the amount of drug that will pass into breast milk. So, it could be either the percentage of maternal dosage or some

dosage divided by clearance factor of some kind. There is a recent paper that came out, but I don't have a slide of it, that looked at a neural network and 26 different chemical factors that could be placed into the network, and there was a 0.96 r-square value compared to clinical study data. So, there are some very good computer models now that can predict this quite well.

We should mention, of course, if there are any inherent and reported toxicities to the drugs, certainly any pharmacologic concerns, and then any allergic or idiosyncratic reactions, but these shouldn't be used as a way to discourage breastfeeding. It should be pointed out that these are quite rare and the pharmacologic, of course, should be taken in context of the age of the infant. Then, we should also report the effect on lactation.

[Slide]

So, in conclusion, at the current state I think you could almost say that it would be better to have nothing than to have what we have now because it causes so much confusion and so much misinformation, but I am not inherently a nihilist so I think I could also say that there currently exists a sound scientific basis for providing meaningful information in a structured way.

DR. CHESNEY: Thank you very much, Dr. Anderson. Our third speaker, and last before we can ask questions, is

Dr. Robert Ward, who is a Professor of Pediatrics and Director of the Pediatric Pharmacology Program at the University of Utah, and he is going to be speaking about drug therapy during lactation and maternal and pediatric issue requiring research.

Drug Therapy During Lactation: A Maternal and Pediatric Issue Requiring Research

DR. WARD: Good afternoon.

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Some of what I am going to say has already been covered but we will go over some of it. The obvious first place to start is that there are two participant during lactation, both the mother and the child. What I have diagramed here is what I refer to as the therapeutic process from drug ingestion, or intravenous or intramuscular administration through absorption, distribution, metabolism and elimination until it reaches the site of action. These processes will occur in both the mother and in the child, and will certainly influence how much drug reaches the child.

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Dramatic changes happen during the time of lactation. As a neonatologist, I am very familiar with 23-week gestation preemies and realize that those mothers often donate their milk, and that child is radically different

from the older child, and nursing may occur through several years of age. During this interval, organ maturation has a tremendous influence on how we are going to evaluate the effects of drug upon the child. Changes in brain, liver and kidney will influence both the pharmacodynamic and pharmacokinetic aspects of the drug. Maternal physiology also changes dramatically after parturition.

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Some of the changes in the mother during pregnancy are pretty ama zing and happen quite early, and they will then reverse after delivery. During pregnancy, plasma volume can expand 50 percent so that for polar drugs that are contained largely in the circulation the concentrations circulating in the maternal blood stream will decrease during pregnancy. Fat stores will increase. So, the distribution of drug during pregnancy will change, and protein concentrations will decrease overall.

In addition, elimination increases fairly dramatically for drugs eliminated particularly through renal excretion. Both cardiac output and renal plasma flow increase, leading to a 50 percent increase in glomerular filtration rate.

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So, these changes in maternal physiology during pregnancy then will reverse after delivery. There are very

few studies that have looked at the time course, however, of those reversals. Let me mention one study from Mark Rogers. This is a very long time ago.

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He followed 7 women treated with digoxin in doses of 0.25 mg/day orally throughout pregnancy. These women had normal renal function. Their dosages were not adjusted during pregnancy for concentrations. He measured the digoxin concentration at term delivery and one month postpartum.

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What he found was that the concentrations at term delivery were really sub-therapeutic, at 0.6 ng/ml, but one month postpartum the concentrations had almost doubled for the group, indicating that digoxin clearance from the end of pregnancy to one month postpartum had decreased almost 50 percent.

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There are a variety of processes by which drugs enter milk -- simple diffusion, carrier-mediated diffusion, active transport, pinocytosis, and reverse pinocytosis, that may allow protein-bound drug to cross into milk. But, for most drugs, they enter milk by diffusion.

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A number of factors influence how much drug will

pass into milk. The lipid solubility, degree of ionization, whether they are protein bound and what the concentration is in the maternal circulation are particularly important determinants. Molecular weight will influence, and then the pKa of the drug. Strong organic bases, if they are passing solely by diffusion, will have a higher concentration in milk.

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The diffusion is controlled by the Henderson-Hasselbach equation, as shown here.

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I have translated it here into this equation that shows that for erythromycin base, a relatively strong organic base with a pKa of around 8, the difference in pH between the maternal circulation and milk -- and, here I have used a relatively high pH for milk of 7.2, leads to 60 percent higher concentration in milk than in the maternal circulation.

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Milk, itself, is a unique and vary variable nutrient. Some of these changes I have mentioned here -- colostrum varies dramatically from that of mature milk. During a single breastfeeding the concentration and the composition of milk will change with respect to its fat content and protein content.

As Dr. Berlin indicated, manually expressed milk and pumped milk have different compositions as well, which changes our analysis and study strategy for drug excretion into breast milk.

The breast milk of moms who deliver prematurely differs from that of moms who deliver at term. The milk from moms who deliver prematurely will have higher protein nitrogen contents, lower lactose, higher caloric density, and slightly higher concentrations of calcium, phosphorus and magnesium.

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Milk concentrations of fat, nitrogen and lactose will vary within a 24-hour period. So, again, this is going to influence the distribution of fat soluble drugs and polar drugs during the day. These concentrations vary during the months of lactation, as Dr. Berlin alluded to, so that looking at one point during pregnancy may not give us an accurate picture of what the situation is later in pregnancy.

They can also vary by maternal diet. Dr. Lawrence reported data from 3-hour nursing periods during the day, and the milk volume for that 3-hour period varied as much as 2-fold during the day. If the maternal concentration of drug is perfectly constant, the amount of drug distributed into milk may vary dramatically as well. These variations

in composition and volume can then influence the conclusions that we are going to draw from various studies about breast milk drug excretion.

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Are animal models applicable to humans? Fat and lactose concentrations vary widely. There are unique proteins in human milk that differ from human serum proteins, much less differing also from animal proteins. Protein concentrations in milk vary widely. Some rabbits have as much as 20 percent of their milk as protein, versus 0.9 percent in humans. Immunoglobulins in milk differ from those in human serum as well.

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This shows a series of animals looking at the fat percent on the Y axis versus lactose percent on the X axis, and you can see this enormous variations in fat percentages and lactose percentages in various animals.

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So, I would conclude that animal data, just as Dr. Anderson said, is minimally helpful to us.

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So, what are our research needs? What I have tried to depict for you are some of the wide variations physiologically in both the composition of milk and in mother and infant during the nursing period. So, we need to

fit these variations into our studies. We need to look at global effects on neonates and infants of the drugs administered via milk, and do systematic prolonged observations, not single kinetic curves after a single dose.

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The changes in milk during lactation have been documented extensively in many sources, but the factors that control those changes are not as clear, nor have I found a good elucidation of those. We also don't know the interaction of the particular maternal disorders for which that mother is taking the particular drug, and the effect of that upon milk composition and volume. Those need study as well.

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What I would propose are, first, surveys. We actually need to look at the longitudinal milk excretion of drugs during lactation from colostrum through weaning. This is what is reality and this is what the child may be exposed to. I think the important place is to look in the neonate and the infant for drug concentrations associated with maternal drug therapy.

We need to pay attention to unusual occurrences. These are what constitute a large bulk of the literature, anecdotal case reports of a particular clinical disorder -- hyperactivity, somnolence, diarrhea, irritability that has

now been attributed to the drug. Those then warrant testing in a controlled fashion. They should help guide us toward the controlled studies that can better inform us about the effects of drug intake during lactation.

We need to know more about the epidemiology of drug use in the United States by region, by sociological features. I have listed some here -- race, occupation, education, age and diet. Those sociological features may also influence how much drug is taken and what "food supplements" are taken as well which may be excreted into breast milk.

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We need controlled, blinded comparisons of infants. For the amounts of drug intake during pregnancy and the number of infants being breastfed, the paucity of literature is really almost inexcusable.

We need a comparison of infants exposed to drugs that are age matched in moms taking the medication compared to infants of mothers not taking the medication. The appropriate control group is, I think, interesting. We need to consider whether we should be looking at infants of mothers with the same disorder for which the medication is being administered, or whether we should look at infants of mothers who are not affected with the same disorder and obviously are not taking the medication.

And, as indicated earlier, we clearly need long-term medical and developmental follow-up. We really don't understand the potential consequences of intake of these medications via breast milk upon the infant when they are older.

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We need to then study factors that will alter breast milk drug excretion. Maternal kinetics, pharmacogenetics, certainly influence this as well; maternal diet; milk composition. We need to validate the appropriate models for analyzing this. John Wilson, who I thought might be here today, has proposed a three-compartment model for this.

We should also evaluate the use of saliva samples, a non-invasive means of monitoring. Certainly, it has been validated for some drugs. We should do it much more extensively to know whether this is an opportunity that we are missing for non-invasive sampling of both mother and infant.

Then, we need to look at the developmental changes in pharmacokinetics. During this interval of breastfeeding from 23 weeks to a child of one year of age, there are tremendous changes in pharmacokinetics.

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I have listed some of these here. We need to look

at the critical ages when clearance pathways mature, when renal function and hepatic enzymes mature compared to the clearance pathways for the specific drug, to guide our studies. This is glomerular filtration, generally viewed as mature by five months. Depending on how you measure renal tubular secretion, some estimate it is mature at 30 weeks, others at a year. Cytochrome P450 3A4 metabolize more drugs than any other drugs in the liver. These generally reach adult levels by 12 months or so after birth.

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I have shown some of this transition here. This looks at the cytochrome P450 3A system, and 3A7 is the predominant fetal form, and you can see that in pre-term gestation that is the predominant form of 3A compared to 3A4, which is the form that starts to mature shortly after birth and reaches significant levels by 1-3 months after birth, and then by a year of age is mature, and there is this transition between they two. They do not metabolize all the same drugs equally, but we have to deal with these change in drug metabolism and how we assess the effects on the newborn as well.

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The scope of studies -- I would propose that every effective drug therapy that may be used to treat women in childbearing age which, unfortunately, starts as early 13 or

12 years of age and lasts until maybe 45, will be administered to them, and some will be breastfeeding infants. The data regarding human breast milk excretion should be part of drug development and labeling. And, I would propose, as others have -- we did this independently, by the way, that we should avoid the rating systems for risk such as the current pregnancy risk system, and maybe just cite the data so that the clinician can decide. Thank you.

Subcommittee Questions for Speakers

DR. CHESNEY: Thank you, Dr. Ward. We now have allotted a minimum of 15 minutes for questions or comments for the speakers, for Dr. Berlin, Dr. Anderson or Dr. Ward, and I am sure Dr. Kweder will be willing to answer questions also. Yes?

DR. FRIEDMAN: I guess this is a question for Dr. Berlin and also for Dr. Kweder. Dr. Ward has pointed out the breathtaking lack of data in this area, and despite Dr. Kweder's admonition that we weren't talking about gathering data, I don't think it is possible to write a very useful label in the absence of data. Currently, many of these labels are written in the absence of data in a very precautionary way. Some people have argued that we should make them less precautionary, but we still don't have data and we still don't really know what is safe and what is not.

I was struck in Dr. Berlin's presentation about

how similar his recommendations regarding gathering data were to the 1987 statement by the American Academy of Pediatrics, which was made in response to an apparently stillborn effort by the FDA to encourage the development of some of this information. I was also struck, in reviewing the American Academy of Pediatrics recommendations, the 1994 ones which all of us use, as to how little information they are actually based on. They are based on occasional case reports, and very small series, and pharmacokinetics in some cases.

This is a very serious issue, and it seems to me that the FDA system, which is designed to look for adverse reports after a drug is released on the basis of preclinical studies which, we have heard, are of very little or no value in this context -- we are not really looking for adverse effects here. What we want is some reassurance that a natural process is, in fact, safe. So, we have to have, as part of the label-making, it seems to me, some way to gather information on this normal process of breastfeeding. Perhaps Dr. Kweder can comment on that.

DR. KWEDER: I am not sure I am qualified to comment on that. I actually have a question for Dr. Ward in that regard. Why do you think it is that there isn't more research in this area?

DR. WARD: Where is Dr. Yafee? I think that there

is actually little funding for research in this area at this point. This is pretty basic, almost mundane kind of research, in a sense, looking at the extent of breast milk drug excretion. It is not very spectacular. Okay? Is this an area of priority for NICHD for funding? It is really not. And, I think that is the predominant cause and, in some respects, I think it relates to some of the discussions this morning about the limited number of people interested in clinical pharmacology and going into clinical pharmacology at this point as well.

