UNITED STATES OF AMERICA

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

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FOOD AND DRUG ADMINISTRATION

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PEDIATRIC ADVISORY COMMITTEE

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MEETING

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WEDNESDAY,
NOVEMBER 29, 2007

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The meeting came to order at 8:00 a.m. in the Grand Ballroom of the Hilton Washington D.C. North/Gaithersburg, 620 Perry Parkway, Gaithersburg, Maryland, Marsha D. Rappley, M.D., Chairperson, presiding.

PRESENT:

MARSHA D. RAPPLEY, M.D., Chairperson

CARLOS PENA, Ph.D., M.S., Executive Secretary

DENNIS BIER, M.D., Member

PRESENT (CONTINUED):

AVITAL CNAAN, Ph.D., M.S., Member

MICHAEL E. FANT, M.D., Ph.D., Member

MELISSA MARIA HUDSON, M.D., Member

KEITH KOCIS, M.D., M.S., Member

THOMAS NEWMAN, M.D., M.P.H., Member

GEOFFREY L. ROSENTHAL, M.D., Ph.D., Member

ROBERT WARD, M.D., Member

SHARON L. DOOLEY, M.D., M.P.H., Consultant

GERALDINE FITZGERALD, C.P.N.C., I.B.C.L.C., Consultant

THOMAS W. HALE, Ph.D., Consultant

RUTH A. LAWRENCE, M.D., Consultant

ANTHONY SCIALLI, M.D., Consultant

AMY J. CELENTO, Patient Representative

ELIZABETH GAROFALO, M.D., Industry Representative

ELAINE VINING, Consumer Representative

RICHARD L. GORMAN, M.D., Pediatric Health Organization Representative

FDA PARTICIPANTS:

LISA MATHIS, M.D., Associate Director, Office of New Drugs, Pediatric and Maternal Health Staff, Center for Drug Evaluation and Research

KAREN FEIBUS, M.D., Medical Team Leader, Office of New Drugs, Maternal Health Team, Center for Drug Evaluation and Research

SANDRA KWEDER, M.D., Deputy Director, Office of New Drugs, Center for Drug Evaluation and Research

CHARLES BONAPACE, PharmD, Office of Clinical Pharmacology, Center for Drug Evaluation and Research

ROBERT NELSON, M.D., Ph.D., Office of Pediatric Therapeutics, OC, FDA

T A B L E O F C O N T E N T S

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

(8:02 a.m.)

CHAIR RAPPLEY: Welcome to our third day of discussion on truly important issues for children and women. I'd like us, because we have new people as part of the Committee today, once again, begin with introductions. If people will say their name, their institution and their area of specialty. You want to start, Dr. Bier?

DR. BIER: I'm Dennis Bier. I'm a pediatric endocrinologist but I'm here as a representative of nutrition.

DR. CNAAN: I'm Avital Cnaan with the Children's Hospital of Philadelphia and I am a statistician.

DR. DOOLEY: Sharon Dooley, Northwestern University, Maternal-Fetal Medicine.

DR. FANT: Michael Fant, I'm a Neonatologist at the University of Texas Health Science Center at Houston. I'm a

biochemist and neonatologist.

MS. FITZGERALD: I'm Geraldine Fitzgerald. I'm a pediatric nurse practitioner and lactation consultant in private practice.

DR. GAROFALO: I'm Elizabeth Garofalo. I'm a pediatric neurologist and a pharmaceutical consultant. And I'm the industry's representative to the committee, a non-voting member.

DR. GORMAN: Rich Gorman, a pediatrician from Baltimore who is representing the professional and pediatric health care organizations on a temporary basis and a non-voting member.

DR. HALE: Well, my name is Tom Hale. I'm from Texas Tech University School of Medicine. I'm a clinical pharmacologist.

CHAIR RAPPLEY: Hi. I am Marsha Rappley, Michigan State University. My area is developmental and behavior in pediatrics.

DR. PENA: Carlos Pena, I am

Executive Secretary of PAC.

DR. KOCIS: Good morning. Keith Kocis from the University of North Carolina at Chapel Hill. I'm a pediatric cardiologist.

DR. LAWRENCE: I'm Ruth Lawrence. I'm a neonatologist, pediatrician, and clinical toxicologist at the University of Rochester School of Medicine.

DR. NEWMAN: I'm Tom Newman and I'm an epidemiologist and general pediatrician from the University of California San Francisco.

DR. ROSENTHAL: Good morning. I'm Geoff Rosenthal. I'm a pediatric cardiologist at the Cleveland Clinic.

DR. SCIALLI: Hello. I'm Tony Scialli, a do reproductive toxicology for a consulting company called Sciences International and I teach at Georgetown and George Washington Universities.

MS. VINING: I'm Elaine Vining. I'm a consumer representative.

DR. WARD: I'm Bob Ward. I'm a hematologist and clinical pharmacologist at the University of Utah.

DR. NELSON: Skip Nelson. I'm a pediatric ethicist at the Office of Pediatric Therapeutics. I'm a neonatologist and pediatric critical care doctor.

DR. MURPHY: Diane Murphy, pediatric infectious disease. And I want to apologize to the committee. I'm going to have to leave at lunchtime. I thank everybody for all their work. This whole committee is in very good hands with the internal and pediatric staff, who have, I think, a very intensive and interesting set of documents and questions to you.

So, Dr. Nelson will represent our office and do that for me.

DR. MATHIS: Hi, I'm Lisa Mathis. I'm Associate Director in the Office of New Drugs, Pediatric and Maternal Health Staff.

DR. FEIBUS: Good morning. I'm Karen

Feibus. I'm an Obstetrician/Gynecologist and a Medical Team Leader for the Maternal Health Team in the Office of New Drugs.

DR. KWEDER: Good morning. I'm Sandy Kweder. I'm the Deputy Director of the Office of New Drugs, an internist with a specialty in obstetric medicine.

CHAIR RAPPLEY: Okay. Thank you all again. And Carlos has some introductory remarks.

DR. PENA: Thank you. The following announcement addresses the issue of conflict of interest with regard to today's discussion of a report by the Agency on Adverse Event Reporting, as mandated in Section 17 of the Best Pharmaceuticals for Children Act (BPCA).

The Pediatric Advisory Committee will hear and discuss issues related to the FDA's Draft Guidance for Industry: Clinical Lactation Studies - Study Design, Data Analysis, and Recommendations for Labeling, which was published in the Federal Register in

February 2005. This statement is made 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 all interests in firms regulated by the Food and Drug Administration present not potential for an appearance of a conflict of interest at this meeting.

In the event that the discussions involve any other products or firms not already on the agenda for which a 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.

We then note that Ms. Amy Celento is participating as the pediatric health care representative, Ms. Elaine Vining is participating as the consumer representative, and Doctors Sharon Dooley, Geraldine

Fitzgerald, Thomas Hale, Ruth Lawrence, and Anthony Scialli are participating as temporary voting members.

We would also like to note that Dr. Elizabeth Garofalo, M.D. is participating as the non-voting industry representative, acting on behalf of regulated industry.

Dr. Richard Gorman is participating as a temporary non-voting Pediatric Health Organization representative, acting on behalf of the American Academy of Pediatrics.

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

We have an open public comment scheduled for 1:00 p.m. I would just remind everybody to turn on your microphones when you speak so that the transcriber can pick your statements and turn them off when you are not speaking. I would also ask that all cell

phones be turned to the silent mode.

Thank you.

CHAIR RAPPLEY: Our first presentation is Dr. Mathis.

DR. MATHIS: Good morning. I would like to take a moment to welcome you. Thank you very much, for those of you have endured two days already, thank you very much for coming back. And for those of you that are just joining us today, I'm really glad that you can be here. We have some very important work to do.

I want to start my discussion this morning talking about something that is going to seemingly be unrelated, but it's one of my favorite stories about medical discovery.

In 1928, Alexander Fleming discovered penicillin. And the story goes that he had actually been running his lab and he went away on vacation. And when he came back, he was in the process of cleaning up the mess that had been made while he was gone, because he hadn't

been there, and he was taking petri dishes and putting them in a cleaning solution by the stack load. And in the middle of doing that task, one of his neighbors in another lab came in to welcome him back and talk about his vacation. And so he stopped what he was doing to have a discussion.

And when his friend left the lab, he looked down at the plate that he had in his hand and there, in an overgrown colony of staph, was mold growing. And around that mold was a circle. And he immediately knew what he was looking at. And that was how penicillin was actually discovered.

A lot of people like to use this as an example of serendipity, or accidental discovery. But I really like to look at this as what happens when a prepared mind looks at something.

Today, we are going to be asking you to look at something that is our Draft Guidance for Clinical Lactation Studies. And

we don't expect that we're going to discover penicillin today, but we do expect that you're going to provide us with some very important guidance about how to make this Guidance work for industry, so we can start getting information on drugs in breast milk.

Why is it so important that we look at drug levels in breast milk? Well, as we know, there is overwhelming evidence that suggests that breast milk is the most appropriate and healthy form of food for infants. We also know that there is not a whole lot of information on drug levels in breast milk. And this lack of information and misinformation often leads to physicians advising mothers to discontinue the use of medications during breast feeding or to quit breastfeeding altogether.

There is also an increasing need to look at drug levels in breast milk because there is an increase in breastfeeding, which is a very good thing.

From 1996 to 2001, national rates of in-hospital breastfeeding, as well as breastfeeding at six months had increased two percent per year. And in populations that don't normally breastfeed, that number was even greater. Also, breastfeeding women took significantly more medication per month than pregnant women and over a third of the medications that were taken were rated as possibly, or probably unsafe, or had no known safety.

So as a physician and a patient are trying to decide what medication to take during lactation, what is the approach? Usually, the first thing that you want to do is make sure that the medication is necessary. The next thing that you want to do is make sure that your choice of medication is as safe possible. You might want to look at a low milk to plasma ratio or think about if the drug is safe when administered directly to infants.

So where can a physician and a patient go to find this information? That's supposed to be the sound of a cricket. It's pretty silent. There's not a whole lot of information out there. And while we do have some references such as Dr. Hale's book, we don't have a lot of information that is out there. So the FDA would like to address this need of getting this information. And on February 8, 2005, a Draft Guidance was published titled, Clinical Lactation Studies: Study Design, Data Analysis, and Recommendations for Labeling. We received public comments from both experts in industry and academia. And as we reviewed those comments and look over the Draft Guidance again, we really realized that the Guidance needed updating, so that way we could incorporate more recent data, and that we needed to reorganize it as well, so that way we could incorporate some of the comments that were provided to us by outside experts.

So today, we ask you to look. We want you to look at the Draft Guidance with us, to hear and discuss information on the labeling of drugs for use by lactating women, breastfeeding physiology, benefits and current research, the physiology and pharmacology of drug transfer into breast milk, and the ethical issues that are related to studying breastfeeding mother-infant pairs.

So again, I would like to welcome you and, I think at this point, we'll turn the podium over to Karen Feibus.

DR. FEIBUS: Good morning. My name is Karen Feibus. I am the Medical Team Leader on the Maternal Health Team. And it is my pleasure to speak with you this morning about the Draft Clinical Lactation Guidance, its study design, data analysis, and labeling.

As we move through this presentation, I would like to approach it as a series of questions and answers so that we can explore what a guidance is. Why we need a guidance on

clinical lactation studies; what the important elements are of the Guidance that you received in your background package; what questions were raised by the public comments we reviewed; and what questions would we like you to address today to help us make this Guidance better.

Guidance documents represent FDA's current thoughts on a topic. They are not laws. They are not regulations. And because of that, they are not binding to either us or to the public. So, if a person or a company chooses to take a different approach when they are looking for different ways to satisfy these requirements, they can do that, as long as they meet all of the requirements of the applicable statutes and regulations. So, when you're reading through a guidance, you'll notice that the term used is "should" and not "must."

FDA wants to provide industry with clear, comprehensive, scientifically sound

guidance on how to acquire clinically useful data from clinical lactation studies. The information obtained from these will be included in drug product labeling to equip clinicians and pregnant and lactating patients with the facts that they need to make well-informed risk-benefit decisions about breastfeeding and medicine use. The knowledge and expertise that you share with us today through your discussions and deliberations will help us to achieve these goals.

In the Draft Lactation Guidance, there are a number of goals listed. To define when data from clinical lactation studies would and would not offer clinically useful information; to provide a basic framework for the design, conduct, and analysis of clinical lactation studies; and to stimulate further study and research in rational therapeutics for lactating patients.

I really like this quote, "No substitute exists for specific knowledge." It

is equally inappropriate to discontinue breastfeeding when it is not medically necessary as it is to continue breastfeeding while taking contraindicated drugs. And this is sort of the theme for our day today because right now, we don't necessarily which drugs are contraindicated and which ones are not. And we would like to know that.

Breast milk is the most complete form of nutrition for infants. It offers a range of health benefits for women and infants. And about ten percent of women of reproductive age are pregnant at any one time. So, while pregnancy may only last nine months, there are a lot of women pregnant at any one time who don't know what to do with medicines that they might need to use.

Pregnant and breastfeeding women sometimes need medicines to treat ongoing medical conditions and acute medical problems. It is not reasonable or realistic to discontinue their medications while they are

pregnant. And it may not be reasonable to keep them from breastfeeding while they are using their medications. It is important to determine when the benefits of breastfeeding outweigh the risks of drug exposure through milk and vice-versa.

Nursing mothers do use medications. There are a number of published studies that have looked at this. And over the 20 years or so of data, the numbers haven't changed very much. Ninety to ninety-nine percent receive a medicine during the first week postpartum. Many of these medicines may be pain medicines that they are using in the postpartum period and there are also other medicines that are used during the postpartum period. About 17 to 25 percent have used another medicine by the time they are four months postpartum and nursing. And five percent receive long-term therapy. Now this figure is a little bit older than some of the other data and so this figure may have changed over time.

Breastfeeding women use an average of three to four different medicines while they are breastfeeding. And this excludes dietary supplements, such as prenatal vitamins. And about two-thirds of medicines used by nursing women may be over the counter medicines and this figure comes out of a just published study.

As we started to look at the public comments we received on the Draft Guidance, we began to update the background section. The background section of the Guidance includes information about the benefits of human breastfeeding and includes information about the transfer of drugs into milk. So, more recent references were brought into the background section since we received the public comments. And in addition, we included information about the healthy people 2010 initiative and the goals.

As an HHS agency, it is FDA's job to try to achieve and meet these healthy people

2010 goals. Part of these goals are the HHS blueprint for action on breastfeeding. And you can see the goals listed here; 75 percent of mothers breastfeeding in the immediate postpartum period, 50 percent breastfeeding at six months postpartum, and 25 percent breastfeeding at 12 months postpartum.

The most recent data that I could find shows that we are getting very close to this 75 percent number of attempting breastfeeding in the immediate postpartum period. However, we are much farther way from these other two goals.

So let's take a moment to consider data that can be obtained from clinical lactation studies. We can learn the extent of drug transfer into milk. What is the infant daily does if the baby is exclusively breastfeeding? This is the information that we most want to know.

We can also learn how a drug affects milk production. Now, this may be challenging

in situations where a drug is used chronically and a woman is already on a drug. She has been on it during pregnancy and she is on it in breastfeeding. So this may be hard to assess. Generally, most drugs known to affect milk supply are known to do so through the drug's mechanism of action and its relationship to breastfeeding physiology. And Dr. Lawrence will be talking to us about this a little bit later this morning.

We can also learn the affect of lactation on maternal pharmacokinetics or pharmacodynamics. Now we know that pregnancy physiology affects pharmacokinetics rather significantly but it is not clear whether lactation is associated with changes in drug pharmacokinetics or pharmacodynamics that are outside the rather wide range of normal for adult women.

In addition, it may be possible to some degree to look at the frequency and severity of adverse affects in breastfed

infants exposed to maternal drugs through breast milk. However, while this is important, it is hard to detect these adverse affects when you are looking at very small sample sizes. It is harder to detect if the adverse affects may not manifest until later in the child's development and it is hard to distinguish affects that may occur due to exposure to the drug in utero, when a baby may get exposed to much higher levels of drug than they will get exposed to through nursing.

For the remainder of my presentation, I would like to move through it according to the sections of the Guidance, so that we can take a look at some of the information that is in the Guidance and some of the questions that were raised by the public comments which were submitted.

So, we're going to talk about the ethical research in mothers and infants, which is the only new section we're going to talk about; existing non-human data; existing human

data and deciding when to conduct a lactation study; study design considerations; data analysis; and labeling.

The Draft Guidance, in its public form, did not contain an ethics section. But some of the public comments noted an absence of an ethics section and other comments made us somewhat concerned that there was a lack of awareness of some of the ethical issues that were relevant to conducting clinical lactation studies. And so we decided that an ethics section would be a good addition to the document.

Some of these ethical issues include the protection of the infant as a research subject and this includes protecting them from a drug exposure perspective, from a blood drawing perspective, and with regards to interference with the breastfeeding process itself. Mothers who medically require medication, also there are some ethical issues involved with conducting the studies for them.

And then there are issues about whether healthy volunteers should be included in clinical lactation studies and what their role might be. Dr. Nelson will be addressing these issues later this morning as well.

With regards to existing nonhuman data, the perspective expressed in the Draft Guidance is that at this time, in vitro and animal studies have not been validated as surrogates for human testing for drug levels in breast milk. And we're making that statement a bit more clear in our next version.

Many comments that we received questioned or criticized the statements in the Draft Guidance regarding in vitro and animal study models, but at this time, upon further review, we feel that this approach is appropriate. And in the future, if an in vitro or animal study model proves to be a reliable surrogate for human breast milk studies, then we will update the Guidance

accordingly and include that new information.

With regards to human data, ideally, FDA would like to have clinical lactation data to inform labeling for all drugs that are likely to be used by lactating women and this pretty much includes most drugs that will be used by women of reproductive age. And this sounds very broad, but it's very important.

So these situations may include the following. Original or supplemental drug reviews where drug use is expected in women of reproductive age, where use of a drug by lactating women becomes evident following the marketing approval process. For example, metoclopramide was not marketed as a drug to increase milk supply, but some women use it that way. Marketed medicines commonly used by women of child bearing potential. A lot of women have asthma. They need to treat their asthma in order to breathe. And so it is appropriate to get clinical lactation information for these medications.

This is just a list of various classes of medicines that are commonly used by women of reproductive age and may become an issue and require use in women who want to breastfeed. It is certainly not an all-inclusive list but it is broad.

So what are situations when clinical lactation studies are not needed? A drug is not used in either lactating women or reproductive age. You don't need studies in such a drug.

The drug is not systemically available in the mother. The drug is not expected to be orally available in the infant.

Well-designed lactation studies in humans have already been done. A company may be able to pull together that data and submit it, rather than submitting a protocol for their own clinical lactation study.

The drug is used to treat a medical condition where breastfeeding is not advised. Something like HIV in this country. Now,

outside of this country, there is a debate going on about this right now. But clearly, in this country breastfeeding when you are HIV positive is still a contraindication.

And also, potentially drugs that are known to interfere with normal infant growth. Those are drugs that probably should not be studied.

There were three primary study designs that were described in the Draft Guidance. The lactating women study looking at milk-only samples; the lactating women study looking at maternal plasma and milk samples; and the mother-infant pair design that involves sampling from both mother and child.

There was some confusion and concern expressed through the public comments regarding how these study designs were organized and presented in the Draft Guidance. And it was obvious to us that the information was not clear and not well enough organized

for the readers of the Guidance and we want to change and improve that.

So, some of the question there were raised are as follows. And some of these questions were raised directly in public comments and some of these questions are questions that we are raising based on public comment. Should milk-only studies always be done first? When should one choose a maternal plasma milk study or a mother-infant pair design instead? Are there situations where more than one of these studies would need to be done for a particular drug?

So let's take a look at what we can learn from these various study designs, in order to help us answer these questions. For the milk-only study, we can learn concentrations of drug and active metabolite in milk. Some people have recommended using the maximum concentrations in milk, but this really overestimates the infant daily dose. Others have recommended using the average

concentration of drug in breast milk. And this is a more accurate infant daily dose estimate and can be estimated either using a rectangular area under the curve or a trapezoidal rule method. And these have been previously described in the literature.

We can also learn what the absolute oral infant daily dose is by calculating it from the concentration of drug in milk and the volume of milk that is consumed. The volume of milk that is consumed can be determined in one of two ways. It can either be estimated, because people have studied and figured out that on average a baby consumes 150 milliliters per kilogram per day of breast milk, or you can take a baby, weigh the baby immediately prior to feeding, weigh the baby again immediately after the feeding and determine what that weight difference is and calculate the volume of milk that is absorbed. Of course, the baby has to be wearing the same clothing, but this method is also

effective.

What else can we learn? We can calculate the relative infant dosage, which is the percentage of the maternal dosage that the baby receives. And you can see the formula there. And when lipid content of milk is very important, you can also calculate a creamatocrit. You basically take a milk sample, you spin it down much as you would with a blood sample to get a hematocrit and you determine what the lipid fraction of the milk is.

With regards to the plasma in milk studies, what can we learn in addition to the information that we can get from milk-only studies? We can determine a milk/plasma ratio for the drug. The drug concentration in milk divided by the drug concentration in maternal plasma. Then, theoretically, you can use the milk/plasma ratio to calculate estimated oral daily infant does.

Now, we're still trying to determine

exactly when this is useful. Because if you can calculate this directly from milk concentration, what would the specific situations be where you would need to or want to do it indirectly through the milk plasma ratio? And theoretically there may be some situations, such as drugs that are taken in a variety of doses or there are a variety of dosage forms. And when Dr. Bonapace gets up to speak about some of these more pharmacokinetic issues, he is going to explore that a little bit further.

And in addition, you can get maternal pharmacokinetic information from this study. But again, as I mentioned earlier, we are not clear whether there are real pharmacokinetic changes during lactation.

With the mother-infant pair design, you can get actual infant plasma drug levels, at least to a limited degree. Many feel that you are really lucky to get one sample from any infant. And it is certainly possible that

a mother participating in a study may absolutely refuse to let you sample her infant at all. Because you are lucky to get one sample, it is very important to identify ahead of time what the best sampling time is relative to maternal dosing time.

Realistically, only total plasma drug concentrations are likely to be obtained because very small volumes of blood would be drawn from an infant. And while it would be ideal to get both total and unbound plasma levels of drug, it probably is not realistic.

In addition, you can calculate systemic dose for the infant. Actual infant oral bioavailability would be complicated and difficult to determine and would probably never be known.

And there is the question of whether we can get that infant adverse event collection. With the small sample size and the short-term assessment in a clinical lactation study, this would certainly be a

very limited assessment, but adverse events should certainly be looked for.

Theoretically, there may be clinical use for qualitative data obtained from noninvasive sources, such as infant tears, infant saliva, or infant urine. But this certainly has not been defined and is just a possibility that is out there.

So what are some other design considerations when we are looking at these studies? How do we support mother-infant breastfeeding pairs when they are participating in a clinical lactation study? A clinical lactation study really should not increase the chance that a mother-infant pair is going to fail breastfeeding because of their participation. And how and when do we use strategies to minimize infant exposure, such as timing maternal dose at a particular time and pumping and discarding milk for a certain amount of time? When is this even appropriate?

Who should be enrolled in these studies? How many weeks postpartum should a mother-infant pair be before they are enrolled in a study? Should these mother-infant pairs be exclusively breastfeeding mother-infant pairs and when is that important? Should mothers be using the drug solely for therapeutic purposes or is there a role in certain situations for healthy volunteers?

And what are some effective recruitment methods? How do we find these mother-infant pairs to enroll in these studies? Could we use pregnancy registry populations to enroll subjects for clinical lactation studies for certain groups of drugs and conditions?