DR. CHESNEY: Dr. Koren?

DR. KOREN: I should say that in Toronto we are now collecting -- we have about 30-40 counselings of women a day about drugs in breastfeeding and we do a lot of these mundane follow-ups. They are not difficult to do. Many drugs are measurable. I must say, most industrial partners, even if they don't have an active program on Prozac or anything, they are very happy to measure it for you, actually at no cost even, because they have a laboratory doing it. So, I don't think there is a good excuse not to do the research, and it is not very expensive research to do.

I do want to add one or two points which are important. Yes, there is a lot we do not know, but there is some generalization about exposure limits and how much

really gets to the infant that we do know. But we do know the risk of not breastfeeding. The risks of not allowing a child to breastfeed are very well known and are measured in both developing and developed countries. So, if the label is supposed to give a risk-benefit ratio, this is known.

As some of the speakers alluded to, I am much more concerned about the number of women who stop breastfeeding because of misconceptions of risk. The real risks of drugs in breastfeeding is not the chemical risk; it is the risk of women not breastfeeding. Dr. Anderson showed one of our studies. We now have studies on five or six different drugs used by many women who just either do not initiate breastfeeding or stop breastfeeding earlier. For me, this is by many-fold higher than the risk of a potential adverse event that may happen.

So, this is kind of the context and somehow the labeling must address this. We know what the risk is of not breastfeeding.

DR. CHESNEY: Dr. Wisner?

DR. WISNER: I wanted to address the issue about the lack of information and what that may be due to. I have done a series of papers on mother/infant serum levels for drugs used in psychiatry since 1985, and some of the impediments are that back then we didn't have very sensitive assays for psychiatric drugs. So, Jim Perel developed much

more sensitive assays and, in addition, he had to develop assays that could be done on small quantities of serum because the IRBs were very picky about how much blood you were drawing from an infant to get the serum level.

The other is ethical issues in that I think I have the only study that is funded by NIMH in which breastfeeding women are randomized to an antidepressant versus placebo, and I could spend about half an hour telling you about the various IRB and ethical objects to that study, the hoops I had to jump through before I could actually get approval.

So, there are a number of systems issues that over the last decade, I think, have really inhibited the acquisition of this type of data.

DR. BERLIN: I want to respond to Dr. Friedman's comments, if I could. I didn't mention the 1987 paper that we wrote on guidelines, but the similarity between that and some suggestions I made are not coincidental because both Dr. Kauffman, who is here for the Academy, and myself were authors of that particular publication, and we have continued to discuss some of these difficulties through the years. I had the pleasure to see, and I have the permission of Dr. Koren to mention that his colleague, Dr. Ito, in Toronto, has developed what possibly is a very exciting in vitro system for studying the measurement of drugs in mammalian mammary cells which may give us a lot of

information so that we may not need to worry about some of these IRB studies that Dr Wisner mentioned.

DR. CHESNEY: Yes, Dr. Gorman?

DR. GORMAN: I would like Dr. Anderson or Dr. Koren to elaborate a little bit on the statement that information they received from healthcare providers was a major discouraging factor for women to breastfeed. Was this just a repetition of what was in the PDR, or was it independent of that that these individuals were discouraged -- the graph that you showed of the falloff of the mothers taking medications in terms of breastfeeding?

DR. ANDERSON: I can let Dr. Koren speak for his own study, but in my experience mothers get very discouraging information from physicians, not especially pediatricians, they are probably more up to date than most people but if they go to their internist or their family practitioner or, God forbid, they ask a pharmacist or an emergency room physician, they are going to tell them to stop right away and it is very often based on what is in the PDR.

DR. KOREN: In July we published a paper in Pediatrics showing that about half of endocrinologists, in that particular example, that treat women with hyperthyroidism told them not to breastfeed. All the evidence-based knowledge does not suggest that PTU is an

issue. So, clearly, this is a group of highly specialized people that know the literature; it is not just any physician in any part of this continent. So, clearly they had a major impact on these women to stop it earlier or not to initiate.

But in another set of studies we looked at the overall advice that women receive from their mother-in-law, from the physician, and we marked it as positive or negative without giving more judgment to this or that. Again, physicians actually, when they told a woman not to breastfeed or that there is no data, women tended not to breastfeed, as you may imagine, because they were afraid or they stopped the drug they need.

Just to show an example, this was very well done by Dr. Anderson about the risk of women not treating themselves. A month ago, a patient in Toronto, suffering postpartum psychosis committed suicide by jumping into the subway with her child. She was treated. She was on an antidepressant but she didn't take it because she was told it would poison the baby. This particular antidepressant doesn't do anything in terms of adverse events. So, I just want to throw into the equation the risk of misinformation here.

So, it is not just that we need more information. People don't utilize the information existing, and they try

to believe that the baby should not see any molecule of a particular drug forgetting the risk, of course, of not because or the risk of a mom not taking a drug and psychiatry, of course, is a big area although it is not exclusive for psychiatry.

DR. GORMAN: In the absence of the sort of scientific data that we would like to have, would it be your opinion that changing the labeling and the PDR would be of benefit to breastfeeding mothers so that it doesn't follow a risk scale?

DR. KOREN: Again, there is huge discrepancy between the PDR, the label and the evidence-based knowledge today. They lag many years. I don't want to go into it but the pharmaceutical industry has a very different paradigm to control the business that is medical-legal, and I am not criticizing it; I understand where it is coming from. But, I guess what I am saying -- Dr. Anderson said it too -- the Academy is doing a terrific job in bringing the information that exists, but it doesn't find its way to the PDR and, even when it does, physicians still tend to be much more conservative in how they use it, and the child and the mother suffer and that is something that we have to take into account very strongly.

DR. WIER: I just wanted to make a comment regarding the utility of animal models. Both speakers

mentioned this in the context of animal models for lactational transfer of drugs. Certainly, some generalizations are made about diverse species such as rodents and rabbits and now markedly they differ from human, but I do think it is important to remember that for certain biopharmaceutical agents those studies have been done in non- human primates and those may be more applicable animal models.

Much more importantly though, the use of animals to predict lactational transfer of drugs is probably the least important use in this context. The first speaker mentioned that the concerns primarily are going to be infant exposure, but also the potential pharmacologics and toxicological effects in the infant, and also the potential for drugs to impair lactation. So, I would like to mention that the applicability of animal models in those other instances can be much higher than was suggested today. The use of animal models then is to help predict those hazards so that one can design safer and more ethical clinical trials, as well as to assist in the design of those clinical trials. So, I don't think we should overbear on the differences in lactational transfer because that is not the primary purpose of those models. It is really to look for the value in the animal models for the prediction of impairment of lactation or prediction of potential

pharmacologic or toxicologic effects in infants.

DR. CHESNEY: Dr. Wisner?

DR. WISNER: I think one of the major issues that I struggle with that was also raised by the speakers is how do you assess effects on the infant so that if you give a mom a medication, what we do, we kind of have her take a baseline of the infant's behavior. But invariably questions like, do you expect the same side effect profile in an infant that you might expect in a mom may or may not be true depending on the drug. I mean, in psychiatry we can see agitation in infants where we might see sedation in moms, and now much sedation is really abnormal in infants always comes up in terms of how do you monitor the infant? Even with long-term development, although we would all like to see studies like that, they are going to involve large numbers of infants because the further you get away from the exposure, the more variables impact on development, the more difficult it will be to assign any adverse outcome to the breastfeeding itself.

So, I think there are a number of important methodological issues that we need to clarify before we can advance this issue of behavioral monitoring and development along. Our own kind of interim solution has been to use the Actograph which downloads a week of activity and sleep-wake data on the baby. We apply it to the infant's ankle. But,

again, that is just one measure of infant behavior and there are all kinds of other physiologic measures that we think should be measuring but we are not entirely sure. So, again, the methodological advances I think are going to be important.

DR. CHESNEY: I know we have all thought at some point in time that one reason there hasn't been more done in this area is that we have gotten away with it; that there haven't been any severe, immediately obvious adverse effects, but it does make one wonder if in the long-run there on growth and development and maturation that Dr. Ward mentioned.

I think in terms of the labeling, that is something that is very much in mothers' minds. Even if you didn't put anything in the label, I wonder if, given no information, they wouldn't decide on their own not to take it because we don't know about long-term consequences. That is just my comment. Dr. Anderson?

DR. ANDERSON: Yes, I think that if we are going to do a lot of this research that is called for we need to focus on areas like the psychotherapeutics where there could be some subtle developmental problems but, you know, we have mothers who are afraid to take amoxicillin at this point, things that are just given to babies all the time and we know exactly how they respond to them. So, I think that is

an issue.

Then, to kind of reemphasize what Dr. Koren said, there was an interesting study looking at, I believe, Lapps, people in the North, who ate a lot of whale blubber, and they took mothers who ate lots of it and they had humongous amounts of mercury in their breast milk, and they had a control group with mothers with more normal mercury levels. They looked at the breastfed infants with the high mercury levels and the other babies with normal mercury levels or who were not breastfed, and the breastfed babies outperformed the other babies all the time. I mean, it wasn't even close. So, even a known neurotoxin can be overwhelmed by the beneficial effects of breastfeeding. So, I think we have to keep everything in perspective before we study things to death.

DR. CHESNEY: Are you recommending mercury for infant formulas?

[Laughter]

DR. HUDAK: Well, I think as a neonatologist, this issue comes up all the time, and for mothers who deliver babies who are born prematurely two things are true. One is that those mothers often are on a panoply of medications that is more abnormal or more concentrated who delivered normally at term. But, the second thing is that I think in terms of a lot of the issues of breastfeeding, certainly

doing everything you can to have a mother who delivers prematurely succeed in her effects to express milk and get on a good, long-lasting breastfeeding program is critical.

I can't remember the last time that I counseled a mother not to pump, not to use the milk and breastfeed. I guess I am struck by the data today, especially Dr. Anderson's review of the literature. I didn't see one thing in there that was a serious adverse event. I mean, this strikes me as complete much ado about nothing, and I think one has to remember that most of these medications are things which have a very short course.

It is inconceivable to me that this is going to have a tremendous impact on babies, even if you were able to study it and I don't think you would be -- you can find out information about serum concentrations and so forth, but in terms of long-term effect on babies, I think that is unknowable except in maybe some of the long-term psycholeptic medications. But I really think that, from a practitioner's standpoint, it is critical to do whatever we can, through revision of the labeling or whatever, to really make note of the fact of what we do know, and that is that breastfeeding is an important advantage to babies. In some studies there is up to a 10-point IQ differential between breastfed and formula fed babies. There are tremendous other aspects of health that are impacted. There is a

tremendous amount of mother-baby bonding and interaction that goes on that is not easy to quantify and I think those are real things, as opposed to these very, very potential sort of diarrhea and a little sedation and so forth of some of these medications and very few really significant theoretical side effects.

I think whatever the FDA can do to maybe write guidelines to revise some of the lactation labeling, and get out general education through the Academy to pediatricians and family practitioners about this, and obstetricians too, it would be very valuable.

DR. CHESNEY: Dr. Kauffman?

DR. KAUFFMAN: I agree completely with the statements just made, but one of the things I wanted to address is that I think one of the pitfalls that we frequently fall into in thinking through this whole thing, and this has been true for at least the past 20 years that I have been involved in this, is that we don't think quantitatively about the exposure. If you just think about it, the drugs are typically taken by the mother in milligram doses. The concentrations in the breast milk of most of these, particularly the psychoactive drugs which have very large volumes of distribution -- that is why they have a large clearance, because their volume of distribution is very large -- the concentrations in breast milk are in

nanograms or picograms, orders of magnitude lower than are taken for clinical exposure. So, the exposures in virtually all of these instances is orders of magnitude lower than what one would expect for any pharmacologic effect. So, if you simply think through it, I agree with you, it is a lot of ado about nothing in most cases, with rare exceptions.

DR. FINK: I am troubled by this. Although, I must say, I favor breastfeeding I think you have to be careful in interpreting those studies as to how much is due to breastfeeding and how much is due to child rearing differences. We have many mothers who go back to work when the baby is as young as six weeks old, and are in a social environment where maintenance of breastfeeding is nearly impossible in terms of job demands. And, until the studies are tightly controlled to look at the child rearing differences versus those just attributable to breast milk I think they have to be interpreted with a bit of caution.

And, I am a little concerned about this idea that maybe a little bit isn't harmful. The allergy side of me says, wait a minute, nobody has brought out on the table how much does early exposure of infants to different antigens in the drugs that they are exposed to predispose them to development of asthma, to allergic disease, and how many of us would feel comfortable if we said we are going to feed children milk that is labeled, "may contain small amounts of

psychoactive substances?" We wouldn't find it acceptable. So, I think we really have to look at this and be a little conservative -- not to discourage breastfeeding but to really demand that there be some good research on it, not just whitewash it and say we are going to forget about the issue of drugs in breast milk.

DR. CHESNEY: Dr. Wisner?

DR. WISNER: I have a very strong bias towards breastfeeding as well. I think it has to be evidence based, and the issue that concerns me is that, at least for psychiatry, all of the mother-baby serum levels that have been published on antidepressants have been for full-term, healthy infants in which the mother was taking no other drugs, with the exception of one case where one of our babies was a 35-week preemie baby. So, for premature infants whose mothers take other drugs that could interfere with metabolism, increased serum levels for the prematures that are ill, taking other medications, I am very reluctant to generalize the findings from full-terms to premature and sick infants because I think it is very likely that the levels may be much higher in those infants and that they may exceed some of the guidelines that we have talked about this morning. So, I see that as more of an issue of being careful about how we generalize the data that we have.

DR. CHESNEY: Yes, Dr. Koren?

DR. KOREN: Just to add to what Ralph Kauffman said, the nice thing is that, indeed, for most drugs the exposure index is very low. It is less than one percent or so. But even more important, based on physicochemical properties of the drug, there is a good Australian way to predict drugs that will have milk to plasma ratio above that, and that is probably the short list that should be studied more carefully. They showed very good predictive value of those drugs that come in the case reports, and I think Dr. Anderson showed it -- phenobarb and so on. We know these drugs, and when they come new on the market the physicochemical characteristics are measure in the laboratory. You don't even need tissue culture in humans and not even necessarily animals. So, I agree that that should probably be a subgroup that should be studied.

I do also agree that the studies about higher IQ in breastfed infants have been very severely criticized. They were never randomized trials. Even the mothers who choose to pump milk to give to babies are different in motivation from mothers who don't decide that, and we all know that many of the manufacturers of the formulas now are chasing this missing thing in the formula to find what will improve IQ. I personally am critically looking at this data because we have to answer about ten such questions every day over the phone, and I do not think there is evidence-based

knowledge that breast milk improves IQ, and I think that is very important not to include in any labeling --

[Laughter]

DR. CHESNEY: Well, I don't wee any other hands up. So, I think maybe we should take a break for 15 minutes and reconvene at 2:45, if that timing is all right for Dr. Hamilton. Please return back at 2:45. Thank you.

[Brief recess]

DR. CHESNEY: Our next speaker is Dr. Holli Hamilton, who is with the Pregnancy Labeling Initiative at the FDA, and she is going to speak to us about current requirements for providing information in a product's labeling on drug use during lactation.

Current Requirements for Providing Information in a Product's Labeling on Drug Use During Lactation

DR. HAMILTON: I am here to explain why we are where we are.

[Slide]

Three paragraphs control labeling, and we passed out copies. It is really only one side of a page. I think this will explain, although may not exonerate us --

[Laughter]

It was implemented with the pregnancy labeling rule in 1979, and it was part of that rule. As I said, it is only one page.

[Slide]

The first paragraph is a general requirement, and all that says is that, if known, you are to describe the excretion of the drug in human milk; the effects on the nursing infant, and I think it might say serious effects but that will follow through the next paragraphs; and pertinent adverse effects in animal or offspring.

[Slide]

The second and third paragraphs are the more specific requirements. The first part breaks into two areas. A systemically absorbed drug is expressed in human milk. Systemically absorbed drug unknown whether it is expressed in human milk. So, paragraph two is the first bullet; paragraph three is the next bullet.

[Slide]

With respect to two and three and clarification, the concern was serious adverse event in infants or known tumorigenic potential. That would be the first cut. That would be risk. No serious adverse event in infant and no known tumorigenic potential.

[Slide]

Then what we did was to tie this to standardized language, and this is the standardized language and this is why so many of the statements when you create charts of what appears in the label appears in the label. Drug is in human

milk and it has a risk for serious adverse event in infant or tumorigenic potential, and this is the standardized language. Because of the serious adverse reactions in nursing infants -- or potential, actually; it is not known. As we have seen, there are not too many known -- a decision should be made whether to discontinue nursing or to discontinue taking the drug -- so, don't drink and drive -- taking into account the importance of the drug in the milk. So, that is the mandatory statement that must follow.

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If the drug is in the milk but there is no serious adverse event or tumorigenic potential, it says "caution should be exercised when the drug is administered to a nursing woman." So, that is the caution statement and that is why it is broken up into that.

[Slide]

Now, paragraph three, with respect to whether it is unknown that it is expressed, says it is not known whether this drug is excreted in human milk because many drugs are excreted in human milk, and then similar language will follow. That is how this is worked out and why you see the labels reading the way they do.

[Slide]

The overview of this is basically if it is unknown, you add unknown. And if it is SAE or tumorigenic,

don't breastfeed and take medicine. And, this is all you can say. No SAE or known tumorigenicity, breastfeed with caution. And, that is how it breaks down.

[Slide]

The results of this are that we have labels with no relevant information. As you have noticed, there is no safe situation. I mean, we don't balance benefit and risk, I don't think, well. It recommends a risk/benefit decision without providing information on risk or benefit, which I think is very hard. There is no requirement for specific information, i.e., stuff you might know that might be useful -- how long after taking the drug is it excreted in breast milk? I mean, is it rapidly eliminated? Things like that.

[Slide]

Current labels, type of information -- we have to thank Terri Toigo and Kelly Clancy who did the onerous job of reviewing the PDR for us. They went online. They did not look at biologics or OTC, but they did look at approximately 800 other labels and cut and pasted the nursing language for us and from this I have extracted: General statements rule of approximately 800 labels, 353 are that general statement only, without any specific information, and then general statement applied to the drug class appears in 52 of them. Commonly, these were estrogens and thiazides. That constitutes more than half of the 800.

[Slide]

To give you an idea of what standardized labels without a lot of information can run into, here the information for patients says -- and this is from a real label, an actual label and there is more than one that looks like this -- patients should be advised to notify their physicians if they are breastfeeding an infant. Then, under advice to physicians who are taking care of nursing mothers, it is not real helpful. It says, it is not known whether X is excreted in human milk. Because many products are excreted in human milk caution should be exercised when X is administered to nursing mothers. So, it becomes circular and it is not real helpful.

[Slide]

Another label that appears, and it is very common -- it is not known whether this drug is excreted in human milk. As a general rule, nursing should not be undertaken while the patient is on a drug since many drugs are excreted in human milk.

[Slide]

It seems to me that this is the only statement you can provide within this arena, right here, that provides a margin of safety, and this does appear occasionally: X is not excreted in human milk.

[Slide]

With respect to other labels, and we looked at these 800 labels, some of them are what I call animal labels. They would be great if you were counseling nursing rats, I suppose --

[Laughter]

The drug is found in rat milk. There were 84. Drug present in other animal milk, and there were 8 of those roughly -- mice, cow, and there was one or two that said present in animal milk without giving species. Level of drug found in rat milk, approximately 46. It doesn't give you a lot on how this was determined, you know, was it peak, was it trough, was it steady state? I don't know, but it says level of drug in rat milk is X.

Then, adverse events in rat pups, and we found nine labels like that, and that is the information that appears there. Where human information appeared alongside animal information, I put it into the human category. Then, there were some hybrid labels that have a bit of both. I tried to use both. This is not all comprehensive but it gives you a flavor of it.

[Slide]

This is an example of an animal label and this is probably information that was submitted, and I am sure it is clinically relevant. So, bear in mind that things like this can happen with available data of this sort. You can see

this is from a real label: Drug X appears in breast milk and the AE was transient growth depression in rat pups. The mothers were treated with 600 times the usual human dose. Then they say X is detectable in human milk. But I don't think there is any way to make a risk/benefit out of this so I don't think this is terribly useful.

[Slide]

Then, there are human labels, and of those 800 about 126 say it is found in human milk but 89 give you the level of the drug. But, again, steady state, peak -- you know, I don't know how they measured that. Then, 31 give you adverse events in nursing babies and these are generally drug class, not product specific, and you will see many of them are older and it sounds like the label has just been passed from product to product in expanding the class.

[Slide]

I tried to pull out some human labels that I thought were somewhat useful. This is a real drug and this is the label, and the N is as bad as it gets; it is an N of 1 but the information conveyed is somewhat helpful. It gives you the amount of drug the patient received, her levels, the infant levels, and then it said no trace of drug could be detected in infant serum. As I said, the N is very bad but I think that it could be somewhat helpful and it would be nice if it were better.

[Slide]

This is another label that is, again, human information that I don't think is bad. I think it has some balance to it. X is excreted in breast milk and may cause irritability or other signs of mild toxicity in nursing infants. The concentration of X in breast milk is about equivalent to the maternal serum concentration, and it gives you the levels and what the infant would be exposed to over the course of a day. Serious effects in the infants would be unlikely unless the mother has toxic serum concentrations. Now, I think if you were a nursing woman and this were a drug that your physician thought you should take, that would be very helpful information.

[Slide]

This is something else that could be useful for a drug that you only have to take once, anesthetic drugs for a procedure, something like that. Concentrations of X in milk are probably of no clinical importance 24 hours after anesthesia. Because of rapid washout, X concentrations in milk are predicted to be those found with other volatile anesthetics. If you elected not to breastfeed for 24 hours, you could pump and then resume breastfeeding thereafter, or something like that.

[Slide]

Future directions -- now, this is where we have

been, what we have got, and this is where we are hoping to go. The proposed lactation labeling rule will follow the pregnancy labeling rule in terms of its structure. There will be clinical considerations, a summary risk assessment and a data section.

[Slide]

With the clinical considerations, the goal would be to provide specific and clinically relevant advice. I mean, it is easy to talk about these things but when you are actually trying to write information down and get relevant, useful information inside a couple of sentences because, you have to realize, this isn't going to be four pages, it can be tough because there are going to be few easy cases that never use versus never worry. I think in some instances there is going to be uncertainty. I think we need more information and better science and methodology. I am not convinced that all the issues related to determining the infant exposure have been worked out.

Challenges include tackling therapeutic alternatives. How that is done in a label, that is not something we have traditionally done but good, better, best. Then providing risk/benefit for mother and infant. As you can see, we make a risk/benefit statement but we don't provide a risk or a benefit for the mother and the infant and now suddenly we have four issues we have to address.

[Slide]

In terms of the summary risk assessment, I think this is really one of the tough pieces. It is providing a concise overview of risk information that bridges discussion of data and clinical considerations. Difficulties are, of course, quantifying risk and extent and applicability of animal data. If that is all you have, that seems to be reasonable. Reliable human data may be lacking in some circumstances.

[Slide]

In terms of the data section, we would like a comprehensive presentation of animal data. We would certainly like a comprehensive presentation of reliable human data; relationship of animal exposure to actual human dose as it appeared; description of data sources and conditions under which hazard occurred. Is it single dose, multi-dose? Was it a toxic dose to the mother? I mean, we have to know more, I think, sometimes than just providing a summary event.

[Slide]

I am referring back to this, and this is basically the heading of drugs. Again, I don't have a lot of information on this but drug use among lactating women probably resembles, in many ways, drug use among women aged 15-44. This is from the National Disease and Therapeutic

Index, and we have extracted by drug class. Antinfectives lead the list. Analgesics are second. Psychotherapeutics are third, and so on.

[Slide]

That leads us to where we want to bring y. I think we can conclude by saying that we think labels need more useful information. They should be addressed, we hope, with science, a good basis for providing the information in the labels. We would like to provide accurate and balanced information on the risks and benefit of taking the drug and nursing. And, all labels must present information that is balanced and scientifically based, I mean, i.e., the risk/benefit issue.

[Slide]

We are throwing the questions to you in summary now and you will discuss them in a minute: Is maternal drug therapy during lactation an important health issue for infants? If so, how should fundamental data be derived to determine if a drug is expressed in breast milk; whether a drug found in breast milk is available to the nursing infant; when drug is available, risk, or lack of risk, to the nursing infant?

[Slide]

What products or types of therapies are most important to study?