How large a sample size do we need? Traditionally clinical lactation studies that have been done are very small, often, ten subjects or less. Is there any value in requiring sample sizes of 30 or more so that some sort of statistical calculations where

parametric testing could be done? Is there a role for this? Is it realistic?

When, if every, is a control population needed? If pharmacokinetics are being looked at, can you use historical populations of non-pregnant women and the information that you already have from those populations as a control? For studies that assess milk production and composition, should we use lactating women who are not using the drug of interest? And when are prospective control populations useful, if ever? Are they needed?

With regards to breast milk sampling techniques, there are two schools of thought. People would like to characterize the complete dosing interval and so some people would like to completely pump a woman out at different intervals following a dose of drug for 24 hours or more. But this clearly interrupts breastfeeding. And so is it really necessary to do that to characterize the

content of drug in milk? Do you need to completely empty the breasts at multiple times over 24 hours with a double electric pump? Or is it reasonable to collect representative milk samples, either to collect a full milk sample with complete emptying of the breasts at a certain amount of time after dosing in one woman and at a different amount of time after dosing in another, or to actually take equal volume samples pre and post feeding, but not to actually completely drain the breasts and to allow the baby to continue to nurse?

We also want to know about the clinical management situations where you should minimize infant exposure to drug when the drug is used in a single dose or limited number of doses. Is there an appropriate way to time the dose or to pump and discard milk for a certain amount of time following a single does study?

With regards to data analysis, I am just going to touch on this very briefly.

There are issues with drug assay development and precision. And some of these issues have been discussed in the published literature already.

The precision in developing these drug assays is a bit more difficult with breast milk because there is more variability in the drug levels. And people think this is due to varying lipid levels in different women's milk. Begg, in his 2002 article describes some different methods for assay development and validation. So there is some information that is out there to guide industry.

I also wanted to make the point in analyzing the data that really the data is described with descriptive statistics. Statistical testing really is not done on the data collected from clinical lactation studies. At the end of the Guidance, there is a section on labeling and I am going to touch on this just briefly. Currently, the nursing

mother section of a drug label is under the special population section. It follows the pregnancy section. There are going to be some changes coming in the future. Currently, there is a draft pregnancy labeling rule that is currently in the clearance process and it essentially an addendum to the physician's labeling rule which is already in use for other sections of the label. And it's going to change the way the information is organized in an attempt to make it as clinically relevant as possible for practitioners who need to counsel patients on the use of drugs in pregnancy and lactation.

So there is going to be a summary statement that is sort of the clinical bottom line, so that if a clinician has no time to read anything but that, that they get the basic message. That is going to be followed by a discussion of human data in a clinically relevant manner, and then any supporting data that is available.

Other issues that we haven't touched on in this presentation that were raised in public comments include the following. Some comments stated that the Guidance implies that nearly all drugs could be potentially used in lactating women and that requiring lactation studies for all drugs that could be used is not practical and would create an unnecessary burden.

And in response to that, we raised this question. Is it a burden that lactating women and their health care practitioners need to make medicine use decisions without adequate data to properly assess risk and benefit? Another question that was raised was that lactating women and infants should not be exposed to a new molecular entity, a drug that has never been out there before, for which there are not sufficient safety data. And this is a very important point but we do need to think about how we will define sufficient data. Will this be drug dependent? Is the

time to test a new molecular entity going to be different drug to drug, depending on what it is, its side effect profile, and how often it is used in women of reproductive age?

The published Draft Guidance included some information about vaccines and it raises some questions. And so we revisited this and held conversations with the center for biologics and decided that this document, this Guidance for industry will address lactation studies with drug products and therapeutic biologics only, the products that are regulated by the Center for Drugs, but not vaccines. Vaccines are regulated for the Center for Biologics and they will have the opportunity to address these issues separately.

With regards to radionucleotide products, there are data published on the radioactivity half lives of various diagnostic and therapeutic radionucleotides. Recommendations about continuing breastfeeding

and pumping and discarding milk should really be driven by their products radioactive half life. Nuclear medicine groups advise patients that most radioactive tracers are undetectable after 24 to 48 hours. And I actually went looking around online and Googling things to see what various practices and groups had out there. And they mentioned that women may need to pump and discard milk during that time. And they actually include in the patient information sheets that they are distributing. So this is being covered.

In addition, guidelines for disposing of body fluids like urine can be used to guide what you do with pumped breast milk. And these guidelines are also already out there.

So before I reach the end of my presentation, I would like to present the questions that we are posing to you today. Once I am done presenting those questions, Dr. Bonapace is going to join us and revisit some of the issues with study design from a more

pharmacokinetics, pharmacology perspective, because he can do a much better job of that than I can.

Question number one. Would data from clinical lactation studies be useful to practitioners and pregnant and breastfeeding patients when making risk-benefit decisions regarding medicine use during breastfeeding?

Question two. FDA is seeking guidance from the Advisory Committee members regarding the timing of study enrollment for mother-infant pairs. Is it important for breastfeeding to be well established before enrollment? Is there a minimum number of weeks postpartum before which mother-infant pairs should not be enrolled? And we would like you to consider both infant feeding issues as well as maternal physiology changes that are going on in the immediate postpartum period.

Should clinical lactation studies only enroll mother-infant pairs who are

exclusively breastfeeding? If yes, why? And if not, what are the scenarios when enrolling nonexclusively breastfeeding mother-infant pairs would be useful?

Given that estimated infant daily dose can be calculated from drug concentrations in breast milk, are there situations where a maternal milk/plasma ratio offers additional clinically useful information?

Based on drug characteristics or existing clinical concerns, are there situations when a mother-infant pair study with infant plasma sampling should be recommended? Are there situations when this should be conducted without a prior milk-only or milk plasma study? And please describe these situations. I think this is really important from an ethical perspective that we are able to define these situations very clearly.

Are there any situations where it is

appropriate to enroll healthy volunteers in clinical lactation studies? Please consider single dose versus multiple dose studies, ongoing breastfeeding where a woman is continuing to breastfeed her baby during and after a clinical lactation study versus a situation where she may be weaning her baby, as well as continued nursing during drug administration versus pumping and discarding milk during the study.

If there are none of these situations, please explain why. If there are situations where this would be appropriate, please describe those acceptable situations.

And lastly, when in the drug regulatory process should clinical lactation studies be requested and done?

I thank you very much for your time and I would like to introduce Dr. Charles Bonapace. He is a clinical pharmacologist in the Office of Clinical Pharmacology and he is going to give us a slightly different spin on

study design.

DR. BONAPACE: Good morning. It's a pleasure to be speaking here this morning. My goal today is to give an overview of the considerations in evaluating the transfer of the drug into breast milk. And I'm going to try to do this from a slightly different point of view. I'm going to try to talk about the clinical pharmacology of the issues which have not been addressed so far.

I think the most important question is, is the drug systemically available? And by that, I mean, is it detectible in milk or plasma using appropriate methods? And if it is not, it is likely the drug is not going to be excreted in breast milk but, of course, it is dependent upon the drug itself and any safety concerns of the drug.

If it is systemically available, is the drug excreted in breast milk? If it is excreted in breast milk, how much of the drug is excreted in breast milk? And we can state

that as a dose in milligrams. And we can stated that as a percentage of the maternal dose, which is known as the relative infant dose, or we can actually state that as a percent of the pediatric dose, if it happens to be a drug which is approved in the pediatric population.

A question which can only be answered from the evaluation of studies in an infant is is the drug absorbed by the infant or in the infant. And if so, what is the exposure of the drug in the infant in contrast to the mother? And if you keep in mind that for a drug in an infant, it's going to depend upon the infant's age of what the clearance of the drug is going to be. So, the clearance may be very different in an infant than what it is in a mother and it may change, whether the infant is younger or older. For instance, if it is one month of age or one year of age. And also, is the drug absorbed in a similar fashion in the infant as it is in the mother,

and does that change, based on the age of the infant?

And keep in mind that a drug may be absorbed equally well in an infant and a mother. But if the clearance of the drug is much lower in an infant, and only a small percent of the maternal dose is excreted in breast milk and ingested by the infant, the exposure of the drug in an infant may be much greater than you would expect. And that's because of the differences in clearance. So this is something that can only be defined by evaluating this in an infant.

Something which was mentioned already is what is the benefit of calculating the milk/plasma ratio? In order to calculate a milk/plasma ratio, you need to perform a study in which we obtain concentrations of milk and in plasma or serum. In order to do so, you have already calculated the amount of drug excreted in breast milk, which is one of the goals of calculating a milk/plasma ratio. And

should this be something which might allow us to estimate the amount of drug excreted in breast milk in situations where we don't evaluate that in a clinical lactation study?

For instance, if a sponsor wants to alter a formulation. So if a drug is an immediate release formulation, they want to come in with an extended release formulation, it's not likely the sponsor is going to perform another lactation study. Is it appropriate to use a milk/plasma ratio in this regard to estimate the amount of drug excreted in breast milk for a change in formulation?

What about situations where a drug is approved with multiple doses so it has 500 milligrams once a day, maybe 1000 milligrams once a day. And if it's 1500 or like 2000 milligrams once a day, the sponsor may only select one dose to evaluate in a clinical lactation study. Is this appropriate to use a milk/plasma ratio to evaluate the transfer of drug for each of those doses and put this

information in the label or should a sponsor evaluate the highest dose, lowest dose, multiple doses? So these are just some questions for consideration.

What I'm going to do is sort of walk through each of the three study designs and talk about considerations for each one. The simplest study design is the milk-only study. This is a study which involves the mother only. It involves the collection of milk-only. So there is no additional risk to an infant if the mother is chronically taking a medication and is currently breastfeeding the infant. This provides the amount of drug excreted in breast milk, which is the ultimate goal. Is the drug excreted and how much of the drug is excreted? It also has the ability to assess the impact of the drug on lactation. So as far as the amount of milk that is excreted and the composition of the milk, this can be determined.

This study has a benefit that

basically it allows us to minimize the exposure of a drug in an infant in situations where a drug might be used on an acute basis, short-term basis, single dose basis, or sporadically. And by that I mean, by obtaining milk and milk-only, you obtain enough information to know, can you delay breastfeeding? For instance, if a mother was pumping and storing breast milk, can you use stored breast milk over a period of time following the dose, which is either short-term or sporadic, and then resume breastfeeding at some time later, so that you can minimize exposure. So this study will allow that information.

But should this always be the first study performed as a lactation study? And I think this may reasonable, it may be a reasonable approach for sponsors who have a drug that they have evidence that they believe it's either not excreted in breast milk or maybe poorly or minimally excreted in breast

milk. Because if a drug is not excreted in breast milk, it doesn't make a lot of sense to do a mother-infant study, just to find out the drug is, in fact, not excreted in breast milk.

It is useful for short-term or for long-term therapy from the situations I just stated for acute or single dose or short-term therapy but it could also be a useful study design in long-term therapy, simply because not all drugs which are given on a chronic basis are necessarily excreted in breast milk or absorbed by the infant. It does assess the -- it will give an assessment of the amount of drug excreted in breast milk and if the drug is excreted in breast milk. And it will allow an assessment of the daily dose to the infant, which can be expressed in milligrams or as a percent of the maternal dose, or if it is approved in pediatrics, of the pediatric dose.

The second design is a milk plasma study. And this is a study which also involves the mother only so there is no

additional risk to the infant, if the mother is currently using the drug and is breastfeeding the infant. This provides all the data from a milk-only study, in addition to obtaining the concentration time profiles from lactating women. And because you have obtained data from serum or plasma in breast milk you can calculate a milk plasma ratio.

You, theoretically, can also calculate a milk plasma ratio from a milk-only study, since you have obtained the data in breast milk and also from Phase I studies and healthy volunteers. But keep in mind, it is going to be dependent upon when the study is performed, but is it likely that the pharmacokinetics of the drug in real life patients who are lactating, who may be still dealing with the physiological affects of the pregnancy could be very different than a very homogeneous set of healthy volunteers. So this actually provides more information based on the plasma concentrations than

extrapolating to a control group, such as healthy volunteers.

And this is an example where it may be useful for short-term therapy. And the reason why this may be useful for short-term therapy is because an accumulation of the drug is less likely to, obviously, occur with short-term therapy than long-term therapy, but again, this can be used with long-term therapy. Drugs that are known or likely to be excreted in breast milk. If a drug is known or is either not excreted in breast milk or not likely to be excreted in breast milk, then doing a milk-only study as the initial study would make more sense to determine that the drug is in fact not excreted in breast milk.

And this may be important for drugs with a narrow safety margin. Since for many of these drugs, the absorption in the infant may not be known unless the drug is already approved in the infant population. And the clearance of the drug may not be known. This

may be more useful, initially, for drugs where we have concerns with adverse events of the drug and not knowing much about the pharmacokinetics in an infant.

And the final study, which is the most complete study, is the mother-infant study. And this is dealing with the collection of either a blood, so either serum or plasma or breast milk and generally limited blood samples in an infant or other fluids. And we'll get more into that in a second. This can address whether a drug is absorbed by the infant. It's really the only study that can truly address whether a drug is absorbed by the infant.

We can calculate the exposure of the drug in the infant because the plasma concentrations are going to depend upon what the absorption of the drug is in the infant and the clearance of the drug in the infant. But this also allows for an assessment for the affect of the drug in the infant, whether that

is an extension of the pharmacological affect of the drug, or whether its an adverse event of the drug.

And the affect of the drug can be assessed in a noninvasive manner. So, for instance, if the drug is a beta blocker or something, you can measure the heart rate. If the drug is a sedative you can monitor for sleepiness or sedation but also in a minimally invasive manner, such as a blood glucose concentration if it is a diabetic drug, and so forth.

So this can not only assess how much of the drug is going to be absorbed and what the exposure is going to be in the infant, but in some ways what is the affect of that? And this is the only study that can assess that.

And this may be useful in the following situations for chronic therapy. But I don't want to state that for all drugs which are used in chronic therapy should have a mother-infant study performed, because

certainly, not all drugs and chronic therapy are going to be excreted in breast milk, are going to be absorbed by the infant, and are going to accumulate. So, it's really a case-by-case basis.

If a drug is likely to be absorbed, if a drug is likely to have a long half life or has a known metabolite with a long half life, and for any of those reasons, if it's likely to accumulate in the infant, that's probably where it's most useful to have a mother-infant study.

And the last point is dealing with a drug. If you have a drug in which it is primarily excreted in urine, the drug is not necessarily metabolized, maybe a parenteral drug approved in adults in which the absorption of the drug is not known but may not be high, it is possible to collect, and by the collection of urine, we're referring to maybe collection of urine from maybe a diaper. So this could be single time points from an

infant diaper to assess whether the drug is detectible.

So this would be more of a qualitative matter to determine that the drug is, in fact, not absorbed in an infant, which is less invasive than obtaining blood concentrations to determine that it's undetectable in plasma. So I realize this may be in very few drugs may necessarily be candidates where this would be possible.

And so at the end of the day, what is potentially known and what is potentially unknown from any of the three studies? Well, what is known are the concentration of drug in plasma or serum in breast milk in the mother; the concentration of drug in the infant, either plasma, or serum, or some other fluid; the ingested dose of the drug, which the ingested dose is the dose that the infant receives in breast milk, not necessarily the dose that is absorbed from the infant; and the oral clearance.

What is likely not to be known is the bioavailability of the drug; the dose actually absorbed from the infant; and the renal clearance, since obtaining urine in, especially young infants is challenging. I'll just leave it as challenging.

And I just want to go briefly over something that was raised earlier. And this is study designs, and this is in the Guidance, to assess the affect of lactation on the maternal pharmacokinetics. The Guidance mentions several designs and two of them, which are the longitudinal design and a multiple arm design. The longitudinal design is a design in which the same group of lactating women are evaluated at multiple time points across lactation. So, for instance, they can be evaluated at one month, at three months, and then maybe at six months.

And the purpose of this is to look at the impact of lactation or changes of lactation and to see what that is doing to the

pharmacokinetics of the drug in a mother, if any. This is probably most useful for chronic drugs, since a mother then will be likely to be receiving the drug during that period of time and the longitudinal design allows each subject to act as their own control, so it reduces the variability between subjects. An infant may or may not be enrolled or sampled with the mother, as far as that goes.

For a multiple design, it's probably more appropriate for an acute drug or very short-term use drug in which a different subset or a different group of subjects are enrolled at essentially the same time points. And this is essentially a pair sample design, since you are going to be looking at a greater degree of intersubject variability, since the subjects are going to be different across those. And it's possible that if a mother would be taking the drug on a short-term or acute basis in a recurring manner, for instance, if it was like a migraine drug where

they might be taking the drug several times a month, this could be possible. But this is more designed for short-term or like acute use drugs and again, infants could or could not be sampled with this.

And so, some of the issues are, what are the benefits of performing these studies? And the question is, what is likely the impact of lactation on the maternal pharmacokinetics, considering that, early on, the greatest change is probably going to be the impact of pregnancy on the maternal pharmacokinetics? So, when should these studies be performed? And if not, is it possible just to enroll a large enough number or selection of mothers and infants into the other three study designs, so that we can actually answer these questions?

We can look at the impact of maturation of clearance, for instance, over a period of time. So if infants are enrolled into one of the other studies at various time

points, we can look at the impact of maturation of the kidney and the liver on clearance. We can look at the impact of lactation at different time points on the pharmacokinetics of the drug, for instance in like a milk plasma study in mothers.

And so, the second question is, when then should these studies be performed in relation to the onset of breast feeding? And just keep in mind how long it would take for the physiological changes of pregnancy to normalize, so it doesn't over shadow the impact of lactation on the maternal pharmacokinetics.

Thank you very much.

CHAIR RAPPLEY: Thank you. We are going to pause for about three to four minutes while we do some changes with our technical equipment. I think, as we begin making that change, I might comment that this issue reminds me of what we have discussed over the last at least two, maybe every, meeting of our

pediatric advisory committee and that is how we have evolved over time from a presumption that it is not possible to study medications in children and that the best we can do is put something in the package insert that says there is no information about safety and efficacy in children and then leave everyone in the field to make their own decisions about how to use medications in children.

We no longer find that acceptable. We understand that it is possible to develop designs and study medication use in children. And now we are extending that to lactating women and their infants. And I think that's a really important place for us to be. So, I think it's great that you are bringing this forward to us and that we are bringing some attention to this important topic.

DR. FEIBUS: And this is Karen Feibus. While it is fresh in everybody's mind and we have a minute, I wanted to mention that the study designs that Dr. Bonapace was just

sharing with us, the multiple arm design and the longitudinal design, and then also one called the population PK design, which is also part of the Draft Published Guidance, as we are considering those three study designs, we are also thinking about them in terms of the other Draft Guidance that published along with the clinical lactation guidance, which is the Draft Guidance for industry on pharmacokinetics and pregnancy. And one of the questions that we have been discussing internally is whether those three study designs belong in the clinical lactation Guidance when we are not sure whether is a real significant affect on pharmacokinetics caused by lactation or whether they should really become part of that pharmacokinetics in pregnancy guidance.

And so that is one of the decisions that we are making is here are these study designs, are they in the right place right now? And so, I'll just throw that out there

to complete your information.

DR. PENA: Okay, so why don't get started with the next talk? Dr. Ruth Lawrence will be speaking on breastfeeding physiology, benefits, and research.

DR. LAWRENCE: Good morning. It appears that my subject is perhaps a step backward from the topics you've just heard about how we should examine drugs in breast milk and how we should examine this issue because I have been asked to comment on breastfeeding itself, its benefits and why this is such an important issue and give you, very briefly, an overview of how breastfeeding happens.

So, with that in mind, I start with the comment that babies are born to breastfeed. Now you may recognize this comment because it's the tag line for the national campaign to promote breastfeeding that was done by the Office of Women's Health beginning about four years ago. And for all

the argument about that incredible campaign, nobody can argue about this statement.

There are many compelling reasons why one should consider breastfeeding and number one is species specificity. Human milk is made for the human infant. There are thousands of species. They all make a milk specifically appropriate to their own offspring. The human is the only species that drinks another species' milk.

The nutritional advantages of human milk span pages and pages of detail, but every single nutritional product in human milk is directed at the optimal growth of not only the body, but the brain, and the development of the offspring.

We know also from many studies that infection protection is provided by human milk because of the many factors in human milk that encourage the growth of appropriate bacteria and suppress the growth of pathogens. Human milk also contains many immunologic products

as well that protect the human infant. And these immunologic products, if you will, not only protect against infection, but in more recent years, have been associated with a decreased incidence in some chronic diseases we associate with immunologic problems, such as Crohn's disease, such as Celiac disease, cystic fibrosis, and very dramatically, diabetes.

The early studies, over 20 years ago, epidemiologically showing that the incidence of childhood onset diabetes was increasing rapidly as the decline in breastfeeding was occurring. Now, that doesn't necessarily prove cause and effect, of course, but in prospective studies following large cohorts of children who were either breastfed or not breastfed and their incidence of childhood onset diabetes has been very supportive of this concept.

And allergy protection as well. Probably no topic has been argued more

commonly in the pediatric literature than whether breastfeeding had an impact on allergy. The very first studies were done years ago in Rochester by Dr. Gerald Glazier, who decided that in his practice he saw so many infants developing allergies earlier and earlier that he did the first study showing that you could influence the onset of allergic symptoms in young children if the mother would not only give up common allergens during her pregnancy, but breastfeed her children. And this is now reasonably well accepted.

Although, of course, one sees frequent articles in the literature suggesting that maybe it isn't true. You have to read the fine print because so many studies on breastfeeding include in the group of breastfed, any children who were ever breastfed. So if a child was breastfed a few times during the hospital stay, this became a breastfed child, where as partially dose related and with exclusive breastfeeding over

a period of time, you can actually make an impact. You have to be very careful about just reading the headlines.

And of course, psychologic benefits of breastfeeding have been enumerated by many authors. When I was in medical school, the only reason we were given that a mother should bother to breastfeed were the psychologic benefits and the special relationship of a breastfeeding baby to his mother. Klaus and Kennel have done incredible work confirming this and changing how we manage infants in the newborn nursery. And have recognized that mothers and babies need to be together from the beginning.

And in our species specificity we see, of course, that all of these species are mammals, taken after, of course, the ability to breastfeed. And most of the childhood benefits rely on this species specificity. But even for the premature infant, and I note that there are a number of neonatologists in

the room today, that unfortunately, very little work has been done on the benefits of human milk to the premature infant.

Now, we are being able to do that because of the benefit of the availability of donor milk from reliable milk banks. And there is even a product now to supplement human milk with a product made from human milk. We have been misled into thinking that supplementing human milk by a commercial product with that name was human milk, but it wasn't. It's really cow milk. But this is a great step forward.

And this is a list of the many respiratory, excuse me, the many infectious diseases that have been impacted by the use of human milk.

Now why would human milk be protective? There are many antibodies, secretory IgA being the most prevalent, which coats the gastrointestinal tract and is believed to interfere with the absorption of

pathogens. But there are living cells in human milk. Lymphocytes, macrophages, which have been shown under the microscope to be able to swallow up viruses and bacteria that could cause trouble.

A very basic need of the human gut is lactoferrin and that influences the pH of the gut and what is absorbed. And it also suppresses the growth of E. coli. The normal floor of the infant gut is lactobacillus. It's not E. coli. And that's why even seemingly benign species of E. coli can cause disease in newborns.

Lysozyme is another product of human milk, an enzyme that has anti-inflammatory products and many other things. The normal flora of human milk is lactobacillus.

A study published in 2004 by Roger Rogan, whom many of you must know, showed that across the board infant mortality in the United States was reduced by as much 21 percent if the child was exclusively

breastfed.

Sudden infant death is another topic of great concern that has been impacted by exclusive breastfeeding. The early studies in Australia that precipitated the back to sleep campaign, that is putting the baby down to sleep on the back, actually showed that breastfeeding had a stronger affect. But the committee did not want to dilute the impact of back to sleep by suggesting that breastfeeding might make a difference. There are multiple studies that have shown that SIDS is much reduced in breastfed infants. Of course, it isn't reduced to zero because we all remember the biblical story of Solomon and his two breastfed children.

As I mentioned earlier, the impact on diabetes and there are even data to suggest that childhood onset lymphoma, leukemia, and Hodgkin's disease is reduced by exclusive breastfeeding, hypercholesterolemia, asthma and what isn't on this list is obesity. Very

good studies showing that the potential for obesity is developed by the age of one and that those infants who were exclusively breastfed, have a much lower risk of obesity in long term.

Now if we just look quickly on some data on Crohn's disease, leukemia and obesity, one sees that there is a dose effect. Exclusive breastfeeding for a longer period of time has a greater influence. And the definition of breastfeeding is very important. As I mentioned earlier, ever breastfed means ever breastfed, maybe once or twice or three times or three days, maybe even three weeks.

The American Academy of Pediatrics recommends exclusive breastfeeding for the first six months of life, continued breastfeeding with adding appropriate weaning foods for the next six months of life. And it doesn't leave it there. It says continued breastfeeding for as long as the infant and the child wish. It was implied in the

materials we received that the Academy said a year is enough. That isn't what they said.

And this is some of the many studies on overweight. This particular study done by Gillman and published in 2001 showed the risk of developing overweight in adolescence by the duration of breastfeeding in infancy and showed that, indeed, the longer one breastfed, the better it was.

Probably the most dramatic data are in the area of development. And food for the brain; human milk contains cholesterol. The brain is made up of cholesterol. Formulas contain no cholesterol and haven't for 40 years. It doesn't matter what a mother does with her diet, high cholesterol, low cholesterol, high fat, low fat, her milk will still contain cholesterol until the last drop is used.

Human milk contains taurine. Now, that's an amino acid that is not on the list of essential amino acids because essential

amino acids by definition mean an amino acid that an adult can't manufacture. Adults can manufacture taurine from basic substrate. Infants cannot. It's an essential item for the human brain. Until about ten years ago, formula contained no taurine until this work came forth in the breastfeeding field and they began dumping synthetic taurine into formula.

And of course the great discussion of DHA and the omega-3 fatty acids. Human milk has always contained DHA and it does contain DHA, whether mothers need to take it in supplementation has not been determined, but it is being marketed everywhere. Maybe you took some DHA today. But it is well-known to be an important factor in brain growth. So, it's not surprising that the cognitive studies following exclusive breastfeeding have shown that it does make a difference.

This just happens to be Horwood's work published in 1998, where they followed a cohort of 1,200 children in Australia and

noted over time significant difference and even measurable difference at graduation from high school to the point of about, to the measurement of about five points different, showing that those children who are exclusively breastfed were more likely to graduate from high school, were more likely to go forward in other educational situations and had better behavior. There are many other shorter term studies that have confirmed this kind of observation.

And we do believe that breastfeeding support is the single best opportunity for pediatricians to impact a child's life. And we can't forget the benefits to the mother. We've been talking here in the first hour about the mother and the medications she might take and how we should look at that. But we have to remember that breastfeeding is the physiologic completion of the reproductive cycle and it's not nice to fool mother nature. She planned that the mother would breastfeed.

The breasts are ready for that. And there is much more rapid uterine involution in a breastfeeding mother, decreased postpartum bleeding, earlier return to pre-pregnancy weight and increased child spacing attributable to lactational amenorrhea. While it is not promoted as a contraceptive, it has been shown worldwide to space children more physiologically.

There are other long-term benefits to the mother. A decreased risk of breast cancer, ovarian cancer, and oddly enough, reduced hip fractures in later life, due to postmenopausal osteoporosis. And you say to yourself, how could that be? Because human milk provides so much calcium and phosphorous, more than the body provides in utero for the growing infant. But what seems to be the difference is that while breastfeeding, the mother absorbs calcium and phosphorous much more effectively and physiologically. And that effect persists about six months post-

weaning because the early studies using densometry showed that women who had breastfed for a year or two had less dense sentinel bones and so forth. But after they weaned, they are back and more firm and better calcified than women who do not breastfeed after pregnancy.

And of course the women at greatest risk for postmenopausal osteoporosis are the women who have never born a child and never breastfed. So that's an important consideration for mothers as well and data is accumulating on the impact of breastfeeding on ongoing rheumatoid arthritis.

So, this is another study reporting the length of breastfeeding as associated with the decreased risk of rheumatoid arthritis, breast cancer, and ovarian cancer.

Now, just a minute or two for a quick overview of the anatomy and physiology of lactation, about which tomes have been written, volumes have been written, but we're

going to do it in about three minutes.

The diagram you see before you is a summation of what happens to the developing breast in the lifetime of a female. Now, all of you neonatologists well know that the breast is used as a parameter in the assessment of gestational age in the premie and the full-term baby, in both the male and the female, because the breast begins to develop in the embryo at about 12 weeks and progresses throughout pregnancy, stimulated partially probably by mother's hormones, so that at birth, both the male and the female have a visible nipple and a very rudimentary ductile system.

The breast stays pretty quiescent until menarche, when the first of the external sex characteristics to develop are usually the breasts in the female. The nipple becomes more prominent, the ductile system becomes more arborized and rudimentary alveoli appear.

The breast continues to develop

throughout menarche until about the age of 28, when the breast has achieved its maximum growth associated with menstrual periods. And then if the breast has not been stimulated by pregnancy, begins slowly to involute, not massively, because we'd all be aware of that. However, this may be why we have trouble with mothers who have their first baby in their 30's and 40's who have more trouble initiating lactation than the 20-year-old or the 25-year-old. That's the middle column.

The fourth column represents pregnancy. Because as pregnancy begins, the hormones of pregnancy stimulate the development of the breast. It begins to arborize tremendously. The alveoli develop. The alveolar cells line the lumen and are ready to make milk. Should the mother deliver at 16 weeks, she will make milk, and at any time thereafter. And some interesting work has been done on the slightly different composition of milk when a mother delivers

prematurely, a little bit more protein, a little bit more sodium. But unfortunately, not enough to fill the gap of the nutritional needs of a premature who is born at 24 weeks.

Now, the final column is what happens during lactation. When the placenta is delivered, which has been contributing hormones that block the breast from responding to prolactin. Otherwise, mothers would be pouring out milk during pregnancy, which would be rather wasteful. So there is something that inhibits the breast from responding, because there is so much prolactin available and circulating during pregnancy. So once the placenta is delivered, that inhibitory affect is gone and the breast is ready to make milk. And therefore, you see the most complex arborization, the very prominent nipple, and areola, and of course, the microscopic showing milk in the ductile system.

Now, to roll lactation, milk production, and release of milk into one

slide, we have a diagram of the ejection reflex here, because it emphasizes the role of prolactin and oxytocin. Now, that's not to say there are no other hormones involved, because there are, to keep the breast going, to stimulate milk production, to contribute to the use of nutrients and everything else, includes all of the hormones; the adrenal hormones, the pituitary, insulin and many others. But the ones we focus on are prolactin and oxytocin.

We know a fair amount about oxytocin because obstetricians have been interested in that for decades, as they try to find out why labor starts. And oxytocin has been attributed to stimulating the uterus to contract. And we do know that oxytocin stimulates myoepithelial cells to contract. There are myoepithelial cells in the uterus. So early postpartum, any mother can tell you that when she puts the baby to the breast, she can feel her uterus contract. We have a fancy

term for that. It's called after pains. But that doesn't go on forever. But that's why a mother's uterus involutes so physiologically and it's kind of back to normal by six weeks. If the effect went on forever, her uterus would disappear. But it doesn't.

Oxytocin, however, continues to stimulate the myoepithelial cells that are in the breast. Those myoepithelial cells are wrapped around the duct system. And you'll see later when Dr. Hale talks about how drugs get into milk and so forth that those myoepithelial cells are wrapped around the alveoli.

Now, there are no other muscles in the breast. All the exercise in the world is not going to change the size of one's breast, so never mind that. But the myoepithelial cells stimulates of the oxytocin will contract and eject the milk from the ductile system. And so, we know that pretty well and we even have synthetic oxytocin that we can use to

stimulate let down.

The other hormone is prolactin. Now everybody in this room has prolactin in their system. It's a physiologic hormone that is very important for all of us. It has an inappropriate name, you might say because it isn't just for making milk. It is associated with other major biologic features and can be stimulated to increase, in moments of stress. So some of us have higher levels than others in moments of sex and other things like that.

But during lactation, it stimulates the lacteal cells to produce milk. And therefore, in this diagram, you see the baby at the breast, suckles the breast, and sends a nervous message through the spinal column to the mother's hypothalamus and pituitary. And prolactin is stimulated to be released and begins the production of milk.

Now, not an awful lot of work has been done on prolactin because we couldn't measure it every well until about 20 years

ago. And now, any laboratory can get a level, if you need it. And they are working on trying to produce prolactin synthetically. That would be a great breakthrough for mothers whose production is languishing. But they weren't sure just what that relationship was, initially.

We do know that during pregnancy prolactin levels are in the hundreds. We do know that when a mother delivers, the placenta is delivered, that the prolactin levels drop down unless the breast is stimulated. And this diagram shows a study following the same women over the first six months postpartum. And you will notice here the red being the baseline prolactin levels done before the baby is put to breast, that they sort of drift down a little bit. So what they did was they did a study where they measured the baseline and then measured the effect of ten minutes of breast stimulus, preferably by the baby, but by a pump, if necessary. And notice the great

surge in prolactin. You'll notice across the diagram that the surges drop down, which distressed the scientists who were looking at that, until they looked at the percent surge over baseline. And that's what you see in this diagram, that the surge seems to be what makes the difference. Even though baseline is drifting down, it's the ability to create a surge in prolactin with a stimulus of the breast that makes the difference.

Now, we know some other things about oxytocin and prolactin. One of them is that there are many century pathways that stimulate the release of oxytocin. A mother can hear her baby cry and she'll tell you she feels her milk begin to drip. She may look at her watch and decide it's feeding time. Her milk will begin to drip. But the prolactin is not released unless the breast is stimulated.

So what this shows is the averaging of a couple of women who were allowed to -- I need to back that up. Let's see, what backs

it up? Okay, there we go.

A group of mothers were allowed to play with their infants, not feed them. Handle them, rock them, whatever. And they had a heplock in and were getting serial prolactin levels. Then, at time zero, they were allowed to put the babies to rest and a prolactin level, serial prolactin levels were gotten. The minute they put the baby to the breast, the prolactin levels rose up and gradually drifted down to baseline over several hours. But the point is that it takes breast stimulation to get a response from the prolactin.

Now, this is a diagram that was first developed by Peggy Neville of Colorado, who has done a lot of studies on milk production and how milk is made. And the purpose of showing it at this point is to suggest to you that it is a complicated process, that all of the constituents of milk do not get into the milk by the same physiologic or biochemical

process, so that even in the beginning, you will see here -- well I had a flashlight -- there we go.

Immediately postpartum, the intercellular spaces are open. So, there is a certain amount of diffusion of whatever might be in the system. So if a mother has had a lot of pain medication during labor, it's much more apt to be in her milk than it will be a week from now. And so some items pass by diffusion, some items are protein bound. There are actually five total processes. The process of lipids crossing the membrane is much more complicated and a lipid membrane is wrapped around the lipid globule which collects and oozes across the membrane into the alveolar space. And that is what makes milk.

And we talk about foremilk and hindmilk, which is just fancy terms for suggesting it takes a little bit more time to get the fat globular across the membrane than

it does to get the sodium and chloride across the membrane. And the volume of milk is believed to be driven by the glucose levels. So it's all intertwined and what is most important is the process changes over time.

So that one of the important things at our drug information line which we have run since 1984 is we cannot answer the question, unless we know the age of the baby. How long has mother been lactating? But also, how old is the baby? Is this a total diet? Is this baby going to absorb and metabolize and excrete everything or is this a newborn? So, the process is not a simple one.

Now, I'm not going to spend a lot of time talking about how you get the baby to the breast, but I just wanted to suggest that successful lactation depends on the ability to put the baby to the breast, to teach a mother where to put her hands and what to do. Babies are born knowing how to go to the breast. We have seen it happen. If you put a baby

freestanding on the mother's abdomen and nobody touches the baby, the baby will find the breast and latch on. If the mother is unmedicated, the baby will latch on within about 20 minutes. If the mother is heavily medicated, the baby may never quite make the trip. But babies know what to do.

It's just mothers don't know what to do. In our culture, they aren't taught. And they don't learn because they didn't grow up in a family where somebody was being breastfed. Nuclear families are small and they don't live generation to generation. So we have had to insert ourselves into the picture to help mothers breastfeed. So, we try to teach them all of these things.

And we're going -- I seem to be going the wrong way in spite of myself here. Oh dear, how did we do that?

I am pursuing this only because I want to just make a final comment or two that bonding is a very important issue. But, what

we're talking about today is risk-benefit ratio. What is the risk of this drug compared to the tremendous benefit of being breastfed? And for decades now, we have been telling mothers they can't breastfeed because we don't know. So, if we don't learn anything else today, we need to take home the message there is tremendous benefit to being breastfed.

And it makes a difference in terms of health care costs because everybody is always looking at the bottom line -- and I've done it again and let it flip through. Breastfed babies are healthier. It reduces the cost of health care to have breastfed babies. And the reducing of health care has been estimated at over $400 a child per year of breastfeeding. And there it is, all of a sudden. And all this reduces health care costs. Thank you very much.

CHAIR RAPPLEY: Thank you, Dr. Lawrence.

I think we'll hold questions and

allow Dr. Hale to make his presentation and then have our questions section at that point in time.

DR. HALE: I might be too far away. Regardless, next slide.

Good morning. I'm glad to be here talking about a subject that has long been needed to talk about.

First off, the reason for the season is what is the problem with drugs and breastfeeding? Well first off, the big problem is the lack of information. That's always been a problem. There has been no funding in this field to do these kinds of studies. Most of them have just simply been done with little funds that we could scrounge up within our departments.

The next thing is the misinformation. The misinformation is absolutely enormous in this field. As Dr. Lawrence said, for years we told moms, you can't breastfeed so you could take this radiocontrast agent or this

agent or that agent. And let me give you a classic example that is just current. Next slide.

Nursing mothers. It is not known if this or whether or if so, in what amounts, sertraline or its metabolites are excreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when Zoloft administered. This is brand new, 2007 out of Zoloft's prescribing information. Now, this is absolutely typical. You see this in everybody's package insert. There are now more than 54 mother-infant pairs that have been studied with Zoloft. We know exactly how much gets into milk. You can probably say that about more than 400 drugs that we currently use. None of it ever gets to the package insert. And this is what pharmacists read. This is what physicians read. And that is where this misinformation is constantly being, has permeated this whole field.

Well, today I hope we can do

something about that. We're going to start with talking about alveolus. This is actually the alveolar apparatus where milk is synthesized. It's created by this wonderful little cell called the lactocyte. We now have renamed it. It used to be called secretory alveolar epithelium, but lactocyte is easier.

Lactocyte is a beautiful cell. It synthesizes the lipids. It synthesizes most all of the proteins that are in human milk. It controls electrolyte environment within milk. It's a beautiful compartment system. And you'll hear me talk about the compartment because milk is a compartment in the human body that is distinct, unique, it is isolated. Nature created it this way so that it was separate from the rest of the body and the environment within human milk could be static, stable, uniform, and not only that, protected from the plasma compartment of the mother.

The environment is, as I said, quite static. The sodium concentration in milk

hardly varies. You can do all kinds of things in the plasma compartment but the lactocyte is beautiful and it controls the environment and the content of milk.

On the surface of the alveolus, you see this myoepithelial cells that Dr. Lawrence was talking about. They have produced kind of like a basket layer of cells. They have oxytocin receptor sites. They are very sensitive to oxytocin. And when oxytocin is fused out of the mother's pituitary, it causes the contractual process, forces milk out into the ductile system.

The milk goes down most of the way to the nipple or into the ductile system and then the vacuum produced in the infant's mouth is what pulls it out of the ductile system and the lets the infant ingest it. So this is the alveolar. It's just a beautiful little system and it controls the synthesis of milk.

Now one question that was brought up about oxytocin, oxytocin can be affected by

certain drugs. There are not many of them. The most prominent one is probably alcohol, which is what can significantly delay or reduce the secretion of oxytocin from the pituitary. Kind of an interesting one.

The first four days postpartum we know that the lactocytes are very small in size. There are large intracellular gaps between these cells. This is the colostral period. At this point in time, you see that substances from the plasma compartment can enter into the milk compartment quite easily. We know that the lipid content in milk in colostral is very small, about one-fourth what it is in mature milk. We know the protein content is moderately low as well. A little bit, it's significant, but it's still somewhat low.

During this stage, medications can come into the milk compartment quite avidly and quite easily. Generally, if we were to do studies in this period, and we don't do them,

but if we were to, you would find milk/plasma ratios generally about one equivalent to the plasma compartment.

The beauty of this, the colostrum in the colostral is that even though the drugs may be able to enter into the milk compartment, the volume of milk produced at this time is low, 30 to 60 cc's per day. So, because the volume is so low, the dose of the drug transported in the colostral period is very minuscule, for the most part, quite, quite low.

During this time period, you would be interested in studying drugs that are used during the colostral phase. You would want to look at drugs that are used in epidural anesthetics. You would want to look at drugs across the glandins that are used during delivery. You would want to look and study drugs during the colostral period that are only used in that time period. That is one thing you want to keep in mind when talking

about the time period when you want to study a drug. Obviously, study them when you use them.

So the colostral period is a unique period. At about 30 hours, you see the plummet of progesterone. But progesterone, with the delivery of the placenta, the progesterone starts to go away very rapidly. And, at about 30 hours, the progesterone levels are at their lowest point and that is when the lactocyte really starts to kick in.

As Dr. Lawrence said, prolactin levels are sky high in pregnancy. They are sky high the first week of lactation. But yet, this whole system has shut down. And it is shut down because of progesterone. So, with the release and disappearance of progesterone, the receptor sites are de-occupied, prolactin then starts to drive this cell like gasoline to an engine and the cell really takes off. It starts to swell and when it starts to swell, it grows in size and all

of a sudden, you see the cells grow together and produce tight, intracellular junctions. And at this point, then you get a very very tight compartment that is almost identical to the blood-brain barrier.

And that's why, when you look at all the drugs in this field, if you just think of it as a blood-brain barrier, you'll get a very good sense of what drugs go into milk and what drugs don't go into milk. So, at about three days to four days, you see the system tighten off and then all of this lactose that was being secreted all during gestation and being eliminated by the plasma compartment of the mother, at about 30 to 40 hours, all this lactose becomes trapped out here and you get this osmotic effect that pushes water over into the milk compartment. And at that stage is when the milk comes in. It's really an osmotic effect from lactose.

So, at this point, drugs to enter the milk compartment must do so by going from the

plasma, they must go through to bi-layer lipid membranes, and then enter into the milk compartment. So, it's very difficult for most drugs to do that. That's why some of the classic pharmacokinetic terms that we use are low molecular weight. For drugs of large molecular weight, it simply won't pass through these bi-layer lipid membranes. If it's very small in molecular weight like lithium or like the amphetamine family, it goes right on through. And it's very similar to the blood-brain barrier.

So, large molecular weight drugs, anything larger than about 800, simply doesn't get into the milk compartment. It's very very tight. Now, you still do see a few gaps in here. There are cells always dying off and leaving little gaps within the milk compartment. They are small in number, but you do see them. Because you can even seen a few large molecular weight proteins from the plasma compartment still in the milk

compartment, months and months down the pike.

Now, we do know of a bunch of protein transporters. The classic one is IgA. Secretory IgA comes from the plasma cell. The plasma cell comes from the Peyer's patches in gut. It comes up to the breast and then it is turned on and it secretes secretory IgA. There is actually a pumping system here.

We know of a number of protein transporters in milk. And we have not known exactly why they all exist, but secretory IgA, we do know, almost 1200 milligrams a day is secreted to a breastfeeding infant. And that's why they are hole or pharynx, their gut is totally perfused and coated with secretory IgA, which produces many of the beneficial effects of human milk, as far as infectious disease.

It's the same transporter system that occurs in all mucous membranes in the human body, the nose, the mouth, the eye, the vagina, the same transport system.

We also know that there are protein transporters not only for IgA, but for prolactin, insulin growth factor, there is a lot of IGF-1 in human milk. Probably it enhances growth maturity of the GI tract.

But also, do you remember a couple of weeks ago there was a story in the news about they were giving oral insulin to children to prevent the onset of, or new onset of juvenile diabetes? There is also a protein transporter here for insulin. There is a lot of insulin in human milk. We never knew why. Perhaps that is why.

So, there are protein transporters in milk. We do know of a few drug transporters. We know of about five or six drugs that are actually transported into the milk compartment. There are transporters on the surface side, right here, that transport the drug over into the milk. The most prominent ones are, if I can get it to come up, iodine, acyclovir, cimetidine, nitrofurantoin and

ranitidine. There may be more but these are the only ones that I know of.

Iodine is kind of the most important one because it is the only one that is clinically relevant. The milk/plasma ratio for iodine is about 15 to 30, really really high. Clinically, it is relevant because you never want to give iodine products to a mother that is breastfeeding because most of it will end up in her breast milk. Classic case of a Betadine douche that a mother was using for weeks, her iodine levels were high, and then the subsequently, the infant's thyroid function went down the tubes, was suppressed from high iodine levels.

Radioactive iodines are a really horrifically dangerous product to use in breastfeeding moms. I generally suggest that they stop breastfeeding because about 28 percent of the dose will go to the mother's thyroid when she takes an oral dose of I-131. About 27 percent will go to her breasts. The

breasts absolutely light up with radioactivity. So I-131 is a real dangerous product.

The rest of these products are really, don't even attain clinical relevant ranges. Ranitidine has a milk/plasma ratio of six. Milk/plasma ratio of six. And this is why I'll have to tell you, I hate milk/plasma ratio. A milk/plasma ratio of six, the clinical dose is about 20 percent of the dose you would use in a pediatric patient. Not even relevant. And that is true with virtually all of these drugs.

So, milk/plasma ratios are fun for scientists to talk about, but clinically, they are more or less irrelevant and not very useful and they are kind of scary at times. You tell a physician that you have an M/P ratio of three or four or six, oh, they're not going to use that drug. But the reality is, if there is nothing in the plasma, there is nothing in the milk.

Most of the rest of the drugs in this field simply diffuse by equilibrium. They are pushed into the milk compartment and they diffuse in milk and they also diffuse out. They come in and out of milk. There is always this equilibrium between these two compartments. There me be a high equilibrium with drugs that are very lipiphilic and like to concentrate in milk or it may be a low equilibrium in drugs that are very polar. And I'll show you some classic examples of that.

So there is this beautiful equilibrium. Don't always assume just because it gets in the milk it stays there. It doesn't. It comes out. There is this in and out production of milk. It goes in and out and it simply follows the plasma compartment.

So, drugs always establish this variable equilibrium. Variable means it goes one way and it's always determined by the plasma compartment. It always is in some sort of equilibrium with the plasma. It goes in to

milk and then it also goes back out. Constantly in and out of milk. The only exceptions of those are a few drugs, as I said, that are actually transported by membrane transport.

High plasma levels lead to higher milk levels. That's almost uniform. I didn't say high. I said higher. This is a very important term because we do know that as the plasma levels start to peak, then the milk levels generally peak as well. They both simply correspond quite closely together.