[Slide]

Finally, what kinds of information about such products are needed for inclusion in labels to allow informed decisions as to the safety of breastfeeding when taking a medication? That is all.

Subcommittee Discussion of Questions

DR. CHESNEY: Thank you, Dr. Hamilton. Are there any questions for this presentation? Dr. Nelson?

DR. NELSON: In making labeling changes or adding things to labeling, can you use data from any source, assuming it is quality data, or does it have to come only through certain avenues, such as industry avenues?

DR. HAMILTON: Usually information is submitted by the sponsor. There certainly have been instances where we have presented information and moved into the label. Now, in terms of third parties presenting information, I don't know and I am going to defer to someone else.

DR. KWEDER: The labels actually are legal documents that really do belong to the pharmaceutical sponsors. So, for us to just take something and put it in the label isn't really typically something that would be done but there certainly have been cases, as Dr. Hamilton mentioned, of us becoming aware of some data and then working with the sponsor to say, you know, we think this is important and it needs to be in the label. Usually, by

taking that approach and having a cooperative discussion, that is the way progress is made.

DR. MURPHY: Before you go on, I wanted to say a little bit more in that area because in the whole are of pediatric drug development that has been one of the big issues. Why can't FDA just take information and put it in the label? And, as Dr. Kweder has clearly outlined here, we have to work with the sponsor in developing the information that goes into the label unless it is clearly a safety issue -- particularly then, we work with the sponsor in trying to create the message that we think it is appropriate. So, have there been instances where the agency has gone out and gathered information, published the process in the Federal Register? Yes. Rare. It has been done but it is a very unusual approach and must rise to the level really of a safety issue for us to be able to do that.

DR. NELSON: Just as a follow-up though, if one of the desires that I heard earlier is just to get information into the labeling, given the difficulty in gathering information even if it is positive information that reflects the safety of a particular drug, not the lack of safety, and if NICHD or other people are sponsoring the research, I guess the question is, is there any way to get that research information into the label so people have access to that information independent of whether it is a safety issue for

the drug. It might be an improvement in safety information that would lead people to feel that it is safe to use.

DR. MURPHY: Again, we would encourage them to work with the sponsor. I know there are times when this is additional effort for the sponsor, to do this, and there have been some situations where a sponsor has preferred not to do this. In that situation, as I said, to be able to get the information in the label we need to have the data; we need to have the evidence-based information; and then we have to have some public submission that this is a concern or an effort, and then we would address it. Would we then potentially go to the sponsor and ask them? That is another possible route but it would, you know, need to come to our attention and that it is a concern that we think needs to be put in the label and then we could approach the sponsor. So, that is another alternative route.

DR. CHESNEY: Dr. Koren?

DR. KOREN: Thanks. I think one has to separate two things. I am sure all sponsors will want to know information which was published and to include it. But I think the same way the agency expects standards from other parts of pharmaceutical research, for example, if someone claimed bioavailability you have very strict guidelines for what you want to see, and if the sponsor would come without it you probably will send them home to come back with it.

So, I think the issue here is the expectations that the agency developed towards this field and not so much if Koren, Atkinson or someone else did the research.

There are several things in the science of this field that you have to recognize. First of all, many of the statements that Holli showed us are not up to date, namely, there is information out there that no one bothered to put into the label. So, I don't know that this should be the expectation.

But, more importantly, the science has moved too. In Australia, Beggs and Atkinson, about 15 years ago, came out with a formula which predicts very well maternal plasma and milk ratios based on lipophilicity, pKa and protein binding. This can be calculated for every drug because these three parameters are known. So, I don't see a reason why they should not be in the label. They are available for every drug. So, it can end up based on Atkinson, and so on, not more than one percent of maternal dose can be expected to be consumed by an infant. That is very useful for the health professional and it exists. But at the present time there is no such expectation. So, I would want to see the agency developing new expectations.

Last but not least, thousands of American women take medications while breastfeeding every year or every day. Why won't we expect the manufacturers to conduct these

studies the same way you ask for other things? These women, unlike pregnancy itself, these women are within the labeled indication. Women, when they are breastfeeding, are allowed to take these drugs by the label but they are exposing another human being. So why not have a set of expectations similar to many other things you do in the industry?

So, my hope, and I am sure it is the hope of many clinicians in this field, is that the FDA -- as the FDA was the leading force in FDAMA and many other things -- will set up a new set of expectations from the industry.

DR. CHESNEY: Dr. Fink, I think you were next.

DR. FINK: I think that this is an area that becomes very complex because if I were an industry sponsor of one of these medications I would do everything possible to avoid any labeling of my drug as safe for breastfeeding without tort reform. We locally have a firm called Ashcroft and Gerel who has been widely advertising on the radio a registry of infants who were exposed to cisapride, where there is medically known toxicity and yet they are already publicizing a class action suit for infants exposed to cisapride. I think this is one area where there really may be, at least by sponsors, a real perceived liability and without some tort reform you would be somewhat crazy to want to label your drug as safe for use during breastfeeding because some lawyer group or some plaintiff's lawyer will

find some way to implicate it in whatever happens to a child. I think this is one area where tort reform might really be important.

DR. GORMAN: Does the FDA have some ability to decide where information on the label gets repeated? Under the lactation use, could you put that it is approved for pediatric use, and then put the conditions in there? The reason being that if mothers know that if pediatricians give it to their children therapeutically, they may feel more comfortable taking it themselves. So, if there is pediatric labeling, could it be then included?

DR. KWEDER: That is certainly something we could explore, how does the pediatric experience translate to this use, for example, where you would have information on neonatal use, at least to understand the safety profile, for example.

DR. GORMAN: What I am saying is if you take a drug like amoxicillin, you say amoxicillin is has a pediatric indication. Maybe it is not labeled for it at the moment, but if it is labeled that could then be included in the lactation section and the mother would then feel more comfortable if their doctor gave it to their baby.

DR. MURPHY: Actually, I think that is a very interesting suggestion because we do that throughout the label, we cross-reference from warnings to clinical studies

and if there is information that might be something that we could do.

DR. CHESNEY: I have a question for Dr. Hamilton which is not originally my question, but is there any reason you can't put in the label that breastfeeding is well-known to be an extremely positive experience, or an extremely positive thing for the infant? I am not phrasing that very well but are you precluded from putting that in?

DR. HAMILTON: I showed you the existing regulations. I mean, I don't think we are precluded from putting that in but, as I said, we are hoping to move forward with the new regulation and that is why we are soliciting your input.

DR. MURPHY: I think that is a very important point. We have been working on this in the area of antibiotics for a long time about antibiotic resistance. For us to have a standardized statement in the label, we have to have, you know, a rule-making process. So, that is one of the reasons you are here today.

DR. KWEDER: But there are examples where we have done things like that before. Sometimes with a rule-making process, you know, all labels will now say X, You or Z, but there have been examples -- the one that comes to my mind is with drugs to treat with HIV. In the lactation section we include a statement about the CDC recommendations against

breastfeeding because of the possibility of transmission. That only applies to a very narrow range of products.

But I guess I would put the question back to the committee, and one of the things we are dealing with here, as I think Holli described nicely, where there is an absence of information historically we have taken a very cautious or conservative and almost restrictive posture, not being very permissive about concomitant breastfeeding and use of a drug for the mother. Do you think that some statement that tries to characterize, in the absence of information, what the benefits of breastfeeding are would be an appropriate thing to include in a label?

DR. CHESNEY: Well, back to our questions to be specifically addressed, Dr. Friedman?

DR. FRIEDMAN: I wonder if you could tell us a little bit about what FDA does in an attempt to keep this portion of the label up to date, and what you foresee in the future, as the labels are changed, in terms of keeping it up to date because as we are successful in encouraging people to do more research in this area that will become an increasingly important issue.

I also wonder if you can comment on the possibility, although the FDA doesn't pick and choose drugs in a particular class, is there any way you could let physicians know that within a particular class of drugs

these ones have information on breastfeeding and lactation effects and these ones just don't have information? Because a physician might prefer to choose a drug from a group that has information and that would encourage the drug companies to gather that information.

DR. HAMILTON: With respect to updating this part of the label, there are no requirements that I can find. With the pregnancy piece, we are looking forward to ICHE2C which requires periodic updating of pregnancy experience but I don't think that applies to lactation.

DR. FRIEDMAN: And it couldn't be applied to lactation?

DR. HAMILTON: Well, I don't believe that currently it does.

DR. KWEDER: It could be.

DR. MURPHY: We do have a requirement for annual submission of information. That is not a labeling supplement. I know we are getting into details you probably don't care about, but we have annual reports in which they are required to update some of the information that is available. Certainly, if there is relevant information in that annual report which we think would be important to get into the label, we would go back to the sponsor and ask for a labeling supplement update.

I think this is an area that the FDA was looking

at very hard. Actually, we have had a number of discussions that we are embarrassed by some of our labels, particularly recently somebody was showing me some of the antibiotic labels. They are in need of updating, and this is a huge task and Dr. Woodcock has made it a priority along with a number of other priorities that we have, for us to try to begin to look at updating many of our labels which are in need of such.

DR. FRIEDMAN: What about the possibility of letting people know which drugs in a class have adequate information on breastfeeding?

DR. KWEDER: I think there are ways to do that creatively that wouldn't even necessarily have to be anything that the FDA did. I mean, the FDA could collect that data and other groups could certainly collect that data and publish it as they see fit.

DR. WARD: But, Sandy, it would be such an advantage if that were in the back of the PDR as a list by generic drug name, rather than by the trade name even, since there might be multiple manufacturers of a given generic.

DR. KWEDER: Just to make sure that is clear, the PDR is not owned by the FDA. That is a private enterprise. But, you know, something on the FDA web page, for example, if there were a component under pediatrics or drugs for special populations.

DR. MURPHY: You know, I think I will take that as a request that Sandy's group should write a paper on this area and submit it --

[Laughter]

-- secondly, as Sandy said, one of the things we have done in pediatrics is to have a web site. Again, we can only tell you what is public information. That is all you really want to know. We can work on that. Right, Sandy?

DR. CHESNEY: Dr. Koren?

DR. KOREN: I want to go back to the advantages of breastfeeding. Without being a motherhood statement, I think there must be a way to include it in the risk/benefit assessment, something to the effect that one has to bear in mind that stopping breastfeeding may have its own risk because clinicians don't always think about it, and it is not just happening to poor Americans or Canadians; even with the well to-do people there are very well confirmed advantages of breastfeeding. So, I think we should be using it as a motherhood statement that needs special ruling but, rather, as you do in any other things. I think it was Sandy who said that with HIV drugs you have to mention that these also transmit the virus. Indeed, in North America we tell women not to breastfeed but in Africa the WHO tells them to continue because the risk of not breastfeeding in Africa is

a risk of mortality. So, here is an example of why this must be there. The advantages of breastfeeding must be put in the statements because that is something that we have relative risks on, on many morbidities, whereas we don't have it on breastfeeding. So, I cannot see how a new system of labeling breastfeeding without talking about the risk of not breastfeeding makes any scientific sense.

DR. CHESNEY: Yes?

MS. CONOVER: One of the interesting things is in the vacuum of lactation information. I run a Teratogen Information Service, and we get people that use our favorite FDA pregnancy codes to make recommendations about lactation really much more frequently than you might guess. So, they will call up and say, well, it is a category B and I would like to use it in a breastfeeding woman -- sort of this assumption that the risks are the same and, of course, they aren't.

So, you know, very clearly we need to, first of all, I mean it seriously, separate the pregnancy issue from the lactation pretty clearly even just in the labeling because I find it so frequently -- and it sounds humorous but it is really a misconception.

The second thing is not only is the impact different on the baby but you really have different strategies you can use in a breastfeeding woman and, for us,

when we answer questions on this it isn't an all or nothing. There are a few medications you would never use and some that you don't worry about at all. But, for us, most of it comes in between so you start dealing with issues like drugs with a short half-life. We suggest that they nurse before they take the medication. Or, for example, with certain agents you can defer nursing for 24 hours. We have lots of strategies that we don't have the option of using in pregnancy women but we do in breastfeeding and we use them all the time for things like dental surgery -- I mean, lots of things. We used to have people tell people they just had to stop breastfeeding forever. Now what we do is, you know use a topical instead of an oral; as I say, defer for a certain period of time. It allows us to give women a lot of peace of mind while they continue nursing.

What that kind of brings me back to is the place in the label when we start discussing clinical considerations of half-life -- that it is not just what is excreted in the breast milk at that minute in time but what might be other strategies that you could use to enhance the safety of the situation.