And let me show you some examples here. We've already talked about the drugs that exit the milk compartment.

This is a classic study done by Ken Ilett and Jonathan Rampono and this is citalopram levels in human milk. This drug has a milk/plasma ratio of two, twice as much in the milk as in the plasma. But notice how the two curves are absolutely parallel. We see this with many psychotherapeutic drugs

that have a high lipid solubility. They generally have a lower molecular weight. They like to go into the blood-brain barrier. They like to go into milk as well. And so you see this beautiful similarity. These two curves are basically parallel.

Now, this is nice. And this is why we say that the plasma compartment often correlates to the milk compartment, but it doesn't always work. Now, this is mislabeled. It's labeled correctly here, but it's mislabeled in your handout. This is a study I did with metformin, Ken Ilett, Peter Hartmann and I did with metformin. And basically, metformin levels were basically static or just about flat in milk. They simply don't go up. And so this is a classic illustration of drug that is quite polar. It's rather small in molecular weight but still very polar. So it's virtually excluded from the milk compartment. It's not very lipid soluble. So, therefore, it doesn't like milk. It rises

in the plasma and then it drops.

Now, this is a classic flaw in milk/plasma concept. What is the milk/plasma right here? It's virtually one. Right? One to 1.5. What is the milk/plasma rate here four hours? It's what, about 0.5 or a half or less. Milk/plasmas change according to the two curves. Milk/plasmas work fine with psychotherapeutic drugs that have parallel curves. They don't work at all with drugs like this. And, ladies and gentlemen, this is the majority of drugs like this. They don't have parallel curves. They have dissimilar curves.

So, any drugs, the penicillins, the cephalosporins, any drugs that are polar and have rather larger molecular weights, this is the kind of curves you are going to see. So, I rather urge you to ignore milk/plasma ratios. They are scientifically fun but clinically irrelevant, for the most part.

Size exclusion really does matter.

Anything much larger than about 800 daltons simply doesn't enter milk in clinically relevant levels. We have known that for a long time. So, there is a cutoff rate here, about 800. Anything much larger simply is excluded. We have looked at large molecular weight products like heparin products. The low molecular weight heparin products are still 2,000 to 6,000 daltons and they don't get into milk in clinically relevant amounts.

But when you get into the range of 200 and 300, like most of the amphetamine families, 250 like lithium, that is even much less than that, less than 100, lithium levels are sky high. The relative infant dose 56 percent. So, molecular weight is really important. Real small, milk levels are going to be much higher.

Protein binding. We've always known that protein binding was quite important because if it stays in the plasma compartment, it doesn't get in the milk compartment. It's

just that simple. Warfarin sodium is the classic example here, 99.9 percent protein bound. It stays in the plasma and never gets in milk. The opposite, lithium, zero percent protein binding, 56 percent of it gets into the milk compartment.

pKa has always been kind of nice. We don't use it too much because, for the most part, you look these up and they're hard to find in pKa's. But basically, what the pKa means is that at various pH's it has different sort of a three-dimensional structure. If you have a pKa that is rather high, like 8.5 or something like that, it comes into the milk compartment and then it take a three dimensional change and it gets trapped. It can't get out of the milk compartment. Because it becomes much more polar, it stays in there and it will not exit out. So drugs with higher pKa's in the eight range generally have slightly higher levels in milk. We call that ion trapping.

The volume of distribution is always somewhat argued. I've looked at many of the drugs in my book, I've done some studies on those. And basically it looks like to me that the higher the volume of distribution, the lower the milk level. And the reason is, it's not in the plasma compartment. It's somewhere else. It's out in adipose tissue, it's in the liver, it's in muscle tissue, it's not in the plasma compartment. So, the higher the VD, it's my impression, the lower the milk level.

Lipid solubility. Obviously, the more lipid soluble, the more you're going to find in milk. And that goes right along with psychotherapeutic drugs. They are much more lipid soluble. Therefore, their levels in the brain are higher, their levels in milk are higher.

The higher the level in the plasma, the more you are going to see in milk. It's just a linear function, almost. Almost always. And therefore, the lower, the less

you are going to see in milk. So, we like to choose those drugs that produce low plasma levels. Fluticasone, budesonide that are used in inhaled preparations produce virtually no plasma levels, because they are trapped in the lung.

Other drugs like the topical preparations that are used all the time like hydrocortisone topically, many of those the transcutaneous absorption is nil to minimal to nil. Therefore, no plasma levels, no milk levels. Very very simple.

The transport process. As I said, there is only about five drugs that we really know that have transport processes. The only one that is really clinically relevant, I think, is iodine. That is the one that is somewhat scary.

Oral bioavailability is really really important. Now, the reality is, and I have looked at this, we don't know much about oral bioavailability in infants. We think it's

somewhat similar, but we really don't have many papers out on it. And I've scratched around and looked everywhere to try to find something about oral bioavailability. We think it's somewhat similar.

We think that, nevertheless, the hepatic uptake from the portal circulation is quite similar to that of an adult. The portal, the uptake in the liver for morphine is quite similar in infants. And that is why that only about 26 percent of the oral preparation of morphine is absorbed. That is why their doses are so much higher orally. And that is why morphine, the studies all show morphine in breastfeeding situation is the ideal analgesic, simply because first-pass uptake is so high. So, drugs that have high first-pass uptake generally have low plasma levels and also, particularly in breastfed infants, they're not going to pick the drug up very well. Drugs that are large in molecular weight like heparin, large molecular weight

peptides and proteins, are simply going to be digested in the GI tract.

Now, it is true, that some of these drugs do get stuck in the GI tract and cause sequela. Classic example, some of the antibiotics. We do know you can get diaper rashes. We do know you can get overgrowth of bacteria and you can get diarrhea from some of the antibiotics when they are getting administered. There is one classic study out there done with about a thousand patients and they found an incidence of about 11 percent of breastfed babies exposed to antibiotics had some incidence of diarrhea. Not really bad, but some degree of diarrhea.

So, we do know that some of these things can cause GI tract sequela, because they are sequestered in the gut.

The tetracyclines, we have known for a long time, are poorly absorbed simply because they chelate with calcium. That is not true of doxycycline. It's absorption is

only delayed, not inhibited like with the tetracyclines.

So, many other products like the proton pump inhibitors, all the PPIs have a half life of about two minutes at a pH less than four. So they don't last very long in the GI tract, even of an infant.

There is a lot of controversy about the galactagogues right now. There is a lot of data out there on these products. We know that galactagogues primarily work by stimulating prolactin production. Prolactin production is very very important for maintaining milk synthesis. We know you need to have so much, somewhere between 60, as Dr. Lawrence's graph shows, somewhere above 60 nanograms per mil is required to maintain milk synthesis. It is interesting, you can make just as much milk at 200 nanograms as you can at six months at 60 nanograms.

So, prolactin doesn't pharmacologically stimulate milk production,

unless you drop down below the 50 range. When you get down below the 50 range, then when you give some of these drugs like domperidone and metoclopramide, what you see is this profound increase in prolactin and milk synthesis comes back.

So, it works great in women that have hypoprolactinemia. It does not work in women who already have hyperprolactinemia. So it's a very important little subtle distinction there.

The two drugs that are used are metoclopramide used in this country. The problem with metoclopramide is that it does pass through the blood-brain barrier. It can cause extrapyramidal symptoms. We have had a stroke reported with it. It causes frank depression in a large number of patients. It is not the preferred drug to use. And it's simply because everyone I have ever seen on it eventually will have some degree of depression with it. So, real significant depression.

Domperidone is the controversial one. And I know the Food and Drug Administration has a black box warning on it. I'm sorry, I don't agree with that. Domperidone is used in 88 countries in the world. It's a beautiful gastrokinetic drug. It's a dopamine antagonist. And the beauty of this drug is that it does not pass the blood-brain barrier. You don't get it into the brain at all. It's a nice gastrokinetic and even the gastroenterologists in this country, I think have a compassionate use exemption now to use it in various cases of GI problems.

Domperidone, though, is not available in the United States. It's used in all the rest of the world to stimulate milk production. It is a HERG receptor antagonist. There is not doubt about that. But in the clinical ranges we use it in, in 10 to 20 milligrams QID, we have not had any reported cases that I have seen of arrhythmias in mothers associated with that.

The old studies that were done with domperidone back in the '80's, '70's and '80's were done in patients post-cancer chemotherapy. They were already hypokalemic. They were in the one to two range. So they were already hypokalemic and that's probably why we saw arrhythmias in some of those patients on domperidone.

These drugs, again, only work if your prolactin levels are low. And if you just remember Dr. Lawrence's beautiful graph there. If you're down in the 50 range or lower, like I had an incident last week where one of our OB/GYN residents, her prolactin level was ten. So, we got her some domperidone and it bounced way back up to about 100 and within three days, her milk supply was completely back.

So again, think of that range, 50 to 10. Normal range for a female ranges from 10 to 20, a male is about 5 to 7. So the problem is in that 50 range.

Drugs that are safe to use are generally the antibiotics. Most of the anti-hypertensions are probably compatible with breastfeeding, the calcium channel blockers. The beta blockers, there are a couple you need to be careful with. ACE albuterol and atenolol have both been associated with floppy babies and poor feeding and respiration, so be kind of careful with the beta blockers.

ACE inhibitors are fine. I do not recommend them in premature babies because the nephrons in the kidneys are not yet complete. Aldomet, hydralazine is fine. Radiocontrast agents are iodinated, true, but the iodine is covalently bound to the benzine ring. It doesn't come off. And so the amount of iodine present in a radiocontrast agent is high but the releasable iodine is almost nil, like 0.1 percent actually comes off the benzine ring. That's why the half life is, on most of those agents, is about 50 minutes. It's gone. It's

urinated out very very quickly.

The American College of radiology put out a position paper. They said it's fine if you want to breastfeed following the use of radiocontrast agents. Again, almost all of them have very brief half lives.

Radioisotopes a little bit more controversial. I have actually studied these quite closely and I can tell you right now, there are only five papers in the world's literature that really look over and look at the breast milk levels of many of these drugs and make recommendations. I took those five papers and made a table in my book.

I think you need to be cautions. There are some, the radioactive iodine preparations, you shouldn't be breastfeeding with those, unless you wait for a long time. Many of the others, the technetium products are quite safe. A six hour half life. Again, watch the half life on those products and you can breastfeed quite adequately.

And so now, we do have some relatively decent recommendations on the use of radioisotopes. But almost always, you need to wait a little while following their use.

Analgesics, hydrocodone and morphine are the classic ones that I really suggest. Codeine, you've got to be a little careful. Gideon Koren published a beautiful little case study of a mother that was a hypermetabolizer of codeine. The tragedy in that case was that that baby was seen several times by a pediatrician and it was never caught. That's the tragedy in that case.

Again, you may find patients that are hypermetabolizers. You're going to find a subset of patients that tell you that codeine doesn't work. And that's simply because they are patients that don't have the enzyme system to break codeine down to morphine.

So codeine is all right, as long as you are careful with it, but hydrocodone and morphine are probably the better choices.

NSAIDs. NSAIDs are just fine as long as you don't overdo them for too long. We do have some case reports of Aleve after two weeks of time causing watery diarrhea in children. So, NSAIDs are just fine, short-term. Ibuprofen, a beautiful product. It hardly even transfers into milk at all. Extraordinarily low levels. So it's an ideal product.

Antidepressants, it's interesting that of all the families of drugs in this field, we have more studies on the antidepressants and the psychotherapeutic drugs than any other family of drugs. And that includes penicillin, cephalosporins, all of these. We have more studies. Like I said, with sertraline alone, more than 54 patients, there are more than 40 or 50 patients with Prozac. We have in the 20 patient range, 25 patients with Paxil. Lots and lots of mother-baby studies that have been done with the antidepressants. We know pretty accurately

how much transfers to the baby with the antidepressants.

We also know, with some degree of certainty that the long term outcome in those babies is fine. It's not been well described at this point, but I think we're feeling better about the long-term outcome in those breastfed babies. We do know that untreated depression is very very severe on infants. The speech and language skills at one year of age of infants born and raised by depressed women it not good. Bailey scores are delayed in those infants. So, the sequela from not treating is horrible. So you've got to treat these moms.

Drugs to avoid. The ergot alkaloids are classic ones here. The ergo alkaloids are all well-known to suppress prolactin secretion. Anything that will bother prolactin secretion will affect milk production.

Pseudoephedrine. This is a study

that Ken Ilett and Peter Hartmann and I did with pseudoephed. We found that in certain mothers in late-stage lactation it drops milk synthesis. We don't have the slightest idea how it does this. We don't know.

Cancer chemotherapeutic agents. You've have to be really careful with these. And generally, I recommend five to seven half lives. You wait five to seven half lives to make sure that you've gotten rid of all of those. And that's hard to do with some of these that have huge volumes of distribution, like doxorubicin and things like that.

Methotrexate. I'm not a big fan of Methotrexate because we have some kinetic studies showing that it seems to concentrate in the enterocytes and GI tract of babies, as much as ten-fold. And I don't particularly like Methotrexate nor recommend its use in breastfeeding moms.

Radioactive iodine products, do not use those. Estrogens. Estrogens we know

clinically and anecdotally are nasty for breastfeeding. Almost invariably, they will suppress milk production. I did see a nice little study done out of -- I was a reviewer, so I can't tell you who did it and I never did find it in the literature afterwards, so I guess it was rejected. But it was a beautiful study that showed mothers placed on estrogen-containing birth control pills, within about two months, none of them were breastfeeding. So anyway, estrogens, I really hate estrogens in breastfeeding moms.

Progesterone within the first 48 hours I think is hazardous because we all know that progestins suppress lactation early, early, early within the first 48 hours to first 72 hours. And then interestingly, by the end of a week or two, all of the progesterone receptors are gone. So that's why, in a week or two, or three weeks, most women do just fine with progesterone products because those receptors disappear from the

breast.

Chronic use of tetracyclines, I generally suggest three weeks and no more with tetracyclines.

Study design, if you can do it, do it at study state, that's a great idea if you can find those moms that are taking it. Many of my studies have been on rather rare drugs and I found them through my website. I have a registry on there that women can come on and I'll put drugs that I am interested in and if they register then I can call them on the phone. I have an IRB protocol where I call them. I can consent them on the phone. I send them very detailed outlines on how they are to produce the milk samples, how they are supposed to pump at exactly the right time intervals to collect milk samples and that's how I have published five or six studies on rather rarely used drugs. Ritalin, dextroamphetamine, and certain other drugs.

I'm getting ready to publish some

data on Betaseron, the beta interferons that we just finished the assay on those.

Choose exclusively breastfeeding moms, if you can. And if you can, try to do it like between one and six months. By the time you get to six months, babies start to go on oral foods, other kinds of foods. Milk synthesis starts to drop a little bit. And so it becomes a little bit questionable. I often sometimes have mothers who want to give me milk samples and they are 14, 16, 18 months postpartum.

I even saw a study not too long ago where the mother had stopped breastfeeding. She was about 20 months postpartum, she had stopped breastfeeding, and two months later she still had a little bit of milk so they pumped her milk and did a drug study on that because she was taking the drug. That's ludicrous. Absolutely, ludicrous. So, let's do this right.

Fore and hind milk samples, all

right. Now, I will admit, the way I do all my studies is I simply, I pump the mother completely. I put the two samples, left and right together, I take my sample out, I give the milk back to the mom, she can put it in a bottle and feed her baby. I know that it is a little bit interruptive. It does cause -- because the moms I generally bring in all have babies that will accept a bottle. Some babies won't. My granddaughter wouldn't accept a bottle. So, if you can find those moms whose babies will take bottles, then I suggest you completely empty the milk.

Now, I know Ken Ilett has suggested that you can take a milk sample before and a milk sample afterwards. And then you can add those two together and you get fore and hind levels. Add those two together and you get a relatively close estimate of what the whole sample is. That's probably accurate. That's probably all right to do. You can do that if you want to.

But that's a little bit more time consuming. The mother has to know how to extract the milk from her breast manually. So it's a little bit more difficult. I always simply pump the breast so there is no question you have got the whole milk sample and you have the right lipid content and you're not worried about fore/hind milk, lipid content in the two.

The ideal method I suggest is simply, pump both the breasts. You can pump them individually, do them individually, which I have done, or you can just combine the two and make one level.

Patient access. In the laboratory is ideal. But for really, really rarely used drugs, remote collection is certainly possible. It works fine. And you can generally trust most of these moms to take a sample at one hours, two hours, six hours, 24 hours. They simply pump. They put it into a tube. They freeze it. They send it to you.

It works fine. I think it works fine. And let's face it, there are not a lot of mothers in America that are breastfeeding and taking Ritalin. They are just not.

And so for these rarely used drugs -- or Avoenex, Betaseron, beta interferons for use for multiple sclerosis. You don't find a lot of moms taking those. So, for those rarely used drugs, I think remote access by some method where you collect these moms, you look at the stage of lactation they are in, etcetera, and you collect the right group, I think you can do it remotely. And IRBs will allow you to do it. Mine does.

Design. You started to calculate the area in the curve. If there is one point I really want to make, AUC is the only way because you want to know what the baby gets throughout the dosing interval. You want to know what the baby gets not just at peak. The peak gives you a super high level and, therefore, erroneous level. You want to know

what the baby gets all day. And therefore, you get that with area under curve calculations.

And if you have metabolites, like you do active metabolites, you need to do those. Particularly, Ken Ilett's study with Prozac, he did not only fluoxetine, but norfluoxetine, the active metabolite. And so with other drugs like Demerol, you'd want to study Demerol meperidine and normeperidine, which has a much longer half life, but it's active. So, active metabolites are really important. I'm not sure how important inactive metabolites are.

Avoid single point peak determinations. I hate these studies, but probably the majority of the literature is with peak studies. It's not a very good way to do it. You never know when your peak is going to be.

The way I do it is I basically look up the pharmacokinetics in the adult patient,

in the mother. I look those up and I look at the curves. And I select points so that I know that I generally get within a peak and then I go on average two to three half lives, if I can, to collect the sample in that patient. So, replicate samples are critical for doing this. So, two to three half lives. You may not be able to do this with replica dosing, but if you can, that's a really nice way to do it.

Maternal and infant samples are wonderful to have, but many mothers refuse. I would say more than half my moms refuse. They simply don't want their babies stuck. It's nice. And that's the same thing that Ken has found in many of his studies in Australia. About a third to a half the mothers will permit their babies to undergo phlebotomy. And so that's always a problem. It gives you nice data.

Some of the data on sertraline that we have and Paxil show us that the plasma

levels in infants are virtually undetectable. Great data to have. It's great to know that what is getting to the infant is minuscule to nil.

Calculating the dose. There are two ways to calculate the dose, the absolute infant dose. That is, how many units per mil of milk. If I come up to you and said there is 50 micrograms per liter of milk, that may not tell you a lot because you don't know what the mom is taking. You really don't know what her dose is. You don't necessarily know how much milk is being transferred to the infant. And so, it's a little confusing to clinicians out there. I always use the relative infant dose and all my colleagues now do this as well. We kind of like this because it tells you a percent of what the mom's dose gets to the baby. So if I tell you ten percent, that means ten percent of the mother's dose gets to the infant. It gives you a feeling for percent.

And so we have, for the last 10 or 15 years, after Bennett published that anything less than ten percent is probably safe, that was just sort of anecdotally out there. There is no really research base upon which that was determined. But interestingly, through the years, it has held up quite well.

Prozac is in the seven to nine percent. Sertraline is one to two percent. There are very few other drugs that are much higher. Certainly lithium is one that is 56 percent. And so, the relative infant dose is really useful. And it's the technique and the term that I always use when I talk to clinicians. Because it gives you a feeling if you know that only one percent of penicillin is getting to a baby, it gives you a good warm feeling.

If possible, do some sort of evaluation of infant outcome. This is nice. In my studies now, we generally have a little sheet that we always as, the mom to fill out.

Does your baby have any higher rate of diarrhea when you went on this drug? We always try to evaluate the outcome. It would be nice to do a Bailey or some sort of neurologic outcome in infants who are exposed to psychotherapeutic drugs. And so we generally try to do some sort of an outcome on infants, just to get a better feeling for how the baby is doing.

There are some mathematical algorithms. Evan Begg from New Zealand published one. Shino Ito and Gideon Koren from Canada published mathematical calculations. You take the pKa, the volume of distribution, et cetera. And they are reasonably accurate but there is nothing better than a human study. There is really nothing better than a human study.

Rodent studies are absolutely worthless. Absolutely worthless. Every one I have ever seen has a milk/plasma ratio of at least one to two. And so therefore, my take

on this is that the alveolar system in rodents is porous. Drugs can get into milk avidly. But not only that, the albumen concentration in rodent milk is much higher than albumen in human. Albumen levels in milk, human milks, are like one-hundredth that of the plasma level in mothers.

So albumen levels in humans are very very low. The high albumen content in rodent probably leads to high milk/plasma ratios, which comes back to the point that these milk/plasma ratios are not good to use.

References. Ken Ilett just wrote a chapter in my new textbook on study design and data analysis. It's outstanding. If you really want to know how to do this, this is an outstanding chapter.

Evan Begg has done some great chapters and some studies on drugs in human milk and time and how to do these things.

So, basically, that's my take on them. And if I can advise you to do

something, it's to do away with milk/plasma ratios. Don't use them. They are a waste of time because you don't know when that was determined. You don't know when it was -- if it is accurate or not. Milk/plasma ratios change over the time course, they do. So they are not accurate to use.

Use area under the curve studies. Multiple point curve studies, if you can. Those are, by far, the most accurate. It gives you a good feeling for what the daily dose of the drug in the infant may be.

As far as choosing drugs to use, I want to put a little point in here. You never ever know what is going to be used. And every other year when I put my book together, one of the things I do is I look at all the new drugs and try to choose those to put in my book and I'm always wrong. I'll get my new book out and within a week, I'll get a call. I can remember I got a call about Viagra after I had not put it in my book. And a couple of years

ago, I decided not to put the five alpha-reductase inhibitors used for prostate hypertrophy in. And not a month my book came out, someone started calling me about that. They're using that to suppress testosterone levels in certain women. You never know what is going to end up in a postpartum breastfeeding mother. So it's a difficult one.

So, thank you for your time.

CHAIR RAPPLEY: Thank you very much, Dr. Hale. We're into our break time. So I'm going to ask the committee, I think we should take a break, if acceptable to you, that will push our questions then into the afternoon. Are people okay with that?

(No audible response.)

CHAIR RAPPLEY: Okay. So, we'll resume here at 10:40 for Dr. Nelson's presentation. Thank you.

(Whereupon, the meeting went off the record at 10:27 a.m. and went back on the

record at 10:44 a.m.)

CHAIR RAPPLEY: Okay, I think we can get started. Dr. Nelson?

DR. NELSON: Good morning. What I'm going to present to you is some material reflecting on the ethical design and conduct of clinical lactation studies. And I'll be basically walking you through the section that Karen mentioned is a new section in the Guidance that is being developed.

So I'd like to start first with the definition of a clinical investigation. It means any experiment in which a drug is administered or dispensed to or used involving one or more human subjects. I think that's important because many people think of research of is what is regulated, which is generalizable knowledge. In the FDA, you give one product to one person, it's regulated, even if you're not generating generalizable knowledge.

For the purposes of this part, and

I'm quoting from the IND section, an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice. So if what you are doing is not medical practice, and you are administering a product, it is in fact a clinical investigation, even if you only do it once.

Now, who are the subjects? Now, in addition to the lactating women, the breastfeeding infant, as a potential recipient of the investigational drug, is considered a subject of a clinical lactation study. And as such, the additional protections for children involve the subjects of research, which is 21 C.F.R. 50 Subpart D apply. And basically, what I'm going to do is walk you through an analysis of clinical lactation studies on the assumption that subpart D applies and basically see what are the implications of that for how those studies should be designed.

Now, there is a key distinction and

that is, whether or not the drug is being administered for a maternal condition that warrants treatment. And this would be two subcategories within that distinction. One would be if in fact it is an investigational product pre-marketing. In other words, that woman is being enrolled in an investigational trial for her own potential direct benefit. Or the other would be the clinical or perhaps research use of a marketed product. And the other question is whether or not the lactating woman is a healthy volunteer, what are the issues there? In other words, there is no maternal condition.

Now, before I go through the different subcategories that I have then created based on those distinctions, let me just give you a brief reminder of what subpart D involves.

Now, the way I approach this is two-fold. The important distinction here is whether or not the research offers the

pediatric subject the prospect of direct benefit. If the answer there is no, then the risk needs to be restricted to either minimal risk or a minor increase over minimal risk, and I'll show you the regulatory language for those categories. If the answer is yes, in other words, the research does offer the prospect of direct benefit to the pediatric subject, in this case, it would be to the infant, then the allowable risk exposure can be more than a minor increase over minimal risk. And I'll just show you briefly these categories so you have an idea of how these categories then are framing the situations of study design that I then will present.

So, if you analyze it this way, basically you've got a two by two table. You can=t do a chi squared on this though, Tooley. Sorry. But you basically have risk here, minimal risk, greater than minimal risk, and whether or not there is direct benefit or no direct benefit. And these just happen to be

the regulatory categories. So as you will see, basically, minimal risk is independent of whether or not there is direct benefit or not. If you have something that is minimal risk, you don't have to decide whether or not there is direct benefit. This is the definition of minimal risk. Basically, the risk involved is no different than either the daily life of that particular pediatric subject, in this case, infant, or what would be considered a routine physical or psychological examinations or tests.

That's the definition. I'm not going to go into tall the issues around these definitions. That would be a whole other hour of conversation. So, that's minimal risk.

The next here is direct benefit greater than minimal risk. This is the language. The risk has to be justified by anticipated benefit. So there is a risk benefit calculus. And what is also important is that risk and benefit of that particular

trial must be comparable to alternatives. This category really is not what we are talking about here, although one could argue the risk of removing of breastfeeding might be evaluated here. But this category really doesn't fit into the future conversation. What we would be looking at is this other category which is greater than minimal risk, no direct benefit. And this category is known as the minor increase over minimal risk. And what I would like to draw your attention to here is with this level of risk, there needs to be a disorder or condition with that particular infant that you are in fact studying. So you will see that the definition of condition or how we understand condition may then play into our analysis of these types of cases.

So that is a very brief run through of these three categories. I might add that there is a fourth category which this Committee is familiar with, because you are in

fact the ones who would see it if it came, and that is if it gets referred for federal review because it can't be approved by local IRB. Try as I could to imagine circumstances under which a clinical lactation study might be referred that couldn't otherwise be done, I couldn't come up with any. So I'm not going to offer any thoughts about what such a federal review might look like. But that is available.

Now, the other important concept, and I think this is often underused by IRBs, is this notion of incremental research risk. The idea here is that if you are looking at the risks of the research, that is what you need to evaluate relative to these categories. In other words, what is the risk of the research to that infant? And this will have an impact when you look at the research on a clinical lactation study in the context of a mother who is in fact receiving the drug for maternal indications. So that incremental research

risk will be an important concept in that context.

So, there are three situations I am going to talk about. The first is a lactating woman, women who are continuing drug treatment for a maternal condition or beginning a new drug treatment for a maternal condition. That's category one that I will talk about.

Category two, the lactating mother is a healthy volunteer who continues breastfeeding her infant. Number three, the lactating mother is a healthy volunteer who stops breastfeeding or pumps and discards her milk during the period of drug exposure.

So those are the three sort of scenarios that I would like to run through, as what I would consider the three circumstances under which a clinical lactation study would be considered to outline the sort of ethical issues that arise in each one of these circumstances.

So let's deal with the first one.

Now, first of all, as has been pointed out, many women with chronic medical conditions continue required drug treatment throughout pregnancy. So that's a fact. Their fetuses are exposed to a higher transplacental doses of maternal medication during gestation than they will experience as breastfeeding infants following delivery, if their mothers choose to breastfeed. In these situations, the benefits of breastfeeding may often outweigh the risks of continued lower dose exposure to a drug that the infant was already exposed to during gestation.

Now, that is a judgment call. One of the questions is what is the data behind that judgment call? But the point is, there is a clinical decision that is made relative to the risk and benefit of continuing breastfeeding in the context of the ongoing need of that woman for her medical treatment.

So the decision then to begin drug treatment for maternal condition may also be a

difficult one for a woman who wants to continue breastfeeding. So, if there is an acute condition that comes up, that's the kind of conversation that one would then have between her clinician, hopefully who is informed, and the woman who wants to breastfeed around the risks-benefits of the medication for her or going untreated versus treating her condition and the risks of ongoing breastfeeding for her infant. And the point is, that this is a difficult decision and that clinical lactation studies, as already have been pointed out, are important to that kind of decision-making process, so that there can be better judgments made around this tradeoff.

One question, for example, if you have a couple of different drugs, one of which information is known, there may be alternative treatments available with a lower documented transmission into breast milk or perhaps a better safety profile. Even if you don't know

what the transmission might be, if there is two comparable drugs, one may have a better safety profile because it has been studied in pediatrics, perhaps.

So those are the kinds of issues that would need to be addressed. My point is, that that is a clinical decision that is made. And the key issue, as I go forward, will be the extent to which the decision then to study the transmission of drug in breast milk here is separate and needs to be kept separate from this clinical decision.

So basically, after the lactating woman begins a clinically indicated medication, it is reasonable to approach her about the possibility of participating in a clinical lactation study of that medication. Now, the important thing here though is there is the health benefit of continued breastfeeding. So you wouldn't want the decision to enroll in a clinical investigation, necessarily, to interfere with

the assessment of the risks and benefits of breastfeeding her infant.

But on the other hand, it's entirely possible that the clinician didn't adequately inform the woman of the risks and benefits around that medication. It's entirely possible that the informed consent process on the part of the researcher may in fact be a more appropriate discussion of what is known or what is not known about that medication, raising the question about what happens then, if in fact the woman decides to change her mind about breastfeeding during the course of a clinical lactation informed consent process. And under those circumstances, the thought there is that basically this would need to be referred back to the clinician.

So the idea here is you really wouldn't want to approach such a woman unless the continued treatment, if you will, is essential.

But let me back up a second. The

other circumstance would be if there is a clinical investigation for that pregnant woman. You wouldn't want to approach a breastfeeding woman to involve herself in a clinical investigation, unless that drug offers appropriate benefits to her own health and well-being. In other words, if you are going to basically interfere with the decision to breastfeed, what I'm talking about is basically, let's say, a pre-market new molecular entity that was important to that woman's health, the odds are, she would then stop breastfeeding in order to do that. So those circumstances may be reasonable to approach her. But if she is simply being approached because she is the available individual who happens to be breastfeeding for a clinical lactation study, that would raise a whole host of different issues. Under this circumstance, it would be prudent, perhaps, for the breastfeeding mother to stop breastfeeding and this is a situation where,

in fact, if you were doing a study of a new molecular entity, doing a clinical lactation study as part of that initial approach, likely wouldn't be prudent, and would likely expose that infant to excessive risk.

Now, I got a little bit ahead of myself. Here is the point about the informed consent. You certainly would want there to be adequate informed consent about that clinical lactation study. And it is entirely possible that the woman who has chosen to continue breastfeeding, after that conversation with her clinician, then receives information that would be perceived as new.

Now, I don't want to suggest that clinicians did not give that information to the breastfeeding woman. However, in the context of another conversation about the research consent, it's entirely possible that that information may be perceived as new, even if it had been discussed before although it might well be new.

It is then possible that this would lead to a reassessment on the part of the woman who is breastfeeding of whether or not she does or does not want to continue breastfeeding. My recommendation there is that basically the researcher should say, well, I would suggest you talk about that with your clinician, given this new information. And then once you have made a decision about what you truly want to do, come back and talk to me again, rather than get into the situation where the researcher becomes the individual engaged in that clinical decision. Now I realize that sometimes that may be the same person, but often that is not.

I might add that I suspect that if you are recruiting through a website, that arm's length exchange likely would keep separate the clinical decision-making from the research decision, although it is possible that you may have information on your website, I haven't looked at it, Dr. Hale, that in fact

informs women before they get to the point where they may want to decide to participate in a clinical lactation study.

Now, what are the implications? To the extent that you kept the clinical decision to continue the drug separate from the research decision, the risks of the drug exposure to the infant does not need to be considered under subpart D. Why is that? We're talking about the incremental research risk. But the key there is this argument hinges on the extent to which the woman's decision to participate in the research is really separate from the decision to take the drug. And there may be circumstances where that is true and there may be circumstances where that is something that would be subject to debate. So that is the key distinction.

The research risk then may not include the drug exposure. There are other things, of course, one would need to evaluate in that risk. The blood testing, even though

50 percent of mothers might not want their infant having a blood test, certainly that would be considered minimal risk and it's reasonable to ask.

And the other thing is you must present no more than a minor increase over minimal risk. What I would argue is given the clinical decision of a lactating woman to take a drug for a maternal condition, given that decision, I think you could consider that infant at risk of drug exposure. You could then consider that infant to have a condition.

Now, in this case, if all you are doing is a blood test, that's probably an unnecessary distinction because that would be viewed as minimal risk. Where this becomes important is, I think, in a situation where you are trying to recruit a healthy volunteer, you can't consider that infant to be at risk to have a condition. The only reason that infant is at risk is because you are trying to recruit that mother to be in a clinical

lactation study. This infant who is going to get that drug exposure anyway could be viewed as at risk in having a condition. And that is the distinction there.

So, let's talk a little bit about the lactating mother who is a healthy volunteer who continues breastfeeding her infant. Now here, the exposure of the breastfeeding infant to the drug is then a clinical investigation. And I would argue that, in fact, it would have to be approvable under subpart D, the drug exposure. Absent direct benefit to the breastfeeding infant, it's hard to imagine why you would choose the mother as your formulation and why you would necessarily decide to deliver your drug in that method. Maybe there would be some creative way to do that at some point in the future, but I couldn't come up with one.

You would then have to restrict it to either minimal risk or no more than a minor increase over minimal risk. I would argue

that the exposure of the breastfeeding infant to any drug administered, and if you don't know how much is in there, you have to presume that the infant is exposed, would present more than minimal risk. So, therefore, you need a disorder or condition, all right, even if you thought you had a sufficient safety profile to be no more than a minor increase over minimal risk. Probably, you would have to be studying a drug that already has a fairly good post-marketing safety profile to even consider that the drug administration fits into that risk category. But let's imagine you do. You need a condition and the bottom line is, I would argue, you don't even have a condition. So, the use of a healthy lactating woman who intends to keep breastfeeding is bottom line, not approvable under subpart D.

Now, here is the only recommendation, if you will, about how to define condition. It comes from an Institute of Medicine report of which many of you are familiar with, where

it talks about a specific set of criteria that negatively affect children's health or well-being or increase their risk of developing a health problem in the future. So again, I would suggest that if you are the infant who is breastfeeding of a mother who is taking a drug for clinical indications, it's reasonable to consider that infant at risk.

But if you are only being placed at risk because someone has asked that mother to be in a research project, I would not consider that an appropriate definition of condition for the purpose of applying subpart D.

So let's then look at this third category. The lactating mother is a healthy volunteer who stops breastfeeding or pumps and discards her milk during the period of drug exposure. So if lactating women are asked to enroll at birth and again, this is in talking to other individuals, this is not my scientific area, but my impression is that there are both scientific reasons, as was

mentioned by Dr. Hale and as was taught to me in prior conversations, as well as practical obstacles to study participation, both to do milk, if you will, early, unless of course you have a need to study the first couple of days, as was pointed out in terms of medications that might be used in the peripartum period.

But if what you are looking for is well-established breast milk, the thought that someone who chooses to enroll at birth but then to stop breastfeeding, to then pump for three weeks until you get -- I can't imagine what kind of incentive you would need to want to do that. Anyway.

However, there are circumstances where a woman who is breastfeeding may decide independently to stop for either personal or medical reasons. And again, although this may raise practical difficulties of how you might identify such individuals and how you could be assured that you in your request for research participation are not, inadvertently,

undermining the benefits that we saw about breastfeeding. One could argue that, in fact, if you could find someone like that, if her decision was independent of your recruitment to enter into a research study, certainly at that point, the infant is not part of that equation. So that would be of someone who decides to stop breastfeeding.

The other approach here would be certainly if an infant -- and it may be on the next slide. So, here the decision to stop breastfeeding should not be affected in any way by the possibility of enrolling in a clinical investigation.

So, the bottom line, as you heard a lot about the health benefits of breastfeeding. If in fact stopping breastfeeding is because you have asked that woman to enroll in a clinical investigation, I would argue that is a bad thing to do. It shouldn't be done. It might be difficult to ensure that, but you could try to ensure that

that decision is not influenced. One could look at issues of financial incentives or other incentives to enroll and try to make sure that you are not making a project so attractive that you are in fact undermining what would otherwise be a woman's desire to continue breastfeeding.

I might point out that it's easy to say that in principle, I mean getting down to what that actually would mean in practice would require a lot more discussion.

Now, alternatively, a lactating mother could decide to pump and discard. And it was pointed out in Dr. Hale's, there are situations where breastfeeding women have already demonstrated that certainly short-term substitution of bottle feeding, which in my experience is usually the 2:00 a.m. bottle and the husband or another caregiver is the one getting up in the middle of the night to deliver that bottle, basically, if you have already demonstrated that that infant has no

problem going to bottle and back to breast, then one could argue that having a short period of time where you are pumping, sampling and then supplementing would not be an issue. But that requires demonstration.

So basically, let me just summarize with my conclusions and then I can entertain any clarifying questions and leave you plenty of time for discussion. A key consideration in evaluating the risk to which a breastfeeding infant may be exposed is whether the drug is being administered to a lactating woman to treat a maternal condition. So the degree to which you can keep the decision, clinical decision away from the research decision that basically there may be situations where studying that would be appropriate and the incremental risk would not be considered excessive from the standpoint of the pediatric research regulations.

So after a drug has been started or continued, there may be limited circumstances

where a clinical lactation study may be acceptable, following an independent decision by the lactating woman to continue breastfeeding. The degree to which you keep that decision separate basically means that really the risk to the infant is whatever sampling processes you have put into place, as well as whether your sampling process undermines the possibility of continuing to breastfeed.

And then finally, absent a maternal condition that warrants treatment, a clinical lactation study involving a healthy volunteer would only be acceptable if the breastfeeding infant will not be exposed to the drug.

And those basically would be the concluding statements on how you might design clinical lactation studies in the context of subpart D. So with that I, at the discretion of the Chair, can answer a couple of questions or you can --

CHAIR RAPPLEY: Thank you, Dr.

Nelson. Yes, I think we will open to questions. We have, actually, about 40 minutes for questions. So we could actually take questions for all of our presenters and then break at 11:50 for lunch, as scheduled.

Is that acceptable to those presenting?

CHAIR RAPPLEY: Okay. So our procedure here is if you signal me, or Dr. Pena, then we put you on a list so that we can move in an orderly fashion. So I see Dr. Fant and then Dr. Ward, Dr. Newman. I've got to write it down here.

Dr. Fant?

DR. FANT: Yes, I have a couple of questions. The first one, Skip, in your presentation, it was well organized and sort of set things out in an organized fashion for me, I appreciate that. But, the way things tend to happen in a practical sense, at least from my perspective is that the question comes up about the maternal intake of a particular

drug and whether or not that is going to be okay for the baby. And so, we generally don't have any information about it. So we sort of say, well, we don't know but usually it's okay. And we think the benefit of breastfeeding is so great that we really think that the risk is low. And the mother eventually makes the decision that is almost based on a, it's not truly an independent decision. It's one that is almost made with sort of an implied affirmation from the caregiver's part that it's probably going to be okay.

In the context of a clinical study, we sort of are putting forth more of a, well we really don't know, sense in the mind of the mother. And I'm just thinking, you know, we may have more situations where the mothers may be disinclined to either take the medication or disinclined to continue breastfeeding. And I just wanted to sort of get your thoughts about that. I'll leave it here, before I ask

my second question.

DR. NELSON: The notion of independence that I was alluding to is the degree to which the approach to the woman around a clinical lactation study is separate from the conversation with her clinician around the risks and benefits of that drug, both for her, and the risks of that drug to her infant in the context of continued breastfeeding. And so the easiest way is to say those should just be two different people and two different processes and that sort of thing.

One could imagine a circumstance where a woman is already inclined to continue breastfeeding, but might be then more favorably inclined to do that if there is a clinical lactation study to feel that she is contributing to the generation of knowledge as well. Now there, one could say sure it is then her altruistic motivation to contribute to knowledge part of that equation, is that

problematic? No, not necessarily. But if one is getting $400 to be in that study, and that is known at the time of the decision to continue breastfeeding, then that, I think, would raise some serious issues around the extent to which the decision to breastfeed is kept separate from the research decision.

Because the key issue in my mind is the drug exposure of the infant. If the drug exposure of the infant is driven by the research question, then that is a much different situation than if the drug exposure is generated by a clinical decision, even if not based on a lot of information. And keeping that separate is very important.

DR. FANT: Okay. One other quick question. Anybody can jump in on this, but it's one that just sort of came to my mind during the course of reviewing the material and listening to the talks today. Given the dynamic and developmental age-specific nature of the lactation process, the physiology, as

well as the developmental age-specific issues related to the babies themselves, what are the thoughts about lactation studies that are targeted at different development ages?

For instance, we have a lot of 20, 23, 24 weekers who have been breastfed. Is that the same or studies done in post-term kid-mother pairs relevant to those pre-term kids? And if we do need to look at those developmental ages separately, are there any obvious breakpoints or ranges that sort of come to mind as being relevant?

DR. FEIBUS: This is Karen Feibus. One of the comments that we received on the draft lactation guidance brought up the issue of premature infants and the fact that milk composition may be different. And if you have thoughts about how we should consider the pre-term group of infants, we would actually appreciate that feedback. We weren't really able to find any information in the published arena that speaks to that issue about how to

approach getting clinical lactation study data from a pre-term group of mothers and infants. So we are still wrestling with that and haven't necessarily figured out exactly how to address it.

DR. WARD: Karen, can I just respond do that?

DR. FEIBUS: Sure.

DR. WARD: I think it's dependent upon the individual drug and its metabolic pathways. You know that there is a breakpoint in GFR around 32 to 34 weeks, at which point it accelerates after glomerulogenesis has ended. You know that CYP3A4 rises and has a sort of a complex interaction with 3A7. So I think it's dependent upon the individual drug as to which ages would need to be studied and their pathways elimination.

So and I would avoid generalizations, I think, about that. But it really is going to be pharmacologically dependent.

CHAIR RAPPLEY: Dr. Lawrence, did you

want to respond to that question?

DR. LAWRENCE: If I could, please. From a practical standpoint, we have dealt with this now for a long time and no drug decision is ever made without knowing the gestational age of the infant and the chronologic age. Because the answer does vary even in situations where we have quite a bit of information.

So let's say we have a drug about which we have some information, we think it is reasonably safe, we then have to factor in the gestational age and correct gestational age of the infant. So, it's always an issue. And you do that based on renal excretion, on hepatic metabolism, depending on what is going on with the drug, considering the blood-brain barrier, fat deposition, all of these things are part of that question every time you answer a question about is this drug safe.

CHAIR RAPPLEY: Any other response to Dr. Fant's question?

Okay, Dr. Ward, did you have another question?

DR. WARD: I have a couple of comments and some questions. Dr. Hale, your referred to the breast lactile as equivalent to a blood-brain barrier, which has generally been described as the P-glycoprotein efflux transmitter or the MDR transmitter. Do we have any evidence that there is a Pgp efflux transmitter transporter in the breasts?

DR. HALE: Not that I know of. Some people have published some papers on some of the transporters, influx and efflux transporters and there is very little known about it. We just really don't know. We know that there are about five or six drugs that are transported. Other than that, there are some suggestions that metformin, the reason we found such low levels of metformin is that there may indeed be an efflux transporter in certain tissues for metformin. But other than that, we really don't know.

DR. WARD: You made some very strong comments about milk/plasma ratios but I would, and I think the key concept is the differences in kinetics between the way the drug appears in the milk and the way the drug is appearing in the serum or plasma of the mother. And I would submit that the AUC in the milk and the mother would be a meaningful number, especially if it was done on a 24 hour milk collection, to help quantify exposure.

DR. HALE: That's true, you could do an AUC of milk/plasma ratio. The problem with that is you have got to do a lot of blood draws for that, to do that. And that's a little problematic in patients.

DR. WARD: Yes. There was something else and I forgot what it was.

DR. BIER: Can I just address that for a second?

CHAIR RAPPLEY: Sure.

DR. BIER: You know, it's very common today that you put a small indwelling catheter

in the arm and you go by every so often and take a little more blood out. It's not a lot of blood draws. It's one stick that stays in for a day. I mean, this is not a big issue.

DR. WARD: And we actually do that in infants for PK studies, not infrequently.

Oh, I know what I was going to comment about and that is that in the newborn ICU setting, it's not uncommon for the infant at birth to have some disorder that prevents oral feeding, you know, gastroschisis, omphalocele, any number of things. Yet moms who want to breastfeed are sort of dedicated to pumping at that time. And I think that's actually an opportunity that we're missing right now for looking at breast milk excretion of drugs.

DR. HALE: That's true. It's quite common. They do pump and store their milk a lot. And it's a good source of drug information. There's no doubt about that. But there again, you run into the point is how

typical is a premature mother's milk at that time interval and her rather lower milk production? How does that characterize a mother that is two months postpartum with a big healthy robust baby that's making 800 cc's a day? How do the two compare? And we don't know that answer.

DR. WARD: Well, I would submit that we have no business trying to extrapolate the studies in a premature baby shortly after birth to an older infant. We have to do the studies longitudinally at developmentally appropriate ages.

CHAIR RAPPLEY: Dr. Nelson, did you want to respond to that question?

DR. NELSON: Well, I just want to make a comment on the indwelling catheter. I think one of the issues that are often debated among research ethics folks is how long can you leave one in, relative to the risk category?

Yes, so but I think it certainly if

you are in a circumstance where the child has a condition, meaning the mother is already going to be taking a drug, then you can leave it in longer. That's the only point there because you have a higher risk category.

The other question, I only bring this up because I know your circumstance at Baylor, the other debate is the location. If for example, you have an indwelling catheter, likely it's going to be an inpatient location. If that infant is not otherwise being hospitalized, where you do that is an issue. And I know, for example, you have a very nice nutrition facility at Baylor that is not a hospital. I know that because in my former life, I was an IRB chair that required something similar so that it would not be seen as risky. So those are some of the complex issues that would have to be looked at.

DR. BIER: I wasn't pressing the issues that have to deal with minimizing things like infection and all that sort of

stuff, which any good investigator is going to do. I was really focusing, and we're not really talking about indwelling catheters that go up to the aorta, the vena cava, you know, we're talking about little things here that are in a vein, which are left in with any realistic type of routine cleanliness, have a risk in a day of essentially zero. But we're talking about ways of doing this, of getting integrated sampling, which is done all the time with virtually no grief or risk demonstrated.

CHAIR RAPPLEY: Dr. Lewis?

DR. LEWIS: Well that actually was something I just wanted to ask Dr. Nelson about. So is blood drawing and an indwelling catheter for a little while considered minimal risk? Because that doesn't seem like within the range of activities of a baby would normally have in daily life or with a physical examination.