Open Public Hearing

DR. CHESNEY: Good suggestion. I think we probably need to move ahead to the open public hearing. I know one person did have something to add and I don't know

if there is anybody else who wanted to make comments. Dr. Yafee?

DR. YAFEE: Thank you very much. Sumner Yafee, from National Institute of Child Health and Human Development. I want to respond to some of the comments made, particularly those of Dr. Ward, about research funding. First of all, I must say, I support the need for more research regarding the excretion of drugs into breast milk and, secondly, I certainly support breastfeeding as the best way to go for the health of the newborn infant and mother.

From a perspective of research funding, I thought of a number of sources of funds. Let me start with the NIH. First of all, anyone in the room can apply for a research grant. There is no prohibition even for Canadians getting to apply for a research grant. The chances of success -- you know, all research grants at NIH are hypothesis driven. So, you have to have a hypothesis.

Secondly, about 90 percent of the grants at NIH are awarded to Ph.D.'s. I have nothing against Ph.D.'s but they are not interested in clinical research; they are interested in molecular biology, using the techniques available to ascertain processes of development or of disease mechanisms -- molecular biology, molecular genetics. So, of the 30,000 grants that are submitted a year, if you

submit one on lactation and you have a hypothesis and you are looking at a mechanism, it will probably be assigned, undoubtedly, to NICHD, National Institute of Child Health and Human Development. It will be reviewed by a study section that may or may not have the same feelings that the group has expressed today, but they will be looking at the science.

Now, from the perspective of NICHD, we have certain priority initiatives that are developed within the source of funding that we have and it is a small amount of money that we get every year from the Congress. I hope this year we get one billion dollars. We are approaching that. We don't have an appropriation yet from Congress, but it looks like we will get a 15 percent increase maybe.

Now, there is one study in which lactation could be -- gathering the data that you are talking about, that is on the drawing board. It depends a lot on politics, and that is a recapitulation of the pregnancy study that was done in the '60s, 50,000 mothers and babies. The plan is to perhaps expand that to 100,000 provided we can find the 500-plus million dollars that are required to do the study.

That would be a natural study in which drugs and lactation effect on the infant, concentration -- everything that we heard today from a variety of speakers could be plugged in because it is going to study the natural,

longitudinal history of mothers during pregnancy. It has been endorsed by the Secretary of Health and Human Services, but her tenure is up for grabs because she is appointed by the President and I can't tell you how that position is up for grabs too, although according to the polls this morning, Al Gore was leading by 42 percent, or something.

Anyway, getting back to the seriousness of funding, within NICHD, which is the natural institute to fund the study of drugs in breast milk, we have a number of priorities that we have developed in pediatric pharmacology which are already on the drawing boards. We are interested in mechanisms of developmental pharmacology, basic mechanisms. That is already out there in applications.

We are interested in working with the National Institute of General Medical Sciences on pharmacogenetic bases of drug action and pharmacogenomics, and that is already on the drawing board.

So, these take precedence. Finally, within or priority area at the Institute level, because we have a wide variety of areas to cover and lactation is only one of many, we do have, together with our sister agency, the FDA, a plan to look at drugs and pregnancy, and we have separated drugs and pregnancy from drugs and lactation, as one of the speakers suggested that this be done.

This initiative, looking at drugs given to

pregnant women for therapeutic purposes will be taking place. One conference is later on this month and another one is in December, and we hope to develop sufficient interest on the part of policy makers to alert them to the problem -- I can count on one hand or certainly on two, the drugs that have been studied in progress women, and there is an absolute necessity to gather more information so that one can prescribe drugs -- obstetricians and general practitioners -- for diseases that occur in pregnancy women, and developing rational therapy for these diseases, which means more research. The same is true, obviously, for lactation. We need the information which everyone has suggested that we obtain and Dr. Hamilton suggested that the label change requires that information.

And, where are we going to get it? I can tell you from my personal perspective, the pharmaceutical industry -- and Dr. Spielberg can contradict this -- is not interested, just as they are not interested in studying drugs in progress women. They have a fear which is justifiable of medical-legal liability, and this will occur particularly in the psychotropic area where drugs' long-term effects are unknown.

So, I would discount the pharmaceutical industry. I would also discount that the FDA would have funds to put into this area. But there are a number of places, including

NIH and NICHD, that would be interested in receiving applications. Again, they have to be hypothesis driven and fundamental, basic in terms of mechanisms that might be at work. But the review of Maternal-Child Health which is part of Health Services Administration, would be very interested in receiving grant requests, and anyone in the room can chat with them but this might be part of the public record.

Also, AHRQ, Agency for Healthcare Research and Quality, would be very interested. They are interested in effectiveness of services delivered, and they will be having a meeting on Monday and Tuesday on improving the outcome of pregnancy and I certainly will bring lactation to them. Just as we have separated, maybe they will incorporate it into their initiatives. They do have a significant amount of money that will be appropriated to them over their current budget.

Then, there is the March of Dimes. They are interested in pregnancy outcome, obviously, not just restricted to birth defects but they might be interested in funding studies concerned with drugs and lactation.

Then, I have singled out ORWH, Office of Research of Women's Health which is at NIH, and you might want to contact them. Pregnancy is an important part of their mission.

Finally, the Environmental Protection Agency is

interested in drugs and chemicals in the environment. Drug exposure of infants -- breast milk is one method of exposure.

I might mention that we, as an Institute, have a global effort to look at developing countries. We have a bequest from the Gates Foundation which enables us to support studies of cooperation between researchers in this country and in developing countries, improving pregnancy outcome. Part of this would involve lactation, and lactation in HIV-positive women where we know that perhaps 60 percent of their infants will develop HIV, and these women will be receiving drugs not only for HIV but for other concomitant infections which are common in this disease. It is possible to gather some information about drugs excreted in breast milk. Even though I know the CDC has put out an announcement against breastfeeding in HIV, that only pertains to this country. There is no question that in developing countries breastfeeding is the only method of survival of infants.

Finally, since Bob Ward posed the question, I wanted to mention the American Academy of Pediatrics. The Academy has a PROS network, Pediatric Research in an Office Setting, in which there is now a new center for child health research. This involves the 55,000 members of the Academy of whom a significant number have agreed to do research with

little remuneration. Now, this is an area where a lot of research could be done regarding concentrations of drugs in breast milk. There is a small amount of money available within the Academy to do this study.

The last suggestion about funding is just go to Congress -- not the government people but go to Congress; tell them what a problem you have about drugs and breast milk and get congressmen or congresswomen interested in the problem and then money will flow. Just as FDAMA originated basically from the Elizabeth Glazer Foundation, having to do with HIV and the basic concept of FDAMA and the pediatric section of 111 came from people on the Hill that were paid for by the Elizabeth Glazer -- not congressmen, but other people.

Thank you very much. If there are any questions about any of this, I would be pleased to answer them.

Subcommittee Discussion of Questions

DR. CHESNEY: Thank you very much for your comments. I think the PROS network is an excellent suggestion.

We have three questions that the FDA has asked us to address. The first one, is maternal drug therapy during lactation an important health issue for infants? Is there anybody who would disagree with that statement? Is there anybody that would say, no, it is not an important health

issue for infants?

[No response]

Maybe we can then go on to the specifics. Moving on to the bullets of that question, how should fundamental data be derived to determine if a drug is expressed in breast milk; whether a drug found in breast milk is available to the infant; and, when it is available, what is the risk or lack of it to the nursing infant?

Comments for question one? Dr. Nelson?

DR. NELSON: I have been wearing my IRB hat here for a little while, trying to think about how a design might look to me if I received a protocol, and it strikes me from Dr. Koren's remarks that the first question can be calculated from known data. So, the real issue is not so much whether it is or is not expressed, although perhaps you might want to confirm that, but what its bioavailability is, with breast milk being considered a formulation, and then what is the impact on the infant.

So, I was thinking to myself, well, how could that be studied. I mean, you recruit women who become pregnant on a protocol -- the usual approach is to exclude that individual and I can't imagine a pharmaceutical company that is dealing with an unapproved agent, where there is an approved agent on the market for the same indication, would feel comfortable keeping that woman on the protocol just for

the sake of finding out what would happen when she decides to start breastfeeding after birth. So, you are looking at, if there is no approved agent dealing with that as a naturalistic experiment, or you are directly going to recruit women who are breastfeeding into your particular trial.

So, then the question comes down to what circumstances would you think that a woman who is breastfeeding would imagine remaining on a drug, and that is going to be no different than the kind of clinical circumstances you get in the office, meaning where a woman believes that the importance of that medication to her own health outweighs the risk that might be presented to the infant, putting aside the question whether the data that they receive when they make that decision is accurate. Let's assume it is accurate data. So, they make that judgment.

Thinking of it from a research perspective, I mean, if you believe that that medication is essential or important to the health of the woman you would consider the incidental risk to the infant as a justified risk. Then the research question would be on the effect on the infant and measuring drug levels in the infant, which could be seen as minimal risk research, giving a blood test and doing whatever psychological or outcome studies, regardless of how

hard that would be to do but doing some kind of study.

But it would be clear to me that this would have to be a naturalistic -- I mean, the key assumption is that the medication is essential to the health of the woman. So, I think the focus ought to be on those kind of medications, the medications where a woman would independently make a decision to remain on that medication, understanding that there is the potential for risk, with the potential for risk being the unknown question.

Once you answer that for a particular drug class the problem is going to be in the informed consent process. We already have the information about this drug and you are on this one. Do you stay on this one we don't know about so you can enter into this incidental study to look at the effect on nursing, or do you switch to this one where the information is known? I suspect most women would probably switch to the one where the information is known.

So, just from a practical matter, those are some of the things I was trying to think through as I was sort of designing a study that could answer that question.

DR. CHESNEY: Dr. Spielberg?

DR. SPIELBERG: Those are some of the same musings I have had. Looking at the question, I think there really are two levels and one I think can already be addressed by data that Dr. Koren has already developed.

From all of our experience cumulatively, we know a small number of drugs which do carry high risk which have been established as causing risk, and a lot of compounds for which we have no information but for which we don't even have anecdotal reports of risk.

Just as Dr. Koren did a bunch of years ago, I put together a list of ten compounds where a single dose or a single pill can cause toxicity and bringing the child to the poison center. Okay? That is terribly important information because it eliminates an enormous portion of the pharmacopeia for which a single pill basically is not a cause for bringing a child into the poison center but if you are on that list, you know immediately that is there.

That can't be put into something like the PDR because that is not an appropriate place but, on the other hand, the information on distribution, likely concentrations, the kinds of things that you can calculate, those compounds with known risk can be very well put together in places like the USP and other sources where you have a single source which is authoritatively reviewed, and peer-reviewed internally by committees, etc., etc., with knowledge in the area. With that key information, those few compounds that really are contraindicated are there and can be added to as new compounds come by.

The second issue is what would we design in terms

of a prospective study? And, I think Skip got it exactly right, you are not going to design a double-blind, placebo-controlled trial where you are going to put people on drug and see what happens. By definition, this is serendipitous exposure.

Then, what kinds of systems work for ascertaining serendipitous exposures? We have heard a couple of ideas around the table. We have heard about registries and things like Motherisk and other places where people come in who are, indeed, breastfeeding where at least the opportunity might exist in the context of obtaining some information on serum concentrations. But even more than serum concentrations it is really outcomes that we are really concerned about. Long-term outcomes I think, indeed, are not going to be ascertainable. I mean, no matter how much we would like to know, if you are exposed to a benzodiazepine when you are three months of age, what are you going to be like at twenty? I don't know, and there are too many intervening variables anyway. So, I think we should at least just erase that from issues. We just can't do that. But we certainly can look at the short-term outcomes.

The PROS network is an interesting kind of an approach. I am looking basically for large, simple designs where you can have a group of physicians who see

sufficiently large numbers of children whose moms are going to be periodically exposed to drug, and a protocol where that serendipitous exposure occurs in the context of appropriate therapy for the mother because the mom needs the drug, be it short term or long term, the people involve don the pediatrics side will be monitoring those kids. Sometimes it will involve a serum concentration. More often it will be looking at outcomes and seeing if anything, indeed, happens to the baby, and accumulate that information in the form of registries in a prospective way. I think the perinatal study was really a retrospective look. I think we can, in fact, do this prospectively through a PROS network type mechanism if you have enough pediatricians involved around the country or, for that matter, in Canada as well, and use whatever serendipitous information comes in and in an iterative way, over time, accumulate information.