DR. NELSON: The concept here is

equivalence of risk. And I think it's fair to say that a short indwelling catheter most commentators would think, you know, we're talking two or three hours, is relatively not an issue. And you know, it even gets complicated. If you're not a very good practitioner in putting in a line and it takes you eight sticks to get one in and were only going to draw four blood samples, that is sort of silly. So it gets into the expertise of the individual who is placing it, et cetera. So it's more complex.

Where it gets perhaps more variability is when you get out to the 24 hour range. There have been reviews at the federal level where that has felt not to be minimal risk. You know, so, but you can get, you probably get a fair amount of variability with the duration of that catheter. And you know, we could debate six hours.

But, yes, I think shorter fits within minimal risk. And one could argue that in

fact placing an indwelling catheter, if you can get in in two sticks and you're going to do six sticks otherwise, in fact minimizes risks and would be better off. So yes, it does, but it's a complex issue.

I mean, the neonates we started talking about are likely hospitalized as prematures. If you're doing a four-month-old that would be coming into a facility for the purpose of a study, which then raises other issues. That's all.

CHAIR RAPPLEY: Dr. Bier, did you have other, -- oh, I'm sorry. Did I cut you off?

DR. BIER: I had another question, but it's different from this question.

CHAIR RAPPLEY: All right. Go ahead. Okay, sorry.

DR. NEWMAN: These are for Dr. Hale. On one of the slides, actually what was on the slide was different than what was on the paper, so it looked like you added it. And I

just didn't understand why. On the slide that said drug study design, the paper says choose mothers at the same stage of lactation but on your slide you actually preferred exclusively breastfeeding mothers. And I didn't understand what difference it makes whether the mother is exclusively breastfeeding or why can't she also be -- if what we're doing is studying her milk, why does it matter if the baby is getting some formula?

DR. HALE: We generally prefer exclusively breastfeeding mothers because we know their milk volume is relatively high. The problem that we run into is those mothers that come in that are partially or largely formula feeding, then the milk supply may not be as robust.

And we also know that as mothers start to add more formula, then the breast becomes more porous, all those cells start to die off. It's called apoctosis. Sodium levels start to rise in milk and so the system

becomes more porous as they start to involute.

And so we always kind of prefer women in a robust, healthy, full phase of lactation, rather though than those that are starting to stop breastfeeding or adding more formula. Because every ounce of formula you add is one ounce of breast milk you do not make. And that kills all those cells off and the system is more porous.

We know this particularly in HIV, mothers that have HIV. Because now we suggest that they immediately stop breastfeeding at six months because as they start to involute, the HIV virus pours into milk at that stage. So, involution is really critical as far as the way the system is impermeable to drugs.

DR. NEWMAN: But I would say if the breast milk of partially breastfeeding women is different and more likely to include higher levels of drugs, because of what you described, that would be important to know. Because the vast majority of women who have a

six month old are not exclusively breastfeeding. The ones who are breastfeeding are not exclusively breastfeeding. And so we would get a misleading impression of the drug level in breast milk if we restricted the studies only to exclusively breastfeeding women.

DR. HALE: Not only that, but at the same time, remember, the dose you are getting from the volume is reduced. So the dose to the baby is actually less.

DR. NEWMAN: But we can, I mean, people can figure that out, --

DR. HALE: Yes.

DR. NEWMAN: -- if they know the volume of milk the baby is getting. But if the concentration is very different, I think you would want to have both sorts of women and maybe stratify and say, this is the concentration in women who exclusively breastfeed and this is the concentration if they are also bottle feeding.

CHAIR RAPPLEY: We have seven people waiting with questions. Are there comments that are directly relevant to this conversation? Dr. Fitzgerald?

MS. FITZGERALD: Yes, I just wanted to support the fact that the rate of exclusive breastfeeding is very low, probably more like 30 percent at three months. In my personal experience and practice, I find people start supplementing very early. More like two weeks.

CHAIR RAPPLEY: Dr. Bier, did you have another question?

DR. BIER: I had a couple of questions for Skip. One is you have the slide, which talked about fetal exposure being greater than the exposure in milk. And the placenta is a very selective, you know, and specific transmitter of substances. And I would guess this is extremely variable, depending upon what the drug is. Right? I mean, I could imagine that there are drugs

which have no fetal exposure.

DR. NELSON: This is the point at which the ethicist has to plead that he was using scientific information from other sources to --

(Laughter.)

DR. BIER: Or not quite scientific information.

DR. NELSON: I have no independent -- right. I have no independent knowledge that would refute what you are saying. It may well be variable. I think the point, and actually, that point is not essential to the point, the decision to continue is pretty much a clinical risk benefit assessment.

DR. BIER: The section question I had is when we are assessing the risks of drugs in breast milk, you know, many of which, you know, in other adults, in adults that have very limited risk, how do we assess that in the context of the other unwanted substances in breast milk that are felt to have major

risks, like dioxins and PCBs which are present in milk at two-fold the EPA, two orders of magnitude higher than the EPA limit? So is adding a drug without much known affect increasing the risk or is it no risk?

DR. NELSON: Well I guess the issue of other substances, just sort of thinking a bit off the cuff, in my mind, would impact on the sort of clinical decision of the risk-benefit of breastfeeding. I'm assuming that, for example, dioxins have been around a long time, that if in fact those had a major negative impact, the positive studies would have in fact began to show that. I don't know if that is the case. I think the issue of the incremental research risk of the drug would still remain the case, if the decision to continue was independent of the risk. And so I guess the decision about continuing would then be a clinical decision of which that information about the other risks of breast milk would have to be part of that clinical

decision. I don't think it impacts on the research decision, per se.

DR. BIER: Well, I'm not sure. I mean, certainly the issue -- I brought up dioxins because it isn't a clear issue, right? But the fundamental fact is, they are present in very high concentrations in breast milk and they give the child a ten year burden of dioxin compared to the infant that is not breastfed.

So, if we have that risk from breastfeeding and we want to study drugs which all other indications in adults and stuff show that there isn't much risk, okay, is doing this drug in a mother who is, doing this study in a mother who is otherwise breastfeeding adding any risk? I'm not sure.

DR. NELSON: But I guess the point is we are agreeing. I mean, if in fact the woman has made a clinical decision to continue that drug and then a clinical decision to breastfeed and then goes into research

independent of that, then in fact, the incremental research risk to that infant does not involve the drug. So, I mean, I don't think we are disagreeing. We're just taking a different approach.

I would not, however, argue that we ought to reinterpret minimal risk, for example, to include dioxin exposure.

CHAIR RAPPLEY: Dr. Rosenthal.

DR. ROSENTHAL: Just a couple of quick comments and then questions, a couple of what I think will be quick questions around medication use in breastfeeding moms.

First of all, I just want to go on record as saying that I think that the guidance document is quite good and a lot has gone into it clearly and it is, I just would compliment the team that worked on that.

Initially, I was considering this as a complex compartment problem, which I figured that if all these bright minds put our heads together, that we would be able to sort

of solve all the coefficients and figure all this out today and go home having succeeded. And now I realize that there are so many wrinkles in all these questions that have to do with the medications, the ethical considerations, the specific study questions, that it is really going to be hard to come up with anything that is much more specific, I think, than the guidance document. But I'm willing to try.

You know, as I was thinking about this, I thought well the first step would be to just look at milk-only studies, because clearly if there is no drug in the milk, then it's really a non-issue and we can at least deal with those agents cleanly. But then, you know, I just looked up the label for coumadin and it says, you know, that coumadin doesn't pass into the breast milk, but that the PT and INR for infants who are breastfed, the mothers taking coumadin, are prolonged. So, you know, anyway, I don't know whether I -- I don't

know. I just read the label. It may not be true, but it's in the label.

But in any event, so I'm going to ask a couple of easier questions. If 90 to 99 percent of moms who are breastfeeding are taking medications, what are they taking? What are the drugs? I mean, can we think about these problems in the context of the specific agents that most moms are being exposed to?

And also, I had a question, I don't know the answer to this, about whether breastfeeding moms use more medications than moms who don't breastfeed.

CHAIR RAPPLEY: Do people want to respond to those specific questions?

DR. FEIBUS: I'm certainly not the complete expert on this, but at least in the articles that I read, including the article from Chet Berlin's group that was just published this month, it appears that they take just about everything. They tend to take

slightly more medications while they are breastfeeding versus when they are pregnant. But they take just about everything. Everything ranging from over the counter products to antidepressants and various other psychoactive medications, to asthma medications. I mean, just about everything.

CHAIR RAPPLEY: Dr. Lawrence.

DR. LAWRENCE: In response to that, I would say that lactating women do take more than they might have in pregnancy. They do not take more than bottle feeding mothers. In fact, probably considerably less.

And any time you do a survey and ask mothers what they are taking, you're going to get every drug in the book. What do they mostly take? Acetaminophen, for instance. Acetaminophen is very well tolerated by the young infant because they metabolize it via the sulfhydryl pathway instead of the glucuronidase pathway, which does not produce a toxic byproduct.

So, we do, when mothers need something for whatever their problem is, acetaminophen is pretty safe. There are things that are relatively safe. So I would be a little cautious about counting up how many mothers have ever taken a pill while they were lactating and assuming that lactating women take a lot of medications because I don't think they do.

We've run this drug information service since 1984 and the average woman doesn't take a lot of medication.

CHAIR RAPPLEY: Other responses to Dr. Rosenthal's questions? Dr. Gorman.

DR. GORMAN: As a former IRB chair, I always get nervous when someone tells me it can't be done. So I would like to propose a potential scenario where a healthy woman with a healthy baby could do a drug study. In our IRB, at least, we thought of bicycle riding as an activity of daily living and a risk that most parents would consider okay. But people

don't ride their bicycles every day, at least not in this particular community.

So, would you consider a situation where you had a drug that would be likely used during lactation, let's take acetaminophen, for example, where some fraction of the population would take it as a potential place where a healthy woman could volunteer, because there would be no more than minimal risk or no more than an activity of daily living?

DR. NELSON: A couple of first remarks. I was sitting here thinking about Dennis' comment. Part of the difficulty with the definition of minimal risk that we have in our regulations is precisely the phrase daily life. There is nothing in the entire world that is similar. There is no other definition of minimal risk in the entire world that I know of, that includes daily life. In fact, CIOMS removed daily life from the definition of minimal risk.

So, one of the questions is that the

tension between what I would call a statistical approach to minimal risk, which is there are certain risks that happen and so why not expose children to research risks up to that risk?

Now, acetaminophen is an example, you could argue at this point, there is enough information, it's probably labeled down. I don't know. If it's labeled down to birth, I mean, fine. It doesn't matter. Well, it's not, but I think you know, maybe there are circumstances where you might do that out of curiosity, but if something is labeled, then we could discuss that. But my own view is that the administration of almost any drug to an infant who doesn't need it, is not minimal risk.

DR. GORMAN: Well, as a chair, I would disagree.

CHAIR RAPPLEY: Are there thoughts about that subject? I'll put you on the list for another question.

Okay, Dr. Fant?

DR. FANT: Yes, this sort of goes along the minimal risk line.

If enrolling a mom is sort of a different slant on the minimal risk, take on minimal risk, if enrolling a mom and baby in a study leads to, as a direct result of that enrollment, leads to the mother choosing to forego breastfeeding or to either temporarily or for a prolonged period of time, does a withholding of breast milk constitute an imposition of more than minimal risk, given the benefits of breast milk?

DR. NELSON: Well, I guess I would say yes. I mean, the extent to which you want the research decision to remain independent of that decision, it's possible that new information comes to light in the course of the informed consent that the woman wasn't aware of or didn't fully appreciate and then that may be a reasonable reconsideration, if you will, of that issue. But that's partly

why I suggested that you turf that back to the clinician so you don't get into a situation where a decision to stop breastfeeding that might not otherwise have happened, happened only because of the invitation to go into a clinical lactation study. That's where it gets a little fuzzy.

So you know, yes, there is a risk. That's part of the risk benefit and that's why you wouldn't want to have a study, necessarily interrupt breastfeeding, because of the documented benefits to the infant in a setting where there is no benefit of a clinical lactation study to an infant, to my knowledge. There is benefit of the knowledge to future infants, but it's not going to help that infant.

DR. FANT: Yes. The reason I ask that is because in some of the different study models that were put forward, you know, one of them was one particularly in drugs that are going to be used for a short period of time,

where the mother may choose to stop breastfeeding for a while, pump, whatever, and then at the end of it, you know, resume breastfeeding with the kid. And we tend to associate risk with the drug, itself. What about just withholding the breast milk, itself? Is that part of the whole risk package that the kid is exposed to?

CHAIR RAPPLEY: Dr. Kweder wants to respond to that.

DR. KWEDER: Yes, I think, Skip, I'd like you to tackle that a little bit. And I realize that you're not here to make great decrees but it does seem like the withholding breast milk question, there has got to be some distinction between withholding a feeding or a day's worth or three days' worth where the benefits of breastfeeding are generally longer term decisions.

DR. NELSON: I think that's why the issue of if you have a setting where you know substituting a bottle is not an issue, then

it's not an issue. If you don't know that, you know, it needs to be then part of that conversation, if you will. I mean, that's, at least when you're talking with anyone about breastfeeding and they say I'd like to substitute a bottle in the middle of the night, most pediatricians then have a conversation about the risks of doing that, if you're not in a setting where you have already demonstrated that that is doable. I mean, that's just part of pediatric practice.

DR. HALE: I think you need to clarify when you say bottle, that you mean a bottle of human milk.

DR. NELSON: Yes, I mean, pumping, storing, and then someone else gets up in the middle of the night to use it.

DR. HALE: Because we can demonstrate problems with substituting bottles of formula, absolutely.

CHAIR RAPPLEY: Dr. Dooley, did you want to respond to this?

DR. DOOLEY: Yes, we've been talking about the importance of the independence of the decision to participate in a research trial, from the decision about taking a medication and the downsides of a woman being approached for a study and then deciding to stop nursing. I think there is another side to this and that is, as a result of being approached by a study, the woman decides not to take the medication and to continue what she interprets as risk-free nursing. So, I hope we always keep that concept in mind, too, because that does happen.

CHAIR RAPPLEY: Other thoughts about this question? Okay, Ms. Fitzgerald.

MS. FITZGERALD: I just wanted to clarify that when we're talking about decision-making that we're probably also including the father in this.

CHAIR RAPPLEY: Thank you. Fathers of the world thank you for that.

Dr. Lawrence, did you have a question

or comment? Your name got on the list a long time ago and I'm sorry.

DR. LAWRENCE: It was a while ago. And I think it was something in reference to something that Dr. Hale had said. And I do completely agree with his interpretation of how to analyze this.

You have to consider lactation as a very different phenomenon. Just not feeding at a particular time changes the dynamics.

And I think what I was going to say was to comment on what happens when you only partially breastfeed. There are two ways of doing that. One is to give formula and the other is after six months to add weaning foods.

But when you begin to wean, it has been well-established, well-documented what happens to breast milk. And the long range, the closer you get to diminishing your milk supply, the higher the sodium gets and the lower the protein gets. And so it does change

many of the dynamics for passage of drugs into the milk itself.

CHAIR RAPPLEY: Dr. Cnaan, then Dr. Scialli, then Dr. Newman.

DR. CNAAN: I have a question for Dr. Hale and a question for Skip. You gave a list of a lot of medications. The group that I didn't see at all is antiepileptic medications. And I wonder if there is any information how those fit into the equation.

DR. HALE: Yes, we have studies on virtually all of them now. Valproic acid, Tegretol. We now have two or three studies on lamotrigine, Lamictal, and topiramate. We have studies on all of them.

Interestingly, most of the newer ones like topiramate and Lamictal actually transfer in relatively high doses. Lamictal is 22.4 percent of the maternal dose transfer.

But it is interesting, the infants that have been studied, the plasma levels trend down as they get older, past a month to

two months and then they trend down quite low. But yes, they have been studied. We do know how much transfers into milk.

DR. CNAAN: And skip, my question to you had to do with, I guess it goes back to Dennis's comment a little bit in that if -- you made the statement in one of the slides that if the pregnant mother was already taking the medication, then if she is taking the medication while lactating, it will probably be a smaller amount, continuous amount to the infant.

Is there a possibility that even though it is a smaller amount, the cumulative effect by that point becomes a concern, like there is some sort of storage, or is that never a concern?

DR. NELSON: I would have to defer to the scientists. Both of those comments make me realize I should strike that from the ethics section if it's not supported in the other parts.

(Laughter.)

CHAIR RAPPLEY: Pharmacologists want to respond to that? Dr. Ward and then Dr. Scialli, okay.

DR. WARD: The issue all has to do with deep compartments and there are a few drugs that will be excreted for weeks after ceasing the administration. Amphotericin was a classic. We were going to do a pharmacokinetic study and we found therapeutic concentrations three weeks after stopping the drug. So it really would be drug dependent.

I would just respond also to the comment about the anticonvulsants. The last academy statement was in 2001 and I don't know if Rich knows that there is another one coming, but -- no, okay. And there are case reports of sedation from some of the anticonvulsants, Phenobarbital, but it's like a lot of things that are the aegis for this whole effort and that is, they are very poorly studied. There is not a nice, comprehensive

evaluation.

CHAIR RAPPLEY: Dr. Scialli.

DR. SCIALLI: I would like to defend Dr. Nelson and urge him to keep his slide the way it is. The things that prevent placental transfer of drugs are few and far between and they are similar to the things that exclude access to milk, such as large, molecular size and prominent charge or sometimes both, and extensive protein bindings.

So, I don't -- I was sitting here trying to think if I know of any examples of things that get into the baby at higher levels than you get across the placenta. And here, we have a data gap because often you infer what the baby's concentration and blood would be based on milk concentration, rather than measured concentration in the baby. But I can't think of any. And if some of you can, please call me collect because I should know it.

But with those changes, the fetus can

excrete drugs across the placenta and therefore, when you give a baby drug in milk, the baby has to find another way to get rid of it, and that doesn't always happen so that some things do accumulate in babies after breastfeeding and can become clinically more important. And I think caffeine may be one such example.

So, you might put an asterisk next to the point, but don't get rid of it altogether because I think you are correct. And the implication for studies, particularly studies involving babies, are if you are doing studies early and you have a kid who appears to have an adverse affect of a maternal medication, you have to wonder is it because of placental transfer and you have still got clinical signs or is it because of lactational transfer? And of course, the SRIs are the classic example of where that was a question, at least at one time.

DR. BIER: I don't actually disagree

with what you have just said. You know, and I'm not a pharmacologist. Given the number of drugs available, and given the limited studies of anything in fetal blood in pregnant women, I mean, how much data are there really available on this in humans?

DR. SCIALLI: Well, for cord blood, it's actually not too bad. Lots of things have been measured in cord blood because it's easy to do. And concentrations in cord blood for almost everything are similar to concentrations in maternal blood, plus or minus some. And there are differences, but there is not much that doesn't get across the term placenta.

DR. WARD: I'll have to just take the opposite approach and that is that the cord blood samples are nearly meaningless because of differences in pharmacokinetics between the mother and the fetus. So you can get a maternal/fetal ratio that flips completely from three to one higher in the mother to two

to one higher in the fetus for the same drug, depending upon the time after dose administration that the baby delivers. So, I think the best description is that we have a dearth of information on both areas. That is, fetal drug exposure needs to be studied in much more detail as does drug exposure during breastfeeding.

DR. SCIALLI: May I respond or have we had enough?

(Laughter.)

DR. SCIALLI: No argument, but I was responding to the more qualitative concept that you get a lot of cross during pregnancy and not very much into fetal blood during lactation. And rather than that, you can use cord blood to give you the whole spectrum of fetal exposure. And of course, term levels are very likely different from levels earlier in pregnancy. I mean, for sure, it's a black box to some extent. But we can sort of broadly say, I think, that Dr. Nelson's slide

is okay.

CHAIR RAPPLEY: Dr. Scialli, you were actually on the list next, on the question list. So did you have another question?

DR. SCIALLI: Yes. I do have a question and I think Tom can probably answer it best, but maybe other people know the answer. And that is, that there is sort of this niggling concern that even for pharmaceuticals that are present in milk in relatively low concentration, that there might be change in taste or palatability and, therefore, a difference in infant nutrition. And you didn't mention that and I wonder if you know whether there are many data on that. I know for ethanol, there are data, but I wonder if there are for other things.

DR. HALE: Well, the only two that I know of that have been mentioned in the literature is metronidazole, Flagyl and ethanol.

The ethanol case has been studied

quite a bit and they subsequently found out that infants really don't dislike the taste of alcohol. It's not the -- it recently came about from they gave alcohol to this group of mothers and they found that their milk production was less. And from that, they assumed that the baby didn't like the taste and came off the breast.

Subsequently, it was found out that alcohol probably suppresses oxytocin release and that is why the latter of the 12 to 24 hours later, there was a big huge rebound in milk production for ethanol.

And metronidazole we know for certain it produces a metallic taste to milk. Babies don't like it. And so they often come off the breast in some mothers. They simply don't like the metallic taste. There may be something else. I don't know of other drugs, but perhaps other drugs might.

DR. LAWRENCE: Well, not necessarily drugs, but a dietary so that some babies don't

like the taste of certain things.

But we need to recognize that a breastfed baby is exposed to many flavors and tastes. And that's why they wean to solid foods much better than the bottle fed baby who has gotten the same stuff every single day, day after day, after day.

And just to comment on the alcohol study, that was hardly physiologic because the study personnel came in with their babies and themselves, were handed pure vodka and orange juice and told to drink it in ten minutes. I don't know of anybody who does that. And particularly nursing women, if they have a little alcohol, they tend to sip it and so forth, except for the confirmed alcoholic.

So that study was very misleading, including whether it really and truly depresses your production. Because for centuries, mothers were told that a little beer, or a little wine, a little something will enhance lactation and, if nothing else,

will allow you to relax and let down your milk. So, these things are all mixed up.

DR. SCIALLI: Can I comment on that?

CHAIR RAPPLEY: Yes.

DR. SCIALLI: Just as a follow up, I was looking for more commitment. Is it something that is important to study, inasmuch as pharmaceuticals generally don't taste very good, which is why they are put in capsules and flavorings are added. Is it important to study, if you are doing lactation studies, is it important to study whether there seems to be taste aversion?

CHAIR RAPPLEY: Or an effect on the baby's subsequent suckling. That gets into the question of outcomes and what kind of study outcomes should be included.

DR. HALE: How would you study that? Taste, I mean --

DR. SCIALLI: Well, presumably, you study it by weighing babies before and after a feed and if there is a decrease, you assume

there is something that interferes with getting the milk to the baby. You don't know if it's milk production or if it is a decrease in suckling.

I just don't have an opinion. I don't know the answer. I just thought I would see if anybody does.

DR. HALE: It is a good point because there are some intranasal products that are -- I can't remember the name of it, it's horribly, horribly distasteful. And I've often worried about babies coming off the breast from that. But I don't know, other than that.

CHAIR RAPPLEY: We have Dr. Garofalo, Dr. Feibus and Ms. Fitzgerald to respond to this.

DR. GAROFALO: Well, I'll just say I've had some experience with very bitter formulations that we took into infant trials and the infants took the formulation. So I think that would be a very difficult question

to answer.

But beyond that, I had a comment, actually about other outcomes and that is, you know, we talked about the fact that a lot of these psychoactive drugs, of course, get expressed. And is some information about breast milk and that sort of thing, although it would tend to happen later in development when these things are marketed, I mean, it is a whole other question about how you do new molecular entities, how you know much of anything about pregnant women or lactating women with new molecular entities.

But I had a question, a specific question for Dr. Hale about you mentioned that you used some developmental or some sort of scales. What is your experience with that?

DR. HALE: They are poor, for the most part. We have used the Bailey. We have used various other. The NCA, I can't remember, there are some other tools that have been used and published before. But they are reasonably

poor. I don't know that we have any good behavioral tools. That's not my area.

But we do ask questions about any unusual symptoms in baby, diarrhea, constipation, etcetera, etcetera, you know, the physical types of things. But you know, behaviorally, that's not a very solid area.

CHAIR RAPPLEY: Dr. Feibus did you want to add?

DR. FEIBUS: I was going to make a brief comment about the taste issue. I was going to say, once again, when you have a mother who is using a drug chronically, being able to assess what the milk tastes like with and without drug would be difficult to do. Not just because you don't know how to ask a baby whether the milk tastes good or not, but because the drug would have to be taken away and then reentered back into the situation.

I had a comment from way back when I was thinking about the comment that was made about dioxin. And it's interesting because a

lot of parallels seem to be drawn even when the government is developing policy on these things about environmental exposures and drug exposures. And while there are some similarities, certainly, in the way that approaching studying them or assessing levels might be similar, we have to remember that these environmental exposures are sort of there for everyone, and it probably varies regionally, but it's already there. And despite the fact that it is in the environment, we still know that with that there, breast feeding still has benefits. And so to some degree, we almost have to accept that as an unfortunate background. And then look at this issue on top of it.

CHAIR RAPPLEY: In the interest of getting to our lunch break, Ms. Fitzgerald, if you have a comment relative to the most recent discussion? And then Dr. Newman is the last person on the list this morning.

All right, then I will add Dr. Hale

as well.

DR. HALE: One thing you need to remember about environmental pollutants is the vast majority of them, not all, but the vast majority transfer in utero in much higher levels. We know, and particularly, when comparing breast milk, we know that with lead and mercury, most of it transfers in utero. Very little of it transfers in breast milk.

MS. FITZGERALD: I was just going to respond to the issue about taste in breast milk. A lot of moms use the herb fenugreek to increase their milk supply. One of the things that it does, is it has the flavor of maple syrup. The mother actually starts to smell like maple syrup and the milk is flavored like maple syrup. And one of the consequences is that the babies nurse more. They like the milk.

Now, how do I know this? Because the mothers tell me. Somehow they know. And I think that if a baby really objected to the

taste of something, they probably wouldn't nurse.

CHAIR RAPPLEY: Dr. Newman?

DR. NEWMAN: Yes, and actually, that was, I was going to mention fenugreek as well. I so much liked Dr. Nelson's presentation because it was an ethics presentation that actually came down and, rather than waffling, sort of said, no, this would not be ethical, until Dr. Gorman made the point --

(Laughter.)

DR. NEWMAN: -- which I have to agree with. That is, to me it is much more in the range of a baby's daily experience to drink breast milk from a mother who may take an OTC remedy than it is to get poked for a blood drawing.

And I wonder if you can comment, I think it's both over the counter medicines and probably more complementary and alternative medicines like fenugreek which are widely widely used.

And so, if we say, I mean, we have actually had a fellow who wanted to study fenugreek in nursing mothers and ran into all kinds of problems with the ethics. But this is widely, widely used already. And so how can we study complimentary alternative medicines or over the counter medicines. It seems like these are within the range of normal daily experience for many many babies and we ought to be able to study them. Otherwise, how are we ever going to find out what gets into breast milk?

DR. NELSON: Tom, I think it's an important problem, so I don't want to be seen as minimizing it. But I guess two comments.

One is the difficulty is this daily life category. At one extreme, we could all agree that say, you know, study Tylenol. I mean, I don't think we'll have much disagreement, but this difficulty is this daily life category has been extended much more extreme at the other edge in terms of

justifying risks that probably many of us would consider inappropriate.

Let me give you an example of a trial that is an old example that looked at IRBs in two different ways, just to show you the differences and that was one, I think, Bob is probably familiar with, using dextromethorphan as a probe for CYP2D6. So that used a sub-therapeutic dose, if there is a therapeutic dose, which I'm not going to say there is one. But it used a lower dose than what a parent might give.

But the difficulty was this was in infants who were less than 30 days of age. And so the question came down to, well, do parents normally give dextromethorphan to an infant who is less than 30 days of age? And if you ask most pediatricians, they would say no, we don't recommend that. So, many IRBs said that's not minimal risk. Some IRBs said that is minimal risk. And those that said it's not minimal risk then had to say what is

the condition. And those that said it's not minimal risk, said the condition is being an infant born with a deficient amount of CYP2D6 was a physiologic condition and therefore merited a minor increase over minimal risk. And they split on that, in my experience in talking to how people did that. So I mean, I think that illustrates, you know, I do believe that ultimately you have to come down one side or the other. And I'm more concerned about the extension of an appropriate risk than I am about precluding that.

And I don't know the data. This is the first I've ever heard about this maple syrup tasting thing. I don't know what data supports it. You'd have to look at it. But just because it's an exposure that happens a lot, doesn't necessarily mean it's something that we ought to support. So that is still a separate question.

CHAIR RAPPLEY: One more comment from Dr. Lawrence and then we will go to lunch.

Thank you.

DR. LAWRENCE: I want to put fenugreek to rest because it does make all secretions smell like maple syrup, it's what is used in synthetic maple syrups. It does not necessarily increase mother's milk supply. It can cause colic. It's in the family with peanuts and chick peas and allergies are not uncommon. And you can't study it. Because how do you get a control that smells like maple syrup?

CHAIR RAPPLEY: Okay, so we'll reconvene after lunch at 1:00 p.m.

And then at this point in time, we do not have anyone who has requested to speak at the open hearing, so we will go right into our discussion at that point and, perhaps, discontinue early. Thank you.

(Whereupon, at 12:04 p.m., a lunch break was taken.)

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

(1:01 p.m.)

CHAIR RAPPLEY: Okay, if we have enough of our committee members to begin, I would like to ask if there is anyone here for the open public session.

(No audible response.)

CHAIR RAPPLEY: No requests for that. We will move into our discussion. We had two hours scheduled for discussion and we are scheduled to break at 4:00. If we begin our two hour discussion now, at 1:00, we can target breaking at 3:00 and not take a break in this time period between 1:00 and 3:00. Is the committee agreeable to that?

(No audible response.)

CHAIR RAPPLEY: We won't take a vote.

(Laughter.)

CHAIR RAPPLEY: Okay, so we're open again then. I won't read the questions, but I will refer you then to the questions that Dr. Feibus had directed to us in her presentation. Oh, they're on the screen.

Thank you. And so we can try to address these questions and give some specific feedback then to the Agency.

Would anybody like to open? Dr. Newman?

DR. NEWMAN: Question one, I move we say yes.

(Laughter.)

CHAIR RAPPLEY: Okay. And Dr. Feibus is here. Maybe I'll just paraphrase what she told me earlier and that is, yes, it seems obvious, but it is an important starting point. So it basically allows us then to spend the time and the effort to deal with the other questions.

Okay, question two, can we have that put up on a slide?

DR. WARD: Could I make one point about just the terminology medicine? I assume we are thinking of the regulated medicines through SEDAR and Seber, but I would maintain, as came out in the morning

discussion, that food supplements and whatever the active ingredients are in those deserve study as well because of their widespread use.

And it's a challenge, but it's not insurmountable to obtain products that have only the active ingredient. USP has a certification program that can provide those.

CHAIR RAPPLEY: So, yes, Dr. Feibus.

DR. FEIBUS: I just wanted to mention that while that is really important, we don't really have the ability to address the food products because they are actually regulated by a different center. So, as we all know, dietary supplements and things do have safety issues because they are regulated in a different way and a different place, we don't have the ability to go there today. But I really appreciate you bringing it up because that is important that people recognize the importance of that.

CHAIR RAPPLEY: So we can note that

we recognize that this particular branch of the Agency doesn't have the authority to authorize that kind of work or study but we, nonetheless, feel it's important to be noted in the public record.

Okay, thank you. Any more discussion about question one?

(No audible response.)

CHAIR RAPPLEY: Question two?

(No audible response.)

CHAIR RAPPLEY: I think one of the important questions here, is it important for breastfeeding to be well-established before enrolling mothers and infant pairs? So, this does go back to some of the discussion we've already had about interrupting or undermining the process of breastfeeding.

So, discussion about that? Dr. Scialli?

DR. SCIALLI: I can't subscribe to the prohibition against enrolling women early. And I'm thinking specifically of the

woman whose baby is in the NICU and can't take oral feedings, who may want to participate in a study and where that participation wouldn't interrupt breastfeeding anymore than it's already being interrupted by the clinical circumstances.

So that would be one exception I would point out to this kind of prohibition.

CHAIR RAPPLEY: Other thoughts about that? Dr. Newman.

DR. NEWMAN: Yes, I would also say this should be a risk benefit calculation. Because generally, one wouldn't want to do that, but if one were studying the medication that is used in the peripartum period by women right after delivery or right before, then this is when you would need to study it.

So, the goal should be not to interfere with breastfeeding at all, but I think it should be a risk benefit discussion.

CHAIR RAPPLEY: Dr. Cnaan.

DR. CNAAN: I want to second the risk benefit discussion. I also think that there might be a distinction in the healthy term baby, whether it is a first baby or a subsequent baby, because the interruption might be a lot less severe for the more experienced mother.

CHAIR RAPPLEY: I was thinking that as a mother, myself, that I probably could not have tolerated participation with my first. But my second, I would have been like, whatever.

(Laughter.)

CHAIR RAPPLEY: Ms. Fitzgerald.

MS. FITZGERALD: Yes, I would agree with that, too, especially in the term moms. We usually work with them after delivery. And it frequently takes them two to four weeks before they really know what they are doing and would be capable then of participating in a study.

CHAIR RAPPLEY: Dr. Dooley?

DR. DOOLEY: I, too, would like to support the concept of recruiting women who are planning to stop nursing at some point. I think we have to acknowledge probably the most earthshaking sociologic change of the last century has been the proportion of women in the workplace. Some women are lucky enough to get three or four or five months off. But whatever time they've gotten off, depending on their job, they're planning to stop nursing when they go back to work. And it just seems to me that we're not going to be influencing that decision. It's being influenced by something else. So I certainly hope we could recruit those women to studies.

CHAIR RAPPLEY: Dr. Ward.

DR. WARD: I just actually want to change a bit of the emphasis about the immediate postpartum period that those women are pumping their milk. And it is in small quantities at times. But I think that actually is an essential time because those

kids are going to get the milk.

DR. HALE: I think a more relevant point here is that the drug study be done at an appropriate time. I know all of these other issues are important, but I think as far as the statement there, that the drug needs to be studied at an appropriate time when it is used and staged in lactation.

CHAIR RAPPLEY: So are people comfortable with that as a recommendation that that be the general concept?

For those of you who are joining us today, for the last two days we have used the notion of advising the Agency about general concept to be included in their document.

Any other discussion, then, about question two?

(No audible response.)

CHAIR RAPPLEY: Question three. We're not technically ready yet. So let me read question three then. It's on page 11 of Dr. Feibus= slide set.

"Should clinical lactation studies enroll only mother infant pairs who are exclusively breastfeeding? If yes, why? And if no, under what circumstances could others be included?" So it's that question of should the study be done on the pair, mother-infant pairs who are exclusively breastfeeding only?

Comments about that? Dr. Newman.

DR. NEWMAN: For reasons discussed this morning, I would say, emphatically, no, that we should study women who are both exclusively breastfeeding and giving other substances to their infant.

CHAIR RAPPLEY: Dr. Ward.

DR. WARD: I want to support that. I think that as Dr. Hale pointed out, though, stratification and comparing those two would be very important because the amount of drug excreted in the nature of the breast milk may be different.

DR. HALE: I would suggest that we

say it's ideal to use exclusively breastfeeding moms. But no, you take what you get. And if you can get moms who are partially breastfeeding, it's probably all right as well.

CHAIR RAPPLEY: Can we describe then scenarios where it would be acceptable, or do you think it's just fine to leave it as we just stated? Tom.

DR. NEWMAN: Yes, I would disagree that they are the first choice. I mean, I think that we would want to study the breast milk as it is being given to infants, which includes both partially and completely breastfed babies. And so, in fact I think it would probably not be acceptable only to study exclusively breastfeeding babies, that one would always want to study both.

CHAIR RAPPLEY: Ms. Celento?

MS. CELENTO: Yes, I just wanted to agree with that. And you know, I don't want it to be reflected that it is ideal to go one

way or another because reality is is that people are doing any and all of the above.

CHAIR RAPPLEY: Dr. Cnaan.

DR. CNAAN: I just wanted to add the concept of generalized ability. If there is a population out there that partially breastfeeds and we want to serve them, then we ought to study them.

CHAIR RAPPLEY: Yes.

DR. FEIBUS: I just wanted to add an addendum to this question. Because the conversation is saying that it is important to get information on both of these populations, does that then change how many people you enroll in the study? Because do these two populations then need to be analyzed or described separately or can you pool this group of women who exclusively breastfeed or don't exclusively breastfeed. And how does that affect how you design your study?

CHAIR RAPPLEY: A response to that?

Yes.

DR. WARD: I would suggest that we don't know the answer to that until we do some of the studies and that that is probably a work in progress.

We may find that indeed the transfer of chemicals in the breast milk differs between the two groups, we may not. And it may be chemically or it may be related to the chemistry of the drug.

CHAIR RAPPLEY: Dr. Kocis.

DR. KOCIS: I want to throw one other point in, which is the balancing between risk and benefit. And speaking on behalf of the infant at this time, I also, while it is not perfect physiology, it is not perfect science, I think there may be an occasion where you want to do these lactation studies in children who are now weaned from the mother in the immediate post-weaning period, where the potential drug or new drug has unknown or potential serious side

effects.

While the numbers may not be perfect for all the things we've talked about with differences in breast milk, physiology and stuff, that that may be a window to begin a series of studies to safely investigate the effects of a new compound on breast milk and then, subsequently, the infant.

CHAIR RAPPLEY: So, that's a new suggestion that we haven't, I think, thought about yet today and that is, to actually target the population who is about to be weaned and then weaned. That there may be valuable information to be gained there.

DR. HALE: But that has an inherent danger. And that is, that many women discontinue breastfeeding when they sense that their milk supply is poor. So they say I'm just going to stop and go to formula.

So that's not a very good population to look at because don't know what their milk synthesis rates are like. It has a risk.

DR. KOCIS: But we also do know, you'll know the duration of breastfeeding. You'll know their pattern of breastfeeding, whether they are suitably partial. And for all the reasons we have talked about, Western American women today, there is lots of reasons why they discontinue. And I think you could design the study to tease that out, to maximize good data. And again, the risk benefit to an infant to a novel drug. I just wanted to bring that point up.

CHAIR RAPPLEY: Dr. Fant.

DR. FANT: Yes, I would just like to reiterate my encouragement that we think about different development, issues that relate to different developmental stages in these kids. You know, think about it broadly.

In thinking about it since our earlier discussion, you know, I think it even extends beyond just what we know about the development age, dependent changes and

clearance, renal clearance, and enzyme expression, hepatic enzyme expression and metabolism.

But there are some things that are unique to some of the kids in this population. For instance, mothers who deliver at 23, 24 weeks, they're going to be pumping if they want to breast feed. That milk is going to be stored. You know, chances are if this kid delivered at 22 or 23, 24 weeks, she got a whole lot of medication that is going to be secreted into the breast milk at fairly significant concentrations.

That milk is going to be stored. It's going to be given to kids who are at particularly high risk to develop feeding intolerance and necrotizing enterocolitis. You know, some drugs may have local affects on the GI vasculature or the mucosal, independent of their systemic absorption. They may have affects on, certain antibiotics

may have affects on the intestinal flora, which may then impact on their ability to feed and establish feedings and maybe develop necrotizing enterocolitis.

So, you know, the effects of the medicinal substances in the milk on babies at different development stages, you know, I think we get into problems if we make too many assumptions beforehand that are too restricted. And we sort of need to think about that in a broad global way, as we go forward. And I'm not sure, I'm not making any suggestions on how we transmit this concern down the line in terms of how this needs to be looked at, initially by the sponsor that has to address it, but I think these issues need to be addressed globally and broadly.

CHAIR RAPPLEY: Any other thoughts about that? Dr. Ward?

DR. WARD: Could I maybe just generalize what I think I am hearing, Mike,

in essence? Doing actually literally, almost a survey about the amount of drugs in breast milk and then asking the question, are there any correlations in subsequent disease processes in the newborn might be important. Is that what I am hearing?

DR. FANT: I think that may be an important question to ask. I mean, are we contributing to some of the episodes of necrotizing enterocolitis now simply because these babies are exposed to things that they are already getting.

CHAIR RAPPLEY: Dr. Rosenthal.

DR. ROSENTHAL: So I just want to be clear then, this is an argument for studying banked milk.

DR. FANT: It's an argument for thinking about the effect of pharmacologic agents in breast milk in newborns, but to extend, to think about the newborn in terms of, you know, the same way this committee was mandated to think about kids is different

from adults. And pre-term kids are different from term kids. And extremely pre-term kids are different from pre-term kids.

DR. ROSENTHAL: I'm just asking -- I think you are raising a very important point, but it adds yet another wrinkle into all this. And that is, that we don't really understand what happens to these agents when they sit in breast milk in a refrigerator for however long they are there. And that may also be another important thing to understand.

CHAIR RAPPLEY: Dr. Kocis.

DR. KOCIS: I think, you know, as I see, starting with no data from lactation studies to gathering good data that is going to sort of give us some baseline information for the vast majority of mothers and infants, and then we proceed down, and sort of my comment about high-risk drugs, well, let's not give it to the kids. Let's not have them exposed first. Let's see just some data and

then we'll do the better studies with the pure breastfed, exclusively breastfed, and then let's move into the higher risk patient, the neonatal premature infant. I think this can be done sequentially. I think the other way to approach it, which would require vast databases and data analysis to begin to look at, you know, premature infant exposure to numbers of NAC which you would need, I'm not doing the sample size, but at least the East Coast or the West Coast, all the neonatal ICUs there, it could be done but we haven't looked that far down in looking at datasets of that size, but, as another approach to answering that question.

CHAIR RAPPLEY: So do you, at the Agency, feel we've given you adequate response for -- have we given you an answer to question number three that is satisfying or --

DR. FEIBUS: I think that the opinions that have been expressed are wide-

ranging and they actually provide a great deal of perspective on how to try to address this issue in the Guidance. And I thank all of you.

CHAIR RAPPLEY: Okay, so we'll move to question number four. Dr. Cnaan.

DR. CNAAN: I think we never did the second part of question two, move the computer down a little.

CHAIR RAPPLEY: Okay. Question number two, the second part is, is there a minimum number of weeks postpartum before which mother-infant pairs should not be enrolled? Please consider both infant feeding issues and maternal physiology and pharmacokinetics issues.

I thought I heard people say that we would not say that there is a certain period of time to not study, that it would be a risk benefit analysis at all ages in all appropriate weeks after birth. Is that correct?

(No audible response.)

CHAIR RAPPLEY: Question number four. Given that estimated infant daily dose can be calculated from drug concentrations in breast milk, are there situations where a maternal milk/plasma ratio would offer additional clinically useful information?

Dr. Scialli?

DR. SCIALLI: I would answer this yes. Tom doesn't like milk/plasma ratios and neither do I, if they are single observations. But area under the curve has been used and can be used. It's more difficult. It's more expensive to do but it should be done. And I think it adds information as, I forget who said it, maybe it was Karen, for making assumptions about different doses or about different dose forms. I think it's information worth getting and as long as you have, you've got the mother there anyway. She's giving you milk. I think it would be a shame not to

collect plasma or serum at the same time and develop the area under the curve for both and come up with a ratio.

CHAIR RAPPLEY: Any other? Dr. Gorman.

DR. GORMAN: I think that if that is the only information you can get because it is a single spot sample, it might be of some use. But I don't see where it adds much, if you already have the area under the curve. You'd have it anyway, but it would be not helpful for the infant dose. Or we're not seeing --

DR. SCIALLI: Yes, I'm saying the answer that I would give to question four would be yes, but only if you use area under the curve for both milk and plasma. For spot samples, I would agree with Tom that it is worth nothing. Worse than nothing.

CHAIR RAPPLEY: Dr. Newman?

DR. NEWMAN: Yes, I guess a situation which I could envision it being

helpful would be if the concentration or the total dose of the baby in the breast milk were very variable from mother-infant pair to mother-infant pair and a big predictor of it was the mother's level. And assuming, I'm guessing that it might be harder to measure drug levels in breast milk than in plasma or serum. I don't know whether this would be true, but either more difficult to get the sample or the lab would look at this stuff and say this isn't blood, we don't do this, and just give you a hassle, if you wanted to measure it in the breast milk. Then if there was a ratio that was relatively constant and a lot of the variability and the exposure to the infant could be explained by the mother's level, then you could get the mother's level and multiply it by some factor and get a better estimate of what the baby would be exposed to, than if you just took a number out of a book for the baby.

DR. HALE: The one time that it

would be useful is with ultra-dosing regimens. For instance, right now we use metronidazole at 400 milligrams a day, 500 milligrams QID. We also use it at two gram stat dose. So, in those instances where you don't want to study the massive high doses, milk/plasma ratio might be useful.

I agree that it's useful to do one if you've got the wherewithal, you've have the patients that will do it, it's great to have the data. Let's just not use it clinically too much.

CHAIR RAPPLEY: Would it also be useful in looking at genetic variation and metabolism of medications so that it might allow you to predict that for a certain mother than going forward, knowing at certain doses she would have higher plasma levels, higher milk levels. Like tricyclic antidepressants, there can be a four-fold difference in plasma levels that people carry with the same dose.

DR. WARD: I think that introduces a whole other area of study that probably should accompany, especially the maternal pK evaluations. Every year pharmacokinetics explains another biologic variation in either response to drug therapy or the kinetics of a specific intervention. And I think all of our studies need to incorporate that kind of evaluation. One of the interesting aspects of that would be the developmental changes during that first year of life in the infants, because that is not nearly as well studied as it probably should be, or at least could be at this point in time. But to simply look for snips and to look for correlations between their single nucleotide polymorphisms and what their rates of clearance are.

CHAIR RAPPLEY: Other thoughts or questions? Dr. Rosenthal.

DR. ROSENTHAL: You know, as I think about the data that were presented that were

shown to illustrate the concept of the M/P ratios, it would be nice to have, to understand those curves because I think there might be an advantage to understanding the time course for equilibration or for response. And all this has been said on some way or another.

But you know, I think if studies allow us to predict variability in the M/P ratio for a given drug, then we will be able to use that information clinically, or we may, in some circumstances. So, I wouldn't dismiss this concept completely.

CHAIR RAPPLEY: Dr. Scialli.

DR. SCIALLI: At the risk of repeating what Geoff said, to not get M/P data would be like looking at Tom's curves with only the infant part and without the maternal part. And I think we all agree that it appears to be more informative to have both curves. So, my suggestion is that collecting both data over time is worthwhile.

CHAIR RAPPLEY: Dr. Garofalo.

DR. GAROFALO: So, I just, for a moment though, want to talk about the feasibility of that. And it's a question of whether or not you say that would give you additional useful information, as opposed to you must have that information to make sense of it. Because the feasibility changes dramatically. Well, I would think, because you were talking about people being able to enroll in these trials over the web and collect their breast milk and freeze and send it to you. But they can't draw their blood, so that's a big difference between those two.

So, I guess it's just in the wording of. Yes, it would provide clinically useful information, but to the point of saying it's a necessity, I think, might be an issue.

CHAIR RAPPLEY: Dr. Scialli.