My guess is that other than the compounds that really on basis of theory would accumulate in high concentrations or would be likely to cause toxicity, or those compounds which we already know cause toxicity -- my guess is we probably will have relatively few problems.

The other thing that I think we really should do because we are studying so many drugs now in children, is get that information in there because if we know in therapeutic use what the side effect profile looks like, and

if we know in ten-fold compared to what the breastfeeding exposure would be, that will be fine. Having said that, the number of compounds that will be studied in the perinatal period is going to be relatively limited compared to the pharmacopeia that moms might be exposed to, and the types of drugs, other than the antibiotics and such, are likely to be different. We are not likely to use lots of psychotropics and such in one-month olds.

But, again, those are just some thoughts about how to try to ascertain things, and it might well be worthwhile discussing in the AAP context how to do some of these PROS studies, and in the USP context how to pull together in a systematic single source what we do know, and iteratively update that.

DR. CHESNEY: Thank you. Dr. Friedman?

DR. FRIEDMAN: I think we also need to give some emphasis to the large number of drugs for which there is no information even on pharmacokinetics. One can do the calculations but this is a 1986 recommendation that came from the FDA, or a guideline that came from the FDA about how to get information on how much drug is actually in the milk, and in most cases it is going to be an extremely small amount, much less than we worry about for pharmacologic effect. Knowing that, having that information in the drug labeling would be very valuable.

I would think that 14 years is probably enough comment period for this, and I wonder if maybe we can get these guidelines out and get information at least on the pharmacokinetics and what is available with respect to the amount of drug that the baby might ingest on every drug that has been approved.

DR. CHESNEY: Dr. Wisner?

DR. WISNER: I actually have a double-blind, placebo-controlled study which is being done in postpartum women, and am beginning to appreciate that that is unusual. The hypothesis, though, is rather different than what we are considering here. My hypothesis is that because postpartum depression can be predicted to some extent -- women who have had previous episodes are at high risk, all this study seeks to do is show whether starting an antidepressant immediately post birth is more effective in preventing recurrences in this high risk sample compared to placebo. The original study was nortriptyline versus placebo. The babies have serum levels done at week three, and we had to build in a set of toxicity monitoring. So we have a pediatrician who looks at the levels at that point and breaks the blind if they are above a certain amount, and they are tracked for the kinds of global pediatric type symptoms that one would typically monitor in a study like this. This is a study in which we are doing the Actograph data because we felt it was

very important to be able to look at that activity level information in an antidepressant-exposed group compared to a placebo-exposed group.

Now, the sad news is that, in fact, we built in a planned interim analysis which showed that, in fact, nortriptyline was absolutely no better than placebo, and we pulled the trial because the justification for exposing the babies, that is, prevention of depression, didn't occur. We are now repeating the trial with cetraline. So, we will have that same kind of data about cetraline.

I guess my point is that even though you are saying this kind of data has to be collected naturalistically, there are certain kinds of hypotheses in other fields, like mine, where there is a chance to collect data with a placebo control that can be justified.

DR. CHESNEY: Excellent. Dr. Nelson?

DR. NELSON: Just to clarify as I was thinking about it, I think it would be more accurate to say that whether or not a placebo group is justified is based on the hypothesis driven towards the women and not towards the babies. There are circumstances, and it sounds like that is one of them, where a placebo group is appropriate for the women's health and question, and then you collect the data in terms of the impact on the infants, which is a more accurate way in terms of what I was saying. So.

DR. CHESNEY: Yes?

DR. DATTEL: I am a little troubled by the thought that we will be able to label products as completely safe for breastfeeding, with the exception of a handful of things. I think despite no matter what elegant studies one designs, the variables are so overwhelming in terms of environmental exposures, individual exposures to different things based on their habits, vagaries of metabolism and methodologies of individuals in terms of how they breastfeed that we will never be able to completely say that. And, I think that labels probably shouldn't say that unless there is absolutely, basically 100 percent certainty that we could. Rather, it might be better to provide information that we do have and that is available in terms of allowing people to make a relative risk/benefit decision for themselves because we are not going to be able to say for 100 percent of all babies ampicillin is safe. You know, that may not be the case for 100 percent; it might be for 99.9. But we can say it is used in children. These are the pharmacokinetics of it, and it is expected that very little is transmitted in breast milk -- whatever information actually is tangible. And, I think the studies are great and I think they should be done but I am not sure that in terms of labeling that is going to give the information we need right now.

DR. CHESNEY: Thank you. Dr. Koren?

DR. KOREN: I agree with Dr. Spielberg. I think that we now have prospectively looked at thousands of women on medications and the babies, for the most part, didn't have any complaints that even led to going to a physician, let alone going to a hospital -- it is naturalistic but it has a lot of information in it.

How safe is safe is always an issue, and it has its own merits and we talk in terms of powers and everything else we know, but do remember that many of these women go on misinformation and some of the way the labeling goes now is clearly scary -- stop breastfeeding or stop medications, and by itself each one has a much higher risk than that little something we haven't found yet.

So, if the name of the game is to balance risk with benefit, the risk of the label now is much larger than the risk of the exposure. And, I don't think our job is to create risk by our labeling. I hope I don't sound too cynical, but we also do studies on how women perceive the risks when they read these labels and, I can tell you, these are very, very scary labels.

For example, as Holli showed, you should be careful because many drugs go into breast milk. Actually, almost all drugs go if you have the right machine to measure it but it is meaningless -- garlic too.

[Laughter]

It is true. It is a small xenobiotic and unless something is large enough or polar enough, it will go. So, this is an example where a wrong concept is introduced -- if something exists, it is dangerous. It ignores totally the dose-response curve. And, I agree that some allergic reactions and other idiosyncratic reactions don't need many molecules but, still, show me one child that had anaphylaxis from oral penicillin even when they are treated. I don't think you will find it. So, I think the science of pharmacology, as it is being practiced in 2000, has to find a way into the label. It is now not there. First year pharmacology students would not approve these labels.

DR. CHESNEY: Thank you, Dr. Koren. I think probably we would all agree that this is a strong recommendation we would like to make, which is that we don't want to create more risk by discontinuing breastfeeding, as you so aptly described in the young woman in Toronto who did not choose to take the drug that might have saved her life because she wanted to continue breastfeeding.

Dr. Kweder, have we answered question number one to your satisfaction? Can we move on to number two?

DR. KWEDER: Yes.

DR. CHESNEY: Thank you. What products or types of therapies are most important to study, those for

conditions common in young women: Those for chronic conditions? Or, those for life-threatening conditions? Why did we prioritize, if we prioritize, and are there characteristics that are common across products or groups that make them a high priority? Who would like to start with that? Dr. Nelson?

DR. NELSON: Thinking about just the feasibility of study design, if you are sitting down to talk with a woman who is nursing about the relative risk and benefit of being in the study, the drug involved would have to be important enough to her health for her to consider taking it, or to continue taking it with the question of risk to the infant. Whether that is common condition, chronic condition -- I mean, clearly, life-threatening would fit that but it would be more towards something where a woman would make a reasonable choice to continue, otherwise we would end up with everybody deciding to go out of the study or not remaining on it for that purpose. So, that would be my guess.

MS. CONOVER: I mean, I think those are really important in terms of the questions that we answer, I would remind you there is suboptimal length of continuing breastfeeding that really is based on how many barriers we place to women in terms of that, and that means that if you have really bad hay fever and you want to do something about

your allergies, and you can't breathe at night and your kid doesn't sleep very well anyway, and we suggest that, you know, it is hard to make a decision about antihistamines and breast milk -- those may not be critical to her health but they are involved in her comfort and if we say month, after month, after month, after month -- you know, if we don't know very much about antihistamines and breast milk; they weren't in the group we chose to study because they aren't crucial to your health -- I mean, we can always use that as an argument and you will find that women will discontinue breastfeeding earlier. So, there are a lot of these things that are not absolutely critical to health but they do involve comfort. I don't mean that women take that lightly because they care deeply about their babies, but if you just keep making things uncomfortable in that sense -- so, it is not like an antihypertensive; it is not like an anticonvulsant, but it makes a difference in her life, even things like NSAIDs or things like that which she might take for a headache -- it makes a difference in whether someone breastfeeds for six months or a year.

DR. CHESNEY: I think that is a very important point. Dr. Spielberg?

DR. SPIELBERG: I think one interesting aspect of this that is very different from pregnancy is that an awful lot of pregnancy exposures occur before anyone knows they

are pregnancy. Here you do, indeed, have choice of types of medication because you know you have a baby and you know that you want to breastfeed.

There are old statements about therapeutic nihilism and don't adopt new drugs that are less well studied in favor of drugs that you know well and have been well studied. For many of the classes of things like medications for headache or antihistamines and such, in fact, data for just a few compounds would be tremendously useful, just knowing that those few compounds are, indeed, safe and have no problems have developed because there are always going to be choices of drugs available out there. So, for those kinds of things and for OTC products and such, I think it would be worthwhile having some basic information but we already do have an awful lot of information on a lot of these products because these tend to be rather widely used. Having that information systematically available to moms and to physicians is obviously of real benefit.

For the other kinds of things, again, one is going to make a choice. For symptomatic things you are going to make a choice of whether I would rather have a slight headache or whether I would rather take a pill, and if you are going to take a pill, have advice on which one of those to take.

For more serious illnesses, indeed, there are

going to be situations where, indeed, maternal health is really an issue. I think of those compounds which, in general, tend to be more, if you will, potent directed towards specific receptors, really looking for significant therapeutic effects, it is those groups of drugs where moms really are going to be taking them either acutely for a life-threatening infection, a life-threatening what-have-you, versus those compounds which are going to be used chronically for serious illnesses where, indeed, there isn't going to be a choice of whether to be on a drug. You have to be on a drug and, therefore, those drugs need to be studied.

DR. CHESNEY: Dr. O'Fallon?

DR. O'FALLON: I have been very troubled by this implicit attitude or information concept here that because lots of women have been treated with these things and no particular problems have been reported, therefore, therapy are probably okay. This comes out of my 25 years in clinical trials. I have seen loads -- I mean, just name it, if you don't look, you don't find. And, stuff is constantly under-reported because there weren't absolute rules in place or procedures in place to make the observations. So, sort of waiting for people to tell you about it I think is going to lead to an under-reporting of the problems.

I wasn't real happy with the answer to that first

question because I don't think we have a very good idea about what the risks really are and I think that they have to be studied. Now, it is such an overwhelming problem with all of the stuff out there that it would have to be done very, very carefully, and I think the idea of a data bank, with well-defined rules for observation, might very well work if you picked certain types of medications. That sort of thing could be done, but I don't think the fact that we haven't heard anything bad about it really tells us anything.

DR. CHESNEY: Dr. Koren?

DR. KOREN: I agree with this comment. We do everything prospectively and we have a protocol that is followed very accurately. The question whether diarrhea reported by a mother is diarrhea that the pediatrician would agree with, but then you have controls.

But I would say there are three groups I would recommend to study. One is drugs that have theoretical basis to assume that the exposure is high, based on known methods to calculate it. And, it can be a drug that just entered the market yesterday. We know the pKa; we know the protein binding; and we know the lipophilicity. These are measured by relatively simple physical ways. So, this is one group that must be.

The second are common drugs for reasons that were

mentioned, and I don't think we should underplay the importance of women treating their pains because women tend to orphan themselves and to be martyrs, and lose their teeth because of many reasons.

The third group are drugs for chronic illnesses because the three studies we completed clearly show that women exposed to 5-aminosalicylic acid, antileptics and PTU -- these are three things we followed, stopped breastfeeding. They stopped breastfeeding although these drugs are safe based on evidence collected by different people. So, I would be concerned about that too.

Now, this sounds like a large group of women and compounds but, to reiterate what Steve Spielberg said, out of all analgesics if one can come up with ones that look to be at lower level in breast milk, this is very important information for the physician to make a decision as to what to give. Clearly, the high exposure ones should be higher.

Last but not least, there are drugs that you don't want a baby to be exposed to such as anti-cancer drugs and radionuclides, which almost goes without saying, and there may be new, very potent molecules that just pharmacologically don't make sense to expose a suckling bay to at all.

DR. CHESNEY: Dr. Anderson?

DR. ANDERSON: Yes, I would like to just emphasize

a little bit opioid products, narcotics. I think that is one instance where we see sometimes a little bit cavalier prescribing and we do see babies getting very sleepy, to the point where they are not nursing enough to gain weight adequately. You know, it is dose related, but it is an area that I think sort of goes the other way from everything se have talked about today, and that might be something to put some effort into.

DR. GORMAN: I am putting on my IRB hat, like Dr. Nelson, now. The naturalistic studies where women choose to continue to take medicines while they are breastfeeding seem to me to have very few problems going through an IRB. The woman has already made the decision for her risk/benefit. But if you wanted to do a control group, getting back to "if you don't look for it you don't find it" or are they really different from other babies, what control group would you suggest?

DR. KOREN: I can just tell you what we do. If we have 30 calls a day, most of them with no problem, we follow up that group too. So it is an observation that is naturalistic, but if the drug in question is an opioid, say, codeine or anyone you choose, you choose a group exposed to a drug, say acetaminophen. You have control on the reporting bias. They are using the same. And, still you measure many characteristics of the two groups to be able to

covary on them, say, women who use narcotics are very different from other women.

Observational studies, as we said this morning, just recently compared to RCTs in several New England papers back to back, we did the same in pregnancy now on anti-hypertensives. There is a lot of value in well-designed observational studies. Yes, if we could do RCTs, but I totally agree with you that ethically, except for a situation like described by Katherine, and then actually she proved with a placebo trial that the tricyclics did not work -- so, very rarely will you have that paradigm. Mostly, I don't think an IRB in North America or anywhere would approve an RTC, but that does not mean that you cannot control. I mean, there are many observational ways to control and we do it all the time. It is not ideal because you may not know what you didn't control for. That is always a problem, but if you have a good hypothesis and good thinking, and you have a good collection of data, you can address most of these things, including socioeconomic and including the IQ of the parents. We do those too.

DR. CHESNEY: Thank you. I would like to make a comment. I would like to add psychoactive or psychotropic drugs to be sure they are included under chronic illnesses because I think many of these drugs we haven't had around for very long. So, although we may have gotten away with

other drugs, we may not get away with these, and I have significant concern both for the health of the mother if she discontinues those, as we have already had the example, and concerns about the effect on the immature or developing brain. So, I would just like to be sure that they are included in the chronic illness category. Yes?

DR. DATTEL: In thinking about what types of therapies or drugs are most important to study, a little bit different than the discussion on pregnancy where you can group women of reproductive age, you actually do have data sources to tell you -- and they are going to be different -- one of the most common drugs, during labor and delivery and the immediate newborn period are exposed to, and I would make sure that I included those, and that takes into account a lot of opioids. Most people have some type of analgesic. They may have long-standing epidurals, they get a 30 percent C-section rate and antibiotics of all sorts. So, you are going to have a list of things that are going to be concentrated in breast milk for the first couple of days. So, if you are going to prioritize, rather than do a whole global thing of the most commonly used, I would look at labor, delivery and postpartum as well as chronic illness.

DR. CHESNEY: Yes, Dr. Luban?

DR. LUBAN: I think we also have to remember that many postpartum women take naturopathic medications, and

those may do something to alter the transmission of the drugs in breast milk. So, they should not be forgotten. As a pediatric hematologist, I am diagnosing more and more infants with easy bruisability because the mothers are taking echinacea and they are breastfeeding.

DR. CHESNEY: Is that a thrombocytopenia?

DR. LUBAN: No, it probably is an inhibition of thrombin.

DR. CHESNEY: Do we have to add alternative medicine as a priority?

DR. LUBAN: Not necessarily as a priority because, obviously, the FDA does not license those but clearly it should be added into a variable in the studies.

DR. CHESNEY: Important point. Yes?

DR. BERLIN: I would like to mention one group of women to answer Dr. Gorman's question about IRB concern. That is, women who have decided to terminate breastfeeding but are still lactating. This is how we were able to get data concerning INH, hydrocortisone and Azulfidine because the mother had decided that she would no longer nurse and wanted to resume taking these medications, and we took advantage of that rather natural situation by collecting samples of saliva, milk and serum and being able to demonstrate passage of the drug or lack thereof. So, there was no infant put at risk. And, one of the many wonderful

characteristics of lactating women is that they are usually pretty enthusiastic about participating in these kind of experiments if you can assure them that the baby will not be harmed, and since they are no longer breastfeeding the baby has no exposure.

DR. GORMAN: Could I just ask one follow-up question? Did you get IRB approval for the very special Hershey-sponsored study?

DR. BERLIN: Yes, as a matter of fact, I did. This was the administration of chocolate to nursing mothers. I did get IRB approval. That was approval for the administration of one Hershey bar to a nursing mother.

DR. NELSON: What type of toxicity monitoring did you have --

[Laughter]

DR. BERLIN: Well, that particular compound has no toxicity but there can be significant withdrawal features.

[Laughter]

DR. NELSON: No dose response.

DR. BERLIN: For those of you who may not know, the herbal content of chocolate, we were interested in theobromine which is a relative of caffeine. So, we did get IRB approval for that. It was an industry-sponsored study. Chocolate, by the way, is quite safe for breastfeeding and may actually be one of the required food groups for

successful lactation.

[Laughter]

DR. CHESNEY: I have had a recurring fantasy throughout this discussion about a whole bank of lactating women who are wet mothers or whatever they were called -- wet nurses, who are available for all of these studies. It is like the volunteers who volunteer to let medical students examine them.

Dr. Kweder, have we given you enough information for question two?

DR. KWEDER: Yes, you have. Thank you.

DR. CHESNEY: Number three, what kinds of information about such products are needed for inclusion in labels to allow informed decisions, by someone, as to the safety of breastfeeding while taking a medication?

DR. KWEDER: I would say informed decisions among clinicians.

DR. CHESNEY: Among clinicians, not mothers.

DR. KWEDER: Well, patients and doctors who may be making these decisions together.

DR. CHESNEY: Informed decisions by patients and physicians. Yes?

MS. CONOVER: Let's see, I know the things I find the most important when I am trying to counsel somebody, so I would sort of like to see those show up. They have all

been mentioned so far but the age of the infant, or if the infant is medically fragile really makes a huge difference in terms of whether agents are acceptable, for lots of reasons -- you know, the permeability of the gut, or how much milk makes up their diet, or how much of an effect it will actually have on an older infant versus, say, a one-week old. Similarly, preemies are medically fragile and really almost fall into their own category as well. So, we really handle newborns differently.

Then, I would just remind you that although I am always kind of interested in how much is in the milk, what I really care about is the impact on the infant. So, I pay a lot more attention to studies that actually look -- and that doesn't involve drawing blood on the infant really or anything else, just things where you actually see jaundice or sedation. It is not that I don't care but it actually tells me that the infant got absorbed and had an adverse effect. So, I am always really interested in those.

We use a rule of thumb, which has been mentioned before, which is if you can prescribe it to a newborn or a two- or three-month old you don't worry as much about it in the breast milk. Although, again, we are not cavalier about that, we don't want an exposure that you don't have to have but it still gives me more of a sense of peace of mind and, similarly, I think to patients. So, that information is

always very helpful, and side effects that you might see in infants, things that you might observe, are interesting to me as well.

Then, just to remind you again, I really like the information on half-life, peak levels, things like that and, you know, you can find those and you can't rely on them completely but they do give you, again, some sense -- and you might even put in suggestions -- I mean, there are strategies and Dr. Anderson has a very elegant, you know, ladder of ways you might make a decision about whether you would use an agent, and ways to make the use of it safer. So, I always find those things extremely helpful. Again, it is never a black or white decision, and so to help people with that I think those things come in handy.

DR. CHESNEY: Thank you.

DR. WARD: Can I ask for a clarification about the preemie being medically fragile? We give them a multitude of drugs. They are extremely tolerant of that. Could you amplify on how you counsel with respect to that?

MS. CONOVER: not to pick on your children, of course, but we do, in fact, consider them differently than we would a 12-month old.

DR. WARD: In which ways? Seriously?

MS. CONOVER: Well, of course, for one thing, they are newborns --

DR. WARD: Yes.

MS. CONOVER: So, they fit into that category, and they may respond differently to an exposure. In fact, we have had some situations where the infant was getting something through breast milk and ended up with a sepsis workup because it was kind of floppy and lethargic. It was also actually a pregnancy exposure as well. So, it was a combination of things present at delivery and the breast milk, and maybe would have gotten a workup anyway but, in fact, it turned out to be a psychotropic medication.

DR. CHESNEY: It is the kind of information though that I think would be helpful to have in some of these labels.

DR. WARD: Right, and we are giving them opioids; we are giving them antibiotics; and we are giving them benzodiazepines, etc. But it would be helpful for us to know the degree of passage of those into the breast milk, and to know that the mother was taking that medication. That would be very helpful. But we do administer an awfully large number of almost every therapeutic class, except probably intentionally giving them the anti-tumor drugs.

DR. FINK: As these studies are done, I think one thing that needs to be looked at prospectively and make sure it is recorded is whether the mother is a smoker or not, because that is going to affect both her liver metabolism of

the drug, possibly the infant's clearance of the drug, as well as a lot of confounding factors that are going to show up in breast milk from the cigarettes themselves.

DR. CHESNEY: Good point. Dr. Koren?

DR. KOREN: Just to give you my wish list of what I hope to see in a new label, the first are two generic statements that I believe have to be everywhere. One is the one I made about the risk of discontinuing breastfeeding. It should be done in the context of that particular drug.

The second is a statement that will reverse the many years of statements here that says that most drugs can be measurable in breast milk. Because many physicians say, "oh, God, they measured it in milk; we have to stop it." But when I give a lecture to medical students, when they hear that most things are measurable -- the same with the fetus -- it changes the whole gestalt. So, it is not a yes or no anymore; it is a dose response. So, if the labeling is supposed to educate, that is something that should be there.

Then, of course, I think, as my colleague said, you want to give as much information about the kinetics -- how much is there? What does it mean per dose for a baby? And, last but not least, if we have data on levels in babies, such as Katherine does in some studies, and follow-ups, short or long, should be there. So, that is the best

label that should be there.

Animal studies I probably wouldn't even put in, unless there is a reason which I can't think of now. It is very confusing. It is a little bit like teratology, telling physicians that the tail is shorter in rats and they call us to ask what it means for a baby. So, I don't know that an animal study, unless it has a very important mechanistic reason, should be there.

DR. CHESNEY: Dr. Wisner?

DR. WISNER: I think the other piece of information I would put in is whether the drug has active metabolites and what the half-lives of the metabolites are. So, for example, for a premature ill baby, a mom who might be breastfeeding there would be less theoretical risk if the mom took a drug, say, like certraline which has a metabolite that has a relatively short half-life than, say, the metabolite of fluoxetine, and there would be less potential, particularly in a compromised infant, for accumulation. So, I think those kinds of pieces of information would help in the selection of drugs in situations where we don't have a lot of data to inform the decision-making process.

DR. WARD: The other thing we really need is the issue of displacement of bilirubin from protein binding, and it is done for most drug classes but we need whether that concentration can produce significant displacement.

DR. CHESNEY: Good point. Dr. Anderson?

DR. ANDERSON: I would also add for those groups of drugs that do affect lactation, that information should be in there also.

DR. CHESNEY: Excellent. Dr. Danford?

DR. DANFORD: I see a potential problem with the issue of inclusion or non-inclusion of long-term outcome data because I think I agree with Dr. Spielberg's comments earlier that the long-term outcomes, particularly neurodevelopmental issues, are probably not going to be available to us. Either acknowledging that or not addressing it in the label would seem to be a difficult choice to make because if we acknowledge that lack of information we may be half way back to the uncomfortable situation that we are in now of making a statement that bothers people a lot that may not be as important as it sounds. If we don't include that information, or don't acknowledge that we don't have it, then are we withholding something that the public and the prescribing physicians ought to know we don't know?

DR. KOREN: Except for several situations, say antileptics for example, children receiving antileptics -- phenytoin is an example -- may affect their IQ and some other cognitive, versus some of the others which do not. So, if mom is on phenytoin, this may be irrelevant

information even to speculate what that level of exposure would do. But to repeat, I mean, we have the data on febrile seizures and the reversal of IQ after it was stopped. Not many women are now breastfeeding on barbiturates as they used to, but I agree with you, in most cases we won't have that information but I can see instances when it may be important. I can see a woman saying, you know, I'm on phenytoin. What will happen to my baby's IQ?" And, we ask these questions, so if you can make a statement based on what is available -- for example, if the level of exposure is one-tenth of what children are receiving in epileptic therapy you may make some inference, but I agree with you that we should be careful not to cause more damage than anything else in these statements.

DR. GORMAN: I would like to reiterate my previous suggestion, realizing the difference between the non-therapeutic use of drugs and breast milk and the therapeutic use that we prescribe them for, that reference from the pregnancy label to the pediatric label be put in there so that parents will have that information of what the experience is in the pediatric population when given therapeutically.

DR. CHESNEY: I think there are probably an awful lot of drugs that we don't know what the long-term effects are. Dr. Spielberg?

DR. SPIELBERG: The other quandary that we will always face is what was alluded to before, which is how safe is it. For the vast majority of drugs my guess is, even if we had in place a good surveillance system and good ascertainment either through an Academy network or other ways, and even if we have relatively well-defined protocols for looking at outcomes, and I think that obviously is key; it is not just saying there is nothing there because, you know, no one complained about it -- even assuming we did that, for the vast majority of drugs we are going to get relatively small numbers, and when we think about what we are talking about an NDA for a new drug and, you know, 3000 human exposures, 5000 human exposures with postmarketing commitments so that we are collecting data on relatively large numbers and using either the rule of 3 or the rule of 5 in terms of what numbers that will rule out for a 1/100 event, a 1/10 event, a 1/10,000 event. I think we are never going to be able to eliminate 1/10,000 events. We will probably never be able to eliminate, for many drugs, 1/100 events. But, what we are going to be able to do is provide information on the outcomes of the babes and, in thinking about how to write those labels we are going to have to be very careful about how we write those outcomes. It probably is going to be something like in X numbers of infants, examined for such-and-such, no adverse effects were noted.

We are not going to get to the standards of "safe and effective." Effective is not an issue for the babe, but certainly even from the point of view of safety, I think it is probably going to be a relatively descriptive label but that is helpful information.

The hard part with labels right now, frankly, particularly in this area is that physicians might be able to read them pretty well. The trouble is everybody reads them now. You can pick up the PDR in any store; you can pick it up online. Looking at all of our labels, you know, as a lay person looking at a label of almost anything -- and I could write a label for water that would scare you from drinking ever again. You know, large quantities of this stuff can cause hyponatremia, death -- pretty rough stuff. So, we really want to write very honest labels based on what the data really show us, and not make generalized statements about safety or what-have-you. I think really provision of data is going to be our best way to go, recognizing, and we are going to have to be honest with ourselves, that for many, many drugs the database is going to be very, very small.

DR. CHESNEY: This issue of the long-term outcomes, what I meant to say was I don't even know that we know what the long-term outcome for children taking dilantin for years is because we have never done a prospective,

controlled study for most of the drugs that we give to children so that we can say after 30 years your IQ is the same as it would have been, or something like that. So, that is a tough one for me.

But, I think if we should maybe always emphasize the risk/benefit ratio, taking in the many considerations that Dr. Koren and others have mentioned. Other comments? Dr. Wisner?

DR. WISNER: The other thing that I think we need to be clear about is the quality of the data in the sense that for some drugs the data is going to be for exposures both during pregnancy and for breastfeeding, and the class of agents that I come across most in that line is for anticonvulsants where I will look for information just about their use during breastfeeding, say, for a bipolar patient, but the only information I can find is data through pregnancy and breastfeeding so it is hard to know how to use that for my particular patient. And, just making the point clear that the exposure during breastfeeding is very different than during pregnancy and breastfeeding, and wanting to make sure that those lines are separate in our recommendations.

DR. CHESNEY: Dr. Kauffman?

DR. KAUFFMAN: I wanted to step back to some comments earlier this afternoon, and that has to do with

this is all very important and this information is very important, and we have talked a lot about how to get the information but that is somewhat moot if we don't have a regulatory mechanism to get that information into the label. There are some 400 primary references in the AAP guidelines since 1986 or 1987, and it keeps expanding. Very little of that information is in the current labeling for those drugs. The USP monographs have this information in virtually every monograph if it is available anywhere. And, I would like to, I guess, ask Dr. Kweder or Dr. Murphy, do you have some idea of what the regulatory mechanism can be as you rewrite these regulations to get this information into the label because right now, I gathered from what you said that there really wasn't a systematic, proactive way to get this information into the label reliably.

DR. KWEDER: Yes, I can answer that question. We are in the positive of revising the regulatory framework for the pregnancy section of the label that includes the lactation section. So, when a new regulation is developed to cover that section, lactation will be part of that.

DR. KAUFFMAN: Can you be proactive then? Let's say Merck does not particularly have any incentive to put that information in their drug that is 15 years old and doesn't have it but the information is available, can you be proactive to get that information into their label then?

DR. KWEDER: Yes, yes.

DR. KAUFFMAN: Minus a safety issue?

DR. KWEDER: For the most part, products will be required to comply with this.

DR. KAUFFMAN: Okay. That is very reassuring.

DR. KWEDER: Like most labeling changes, it will probably be phased in over time but ultimately, hopefully, we will get there.

DR. KAUFFMAN: That would be a major step forward. Excellent!

DR. ANDREWS: I would like to make a comment about that. Similar to a discussion that we had in the morning session, that is, in all likelihood the label will never have all of the information that is publicly available in the published literature because it is not only the sponsor recommending certain articles and scientific evidence to be included in the label, but it is also a process of negotiating with the FDA what type of evidence is allowable. Current standards for clinical type data usually revert to the randomized clinical trials. It is very difficult to get epidemiologic data included in the labels today, and I think that is changing and I think that is very good. But we might want to also think about referring the reader to other sources of information that are available and compendia of information that can be more comprehensive and that are

updated more frequently than the labels are.

DR. CHESNEY: Thank you. Dr. Kweder?

DR. KWEDER: I just wanted to clarify. I think the people on this side of the table are probably more familiar with the pregnancy labeling initiative than the pediatric group. We are in the process of trying to develop a proposed rule on pregnancy labeling. We don't have anything published in The Federal Register. We have met with our committee a few times to go over some general concepts related to that. It is extremely difficult and we are just beginning to tackle the lactation subset of that, which is what brings us to this meeting, but you didn't miss anything. There is nothing out there in The Federal Register of published at this point in time. And, some of the issues that Elizabeth raised are issues that we have to grapple with in any section of the label. This will be a very complicated process because we are not talking about, for the most part, labeling that rests on randomized, controlled trials, which is the gold standard of what has the agency has always been the most comfortable with. We are talking about how to bring other kinds of data to the label so that it will provide useful information for people who are making decisions about drugs in their own life circumstances.

DR. CHESNEY: This situation reminds me of what we

went through when we discovered -- what was the mercury compound as a preservative in vaccines? -- thimerosal, when spent hours and hours and hours adding up the concentrations of mercury that we were giving to premature infants and older children, and many, many experts on many, many conference calls, and really we knew absolutely nothing about what we were doing, except that it seemed like an excessive amount of mercury. But George Petaire, who has been the editor of The Red Book for many, many years said, very wisely, lack of information has never prevented us from making definitive decisions. We need a lot more information.

There were some questions over here. Yes?

MS. SCOTT: I have been listening to all the discussion, both this morning and this afternoon, and I think we have progressed but I am still feeling for women the issues of safety -- somehow I am not comforted by much of what has been talked about today, and I think women, with access to information -- it is so confusing. While I can appreciate, you know, burdens that have been mentioned several times on FDA and industry for making these changes, I kind of see myself probably in that role twenty years from now dealing with some of these same issues because I don't think we are quite ready to bite the bullet and insist that there be a new standard for the regulation of drugs that

really looks at this whole issue of pregnant women and lactating women.

I know we are trying to make incremental changes here but I really get a sense that we are going to be moving much too slowly to be helpful to women for the safety of their own health and for their children. So, I think in order to have options and choices, and to be able to weigh risk and benefit, not only on life-threatening situations but the quality of life that has been brought up several times. You know, women also have to be concerned about their quality of life in taking these drugs, and I don't think most women would be satisfied to hear or be convinced that a medication is safe because it has been given to a premature infant. I mean, it hopefully was given for some indication and we are really talking about how these drugs are going to act on healthy children and what those ramifications are.

So, I would like to urge the FDA, by whatever means necessary, that you be stronger in requiring the data gathering both in the application for a drug and postmarketing or registries, whatever; that you really take a strong stand in getting this information because women need it because they need medication and for the safety of their children.

DR. CHESNEY: Thank you. Yes?

DR. KOREN: Just to reiterate what Julia said, it is not the information, the scientific information, but how women perceive risk and what they do about it. Very few groups deal with this. So, it will be very effective to bring the knowledge base here. Then, how to write it will take a different science. We are doing it now in Toronto, and we have big surprises of what you show to women and what they understand even if you are sure that it is safe. So, I am just throwing it in; it is not to do with the questions we were asked but more for the FDA. We will have to ensure that what we write women will understand even if it is written for physicians. We also have interesting results on how physicians perceive risk. In other terms, what we write is not what people understand and that has to be acknowledged and included in this very valuable process, otherwise it will be another thing on the shelf that doesn't really go to public health effect.

DR. CHESNEY: Communication is everything. Dr. Wisner?

DR. WISNER: Very much along the same lines as what Dr. Koren was saying, for the American Psychiatric Association, we had a work group and what we decided to do was develop actually a process model that really defines what the practitioner says to a woman, what kinds of things should you include if you are talking to her about

treatments during pregnancy? So, there are all the available treatments and the pluses and minuses, and then what is the natural history of the disorder, and then a whole section on medical-legal aspects because what we felt was this same gap, that the information may be there -- and then there are all the different aspects of how women understand the information, but there is also this idea about how do you structure the information in a way so that it really becomes one that respects her values and her making the choice but delivering a complete set of information as well? So, there is another element to all this.

DR. KWEDER: I would just like to respond to that. We have recognized from the very beginning that this is going to be one of the toughest rows to hoe for this. We are well aware of the fact that when people read current labels what might make perfect sense to a scientist comes across very differently to someone who is a lay person reading it or a clinician in an office who is worried about her own medical-legal risk. We are trying to tend to that and we will be bringing in to help us some experts in risk communication. We think that this is something that we have not done very well, and I want to acknowledge, Dr. Koren, we are very appreciative of some of the research that the Motherisk group has done in this area, where they have done

specific studies where they have attempted to be reassuring in how they characterized risk, and found out that what was reassuring to a clinician was not at all reassuring to a patient. So, that has been very helpful.

DR. MURPHY: Let me start with the bad news, again, the Food, Drug and Cosmetic Act is for us to look at products that are proven to be safe and effective and our professional labeling is the way that we are supposed to spell it out in the patient insert.

As anybody who has listened to us for the last year and a half knows, it has taken us two decades of pleading with people to look at products in children, and you have heard these numbers numerous times and they haven't been studied. You are right, it is an arduous process. It has to be based on a very carefully thought out -- and this group is trying to do that and seeking external advice on how we do it.

The good news is that just a decade ago we didn't even have any gender differences. I mean, we all know men and women are different but for some reason that was never something we were going to look at until recently. So, we are making progress in being able to look at the areas that we think are important and where we might find differences or areas that are not being addressed at this time.

I think one of the really exciting things is the

one that Dr. Kweder just brought up, and again I mention Dr. Woodcock because I think this has been an initiative of hers, and that is the whole concept of risk management and how the agency communicates the information that we have. Right now, we are not the research arm of NIH; we are not the health professional societies. We seek input from all of those so we can provide the best information, but we look to all of these entities to participate with us in moving the field, be it risk communication for women, for children, for antibiotic resistance, whatever it is, all of that we need to leverage each other in our collective knowledge in moving this field forward.

So, I guess what I am saying to you is we will keep working on this. You need to go back and talk to your individual organizations and also work on this. So, thank you.

DR. CHESNEY: Dr. Kweder, do you or Dr. Murphy want to do summary comments or do you need more information?

DR. KWEDER: I think you have done a great job of outlining for us a lot of the concerns that you have, both in the area of the science and also some of the really practical considerations about how we might do this better. I really just want to thank you all for taking the time to

really think about these issues. We truly appreciate it. It is really refreshing.

DR. CHESNEY: Let me once again thank Dr. Murphy and all of the people who have worked with her to make the last two days so informative and so well organized, and four totally different topics that we have all enjoyed participating in. Thank you all.

[Whereupon, at 4:51 p.m., the proceedings were adjourned]