DR. SCIALLI: I agree. The question is would it provide clinically useful information? I think the answer is yes. Is

it essential to have it, if you don't have a choice, if you can't get it? Yes, half the picture is better than nothing.

CHAIR RAPPLEY: Other discussion on question four? Yes.

DR. FEIBUS: I'm going to throw a spin on this again. Hypothetically if, let's just say hypothetically we were to decide that it is always most ideal to get a study where you have both plasma and milk levels, so that you can get the M/P ratio, should that be the study that is recommended first? Should a milk-only study then be the fall back study or should the milk-only study still be the first study that is looked for in certain situations? How do you balance that?

CHAIR RAPPLEY: Thoughts? Dr. Ward.

DR. WARD: Yes, I would suggest that the first study to be done is the serum plasma milk study of the mother, so that we understand her kinetics and then the transfer

rates and rate constants into the milk. And then I think we're maybe in a better position to make estimates of what the dose would be that is administered to the child.

CHAIR RAPPLEY: Dr. Gorman.

DR. GORMAN: I would like to echo part of what Dr. Ward just said, in that the serum study on the mother should be the primary concern at the beginning of study of drugs because we want to make sure we're treating that mother appropriately and then worry about, at the same time, if possible, the expression in the milk for the baby's safety.

CHAIR RAPPLEY: Dr. Scialli.

DR. SCIALLI: And as a practical matter, I would suspect that the kinds of studies that will be planned based on the Guidance, the subject woman will not mailing frozen breast milk in, but will probably be present in the laboratory or in the clinical facility. And so drawing her blood wouldn't

be as difficult a problem as it would be for Tom doing his mail-in studies.

CHAIR RAPPLEY: Dr. Kocis.

DR. KOCIS: And again, looking at rare diseases, rare drug use and extrapolating this beyond, you may need to pool patients from around the country to get enough who have it. I mean, if it's a common drug, you're using a lot of people, of course you can do that with single center.

Now, when you are looking at a rare use of a drug with potentially rare complications and stuff that going in a broader way, you know, I just wouldn't say must have A, B, and C. I think it goes back to the drug, its risk, and the logistics of it.

So ideally, more and better information is always better. And yet, there are times when you are stuck getting one of the curves less information because of the circumstances of the drug use and etcetera,

etcetera.

CHAIR RAPPLEY: Dr. Feibus, any -- let's see. Did you want to add anything, Dr. Rosenthal?

DR. ROSENTHAL: You know, I'm not sure if this is relevant but you know, I'm just thinking about whether there aren't times when what we want to measure in the breast milk is not the drug at all but something intrinsic to the breast milk that might change. So, you know, I'm just scratching my head and thinking well what about if moms are taking medications that sequester, you know, cations or something. Then, will that have a change that is relevant to the infant and should we not, in some cases, be measuring the consequences of the maternal medication in the breast milk rather than the agent itself. And I don't know an answer to this question and it may not be relevant in a practical sense, but I just bring this up.

DR. HALE: That's an excellent question. We do not have any data at all on that. I've often thought and wondered about that myself, to look at the protein content, lipid content, which is, sometimes I do that. But it's a wonderful question and we don't have an answer to that.

CHAIR RAPPLEY: Dr. Feibus, any more spins?

DR. FEIBUS: I have no more.

CHAIR RAPPLEY: Yes, I'm dizzy, too. So number four, did we adequately answer that for you?

DR. FEIBUS: Yes, thank you.

CHAIR RAPPLEY: Okay. I'll move to question number five.

"Based on drug characteristics or existing clinical concerns, are there situations when a mother-infant pair study with infant plasma sampling should be recommended?" And then further, "Are there situations when a mother-infant pair study

should be conducted without a prior milk-only or milk/plasma study?"

Thoughts or comments? Dr. Scialli.

DR. SCIALLI: Well, one instance that comes to mind is that if you know or suspect that the pharmaceutical is not excreted by the infant or metabolized by the infant at the same rate as in the adult, you certainly might want to look for accumulation.

CHAIR RAPPLEY: Dr. Ward.

DR. WARD: Again, I think it is going to be relatively specific about the pharmacology of the individual drugs. But I think they are, almost in some situations, at some point, you want to know about the actual amount of drug reaching the infant's circulation.

And if it is important enough, I think for us to study in the mother and the milk, and we're really concerned about its affect upon the infant, I think we really

have to know about the exposure.

CHAIR RAPPLEY: Dr. Gorman.

DR. GORMAN: I like going behind Bob because he says exactly what I want to say.

You know, when you put on the doctor hat, you know, you want to make sure that the drug is being used effectively in the mother. And you want to make sure that the infant suffers no adverse events or therapeutic events that may not be adverse, but just not -- so this should be the gold standard. And then all other studies should be surrogates or clinical markers, or however you want to think about them in side the FDA.

CHAIR RAPPLEY: Dr. Hale, did you want to say something further?

DR. HALE: Nothing other than I concur. We have to study the baby. And particularly with drugs that produce high milk levels, such as anticonvulsants, psychotherapeutic agents, antidepressants. We really need to know what is going in the

baby and what is happening there.

CHAIR RAPPLEY: You haven't asked us but what about clinical outcomes? So I'm intrigued by the notion that coumadin can have either negligible or no measurable level in the infant, yet causes the same or similar clinical pattern. Is that not true?

CHAIR RAPPLEY: Okay.

DR. SCIALLI: Tom might want to comment on this. I don't know -- I know of several reports of babies whose prothrombin times were checked and they were normal. I don't know of any reports where there was prolongation. So I'm not sure where that came from. It may be a report I haven't seen.

DR. HALE: It came from the label.

CHAIR RAPPLEY: Well, even coumadin aside, still there is a question of whether there is a measurable amount of the medication in the baby. And then there is question about what, how is that associated

with clinical symptoms or conditions?

So, for some of these medications, there might be predictable things that we would want to monitor. And it might be that a negligible amount of medication results in respiratory suppression or sedation. Or it might be that a supposedly therapeutic level does not result in those. So, it seems to me that there is an important role for clinical outcomes as well.

Dr. Nelson.

DR. NELSON: I was just going to add that if you have a medication that is widely used, I mean, it would be fairly easy to get a fairly large population where doing just sparse population pK. And then if you have some pharmacodynamic measure that you can even look at, you could actually develop information in neonates where you could never give that drug to that neonate because it would never be clinically indicated, or even it if was clinically -- you know. So this is

an opportunity to that could actually provide information about the pharmacokinetics and pharmacodynamics in neonates that would otherwise be unavailable.

CHAIR RAPPLEY: Dr. Lawrence.

DR. LAWRENCE: There are sort of two items here. One is the occasional clinical report where an infant has an untoward outcome, maybe a seizure or something. They look at mother's history and they say, oh, she's taking drug X, ergo, cause effect. And that gets in the literature, which is very bad because babies have seizures unrelated to any medication.

The other issue is that many of these drugs we give to newborns. And that's always the first question I ask. Is this a drug we would give to a newborn? And therefore, have we already decided it is reasonably safe? You do have to look at accumulation.

With respect to the coumadin, many

years ago, there was a presumed case of bleeding in a baby whose mother was breastfeeding and had taken coumadin. No levels ever taken, but it's another example of where historical clinical outcome has been attributed to something without any proof.

CHAIR RAPPLEY: Dr. Scialli.

DR. SCIALLI: That wasn't coumadin. It was a vitamin K antagonist. It was not coumadin. It was also a baby who was reported as having excessive bleeding at the time of a herniorrhaphy.

And as a surgeon, I can tell you, when you get excessive bleeding, you love to blame it on something. But it wasn't coumadin.

CHAIR RAPPLEY: Dr. Newman.

DR. NEWMAN: Yes, but I just, I think the general point that I agree with Dr. Rappley on is that, yes, it should be done and that the plasma sampling should not necessarily be restricted to levels of the

drug. But if there are other biologic effects, whether it is the PT/PTT for coumadin or it's something if the mother is taking a hormone or a thyroid antagonist or something that could affect the baby in some way, where there was a blood measurement other than the level of the drug that might be relevant.

CHAIR RAPPLEY: Dr. Dooley.

DR. DOOLEY: Someone had mentioned the term gold standard for the mother-infant pair study. I just want to throw out another little thought and that is, especially when you are looking at things, everything from seizures to behavioral changes who might be exposed in this setting, that we keep in our minds the concept of a control infant and for whom the evaluator is blinded to whether or not that infant is exposed or not. Because so much of this is kind of fuzzy.

CHAIR RAPPLEY: Dr. Ward.

DR. WARD: I would just reinforce

that. Many times what is described as changes in stool pattern and feeding activity that from being a pediatrician to being a parent are rather frequent.

CHAIR RAPPLEY: So I think that is something also that hasn't come up previously today. And that is, to have a control population whenever possible, in select studies. Is that fair?

DR. DOOLEY: Specifically, when looking at baby outcomes, I think that, not for the milk or mother's plasma or anything, but the baby outcomes.

CHAIR RAPPLEY: Did we answer that bullet under number five for you?

DR. FEIBUS: Yes.

CHAIR RAPPLEY: Okay. All right. Question number six. "Are there any situations where it is appropriate to enroll healthy volunteers in clinical lactation studies? Please consider single versus multiple dose studies, ongoing breastfeeding

versus weaning, continued nursing during drug administration versus pumping and discarding. If no, why? And if yes, describe the acceptable situations."

So we've talked a fair amount about this. So maybe people could begin to crystallize what we think are major recommendations after all of this information we processed today.

Thoughts about that? Dr. Hale, go ahead.

DR. HALE: I would say, yes, it is acceptable, absolutely, with one exception. And that is when the infant is exposed to the medication. Obviously, and it was brought up in the ethical discussion, that if you can feed the baby breast milk, you know, via a bottle during the procedure, that there is no problem when using volunteers to do those kinds of studies. I've done them myself many times. I think it's quite suitable.

But you want to be more cautious

when you're talking about medications and exposing those infants overtly to those medications. That's probably not necessarily acceptable.

CHAIR RAPPLEY: So, I hear that then as supporting the premise Dr. Nelson presented to us that if, as we consider risk to the infant, exposure that is driven by the research question is not minimal. Exposure driven by a different kind of clinical decision on behalf of the mother could be considered in a different light. But if it is in fact the design of the study and the research question that is driving the exposure of the infant, that exceeds minimal risk.

Is that fair, Skip?

DR. NELSON: I believe so.

CHAIR RAPPLEY: Okay, so Ms. Fitzgerald and Dr. Gorman.

MS. FITZGERALD: I just wanted to mention one population group that might help

solve a problem. In doing mother milk studies, the use of surrogate moms might be an option. There also may be moms that would be interested in relactating or continuing lactation just for the purpose of studies. And that would eliminate the problem with the baby.

CHAIR RAPPLEY: Dr. Gorman.

DR. GORMAN: I continue to respectfully disagree with my two learned colleagues. And I think that, and I will explain my premises on which I base this discussion.

I know that Dr. Nelson and I are on different ends of the minimal risk discussion. So I don't want to let anyone be in any doubt that we're at the different ends of that particular spectrum. But we let mothers, I assume that most mothers want what is best for their baby and what is best for themselves, and probably in that order.

So, I don't think mothers would

expose their children to risks that they felt were inappropriate. And if they were appropriately explained, I think that mothers can consent to having their children exposed to what I would consider minimal risks.

If the drug was generally safe in adults, or presumed to be generally safe, and if it was a drug that would be likely used in pediatrics or the mother would be exposed to in a fairly high percentage, and I'm going to use the example, I used acetaminophen before and I think that's way too Skip's end of the minimal risk, I'll use Pepto-Bismol this time.

On Pepto-Bismol, there is warning. Do not use in children under 14 because of the risk of Reye's Syndrome. But I suspect there is a fair number of mothers with dyspepsia. True? Isn't that true? I think it's on the bottle still. Bismuth. Yes, okay.

So there's a poor mother who wants

to take this for her upset stomach and she decides she doesn't want to take Pepcid or Axcid or whatever else, and yet she sees this warning and she'll want to know whether it's safe. I think there is a situation where I would let that mother take Pepto-Bismol and expose her child, potentially expose her child to bismuth, as no more than a minimal risk.

CHAIR RAPPLEY: Dr. Newman?

DR. NEWMAN: I mean, I guess I would say commonly used over-the-counter medications and complementary and alternative medicines. We need to study them and I don't see how we can, if we have this, if we say you can enroll healthy volunteers. These are not people who are sick who are using these -- well, they may have a symptom. I guess the question, you know, are they sick or not? But especially the ones who are taking supplements, you know, they are mostly healthy. And I think we would like to be

able to tell whether those supplements get into breast milk.

CHAIR RAPPLEY: Dr. Nelson.

DR. NELSON: I suspect there might be protocols where, in spite of differences of statement around principles, we may all end up agreeing. Because whether or not you say to that woman, what do you normally take when you have dyspepsia and she says Pepto-Bismol, and you say okay. I mean, to what extent that then is a shift to incremental research risk is an open question. The question I would put back to Tom and I will admit it is somewhat rhetorical, is if we don't know already the transmission into breast milk, the principle of minimization of risk, which is not in subpart D but in subpart A, basically would argue that if you don't know it, you shouldn't study that first. And I will point out that if in fact you are looking at say over the counter cough and cold product, you do have someone under

the age of two who would potentially be the recipient.

CHAIR RAPPLEY: Dr. Scialli and then Dr. Lawrence.

DR. SCIALLI: As I understand the question though, it isn't about the woman who has upset stomach who wants to take Pepto-Bismol and then is going to get studied. It's about the woman who says I don't have an upset stomach, I never get an upset stomach, I don't intend to get an upset stomach. I'd like to join your study and take Pepto-Bismol and expose my baby just to see what the levels are.

I think that is the question. I haven't given the answer, but I think that is the question.

CHAIR RAPPLEY: Can I let Dr. Lawrence respond first and then Dr. Gorman?

DR. LAWRENCE: Well, I was going to comment that there are other things in Pepto-Bismol, including silicone. And we did, in

Rochester, do a study of giving antacids to lactating women and measuring the amount of silicone in their milk appropriate to the fact there were silicone in breast implants. And the level of silicone before us down here, you take a tablespoon of it, it goes up like this, and this amount over time.

So while we are looking at breast implants, we are giving mothers medication to raise the silicone level far more than any breast implant ever did.

CHAIR RAPPLEY: Dr. Gorman, then Dr. Bier.

DR. GORMAN: It was just, the selection of Pepto-Bismol, was to push the risk envelope a little further for Skip, so that I could make a little nervous, because there is a drug that we don't recommend for children because of the risk of Reye's disease. And yet the point that you are making is exactly the one that I want to take it. Healthy volunteers are, by definition,

healthy. But you could argue that during the course of lactation, a substantial number of women will take Pepto-Bismol. And should we know whether or not we can take that labeling off the side so they can use it safely with their child? Because there will be someone who will choose a potentially worse medication because you can't take Pepto-Bismol.

DR. SCIALLI: I wasn't suggesting not studying Pepto-Bismol, but as I heard Dr. Nelson, you study it in women who are going to take it anyway, rather than women who don't use it and who are just signing up for your study because they want to advance science.

DR. GORMAN: I would agree it would be a more appropriate sample.

CHAIR RAPPLEY: Dr. Bier wants to contribute here.

DR. BIER: Well, I think a categorical note to this answer will set us

back several decades, if not generations. I mean, there are going to be a vast number of drugs in a vast number of circumstances in which this is going to be an acceptable mode of study.

We were not generally talking, I mean, none of us would agree with drugs with known serious consequences for long-term three month feeding studies. But you know, I think most, the vast bulk of the drugs we're going to talk about are not going to fit into that category. And I don't agree at all with a no answer here.

CHAIR RAPPLEY: Dr. Nelson.

DR. NELSON: Well, I'm going to go back to the minimization of risk, which is in subpart A. I mean, if in fact, as people have pointed out, most women are not exclusively breastfeeding, if in fact it is possible to pump and supplement during the time of a single dose, and you're not talking about a medication that has any great half

life that would last longer than the six to eight hours, in fact, I mean, we're talking about something that may not be necessary. In other words, you may not even need to do an exposure to the infant in order to determine your maternal plasma/breast milk study.

Now, if you find that there is some in there, then you're going to have to figure out well, what does it mean relative to that dose to the infant, it then becomes a whole separate question. So, certainly, the sequence of events would be very different. And then the debate about what to do, once you know it is in the breast milk, I think would be on a much different footing, at that point.

CHAIR RAPPLEY: It seems to me that the design could have a lot to do with your minimizing risk. And this might the example where some of our established research networks, so our PROS network, our family

medicine GRIN network, which is a consortium of family medicine practices, I mean, I don't know who would fund this, because it wouldn't be related to a specific sponsor, but could establish a registry for the breastfeeding women in that practice and could develop a protocol by which they look at various levels of risk and various patterns of medication use in lactating women and the affect that that has on their infants.

And in that way, you could begin to sample these sort of commonly used medications. You could come to understand whether they are as benign as we always assume they are, or and maybe affirm that they are in fact benign. And you could also tap into these very widely used meds among women of child-bearing ages well. But it would require some degree of infrastructure to do that.

Dr. Kocis?

DR. KOCIS: I'm going to really get

crazy here. So, I'm going to take a devious approach to this and what could happen. So I first want to say, I don't want to say no. I do want to balance that with it be preferred not to. But I could certainly imagine lots of circumstances where it would work out and would be safe and acceptable to do it in normal volunteers who won't take the drug, have never taken the drug, and you're going to expose the mother and then the infant to it.

So, I could imagine that in some parts of the world or in the United States that there would be mothers with infants who are breastfeeding who are enrolling in these lactation studies week after week, month after month, as we do for blood donation, as you watch TV, kidney donation and things like that, where since the mother is not going to gain any benefit, the infant, now taking the perspective of that, is now being exposed to drugs that he or she wouldn't take. And

likewise, the mother wouldn't take, except for the fact that there is this research protocol that is out there that is paying $400 or $600 or whatever.

So, I just, you know, I don't want to go to either end. I just think we should consider that because it might happen.

CHAIR RAPPLEY: Further thoughts on question five?

DR. PENA: Six.

CHAIR RAPPLEY: Six, sorry. We don't want to go backwards. Yes, Dr. Newman.

DR. NEWMAN: So I just want to go back and ask Dr. Nelson specifically about fenugreek and how we could do our study. We met with lactation consultants, 25 of them at Keiser, and their number one research question they wanted us to help them answer was, does fenugreek work? And they are using it, or many of them are, and they believe it works. And some of the other ones don't believe it works. And so, they said, we need

to do a randomized trial and figure out if it does work.

And then we ran into difficulties with the ethics of that or not knowing exactly what was -- the trouble was being able to characterize the medication and the FDA wanting studies in mice and so on and so forth that made it not feasible.

So, given that this has been widely used, one of lactation consultants, for her dissertation, did a survey and found, I think, 75 or 80 percent of her colleagues believed that it worked and were using it. Well, how can you study something that is in widespread use and find out whether it in fact works?

DR. NELSON: I'm not going to answer your question, Tom, partly because this is the first I have ever heard of this compound. And I think it would imprudent for me to give an opinion on the record about how to study or not.

I'll only point out that the problem you --

DR. NEWMAN: I have been eating it.

DR. NELSON: Fine. And I feel better for it.

But the problem you point out is not specific. It's, I think, a problem whenever you have widespread off label use in a situation where there is an inadequate database to support that use and when one tries to get that database. And there have been situations in drug development where clinicians have been using drugs off label in their practice, where in fact there is inadequate preclinical toxicity study to support that and the FDA said you can't study it.

So, it's a general issue that I think a short answer probably would not do justice to and I would rather not try to do that.

CHAIR RAPPLEY: Dr. Lawrence.

DR. LAWRENCE: With respect to fenugreek, it's a natural product and it's a ground up plant that you get. And there is no control over quality or quantity. So what you have given one woman may not be what you give the next woman.

And this is the trouble with all the herbals, including St. John's Wort which is being suggested for depression, that people who are not pharmacologists, or know nothing about the subject get enthused about apparent work or not working and then they do studies which are not appropriate to answer the question.

But fenugreek is just a plant. And whether this plant and this plant are of the same strength, we do not know.

CHAIR RAPPLEY: I have another question to ask Skip to think about. It occurred to me as you were talking about how we don't want to disincentivize people or incentivize people to discontinue either

breastfeeding or appropriate medications as was pointed out.

What are some appropriate ways to actually recruit patients? So I'm thinking of all sorts of studies that put out flyers in the clinic waiting room. Would it be appropriate to put up a sign, for example, that said, if you are thinking about stopping breastfeeding, please talk to us about a possible research study. Would that be sort of crossing that line because it somehow encourages people to stop? Or is that kind of solicitation of a normal volunteer, healthy volunteer ethical?

DR. NELSON: Well, the honest answer, I think it's very hard to say. And it would make me a little nervous if I was sitting in my clinic and there was a sign saying if you're thinking of stopping breastfeeding and I was someone who was a supporter of breastfeeding. I mean, I think there probably relationships with clinicians

who could then make referrals or other mechanisms. I have less problem with a website where people go looking relative to drugs. I think if someone is on a drug and they are worried about the topic, they may in fact want to be part of a study. I don't think you would find a problem recruiting women who are breastfeeding because they want to breastfeed who are also on a drug that there is very little known about. And they would be willing to do that with very little reimbursement that would raise questions of undue influence.

But it's a hard question. And there is not a lot of data to support it. I might also just say, in the interest of fair disclosure, is I'm giving a shorter answer because I have a teleconference at 2:00 that I have to take. And I was kind of hoping you would go on to a non-ethical topic for a while.

CHAIR RAPPLEY: We could do that.

Thank you, Skip.

Dr. Scialli and then Dr. Rosenthal.

DR. SCIALLI: I have an ethical question, but I don't want you to answer, Dr. Nelson. Go do your call. Because I think actually that the pediatricians in the group could probably answer this for me.

In looking at healthy women who are not on a drug and recruiting them to be part of a study where they are going to take the drug and not expose the infant, would it be acceptable to, as part of the study, after they have been recruited, one of the procedures is to have them collect untreated milk and freeze it in anticipation of them giving it to their child while they are on the study taking the drug. And that's a practical issue. I guess what I am saying is, is it acceptable to encourage freezing of milk in anticipation of stopping nursing?

DR. HALE: That's exactly the way most of us do it.

DR. SCIALLI: So, that's okay.

DR. HALE: Bring your bottle in with your stored milk. Use this during today while you are on the medication.

DR. SCIALLI: They don't have stored milk until they enter the study. And you tell them as one of the procedures you're doing in the study, you're going to collect milk to store. That's okay.

CHAIR RAPPLEY: Ms. Fitzgerald and then Dr. Gorman.

MS. FITZGERALD: Yes, just to add to that, women will pump and store for a variety of reasons, particularly if they know they are having surgery or going back to work. And some will pump as much as two or three months worth of milk supply for the baby, if they have to.

DR. SCIALLI: I know it's done. I guess I was wondering whether there was an issue with having a woman do it, just as part of a protocol. Yes, I mean, I understand

it's done all the time. But I see people generally feel, yes, it's not a problem. That suits me fine.

CHAIR RAPPLEY: Dr. Gorman and then Dr. Dooley.

DR. GORMAN: I just wanted to change the sign in your waiting room to say when you are getting ready to stop breastfeeding, talk to us about a clinical trial.

CHAIR RAPPLEY: Okay, that's good.

Dr. Dooley wanted to comment. Did you want to address that specifically?

DR. SCIALLI: You could actually have the sign say please talk to us before you decide to stop breastfeeding. Because if the woman is three weeks postpartum, you might want to have a different conversation.

CHAIR RAPPLEY: Dr. Dooley.

DR. DOOLEY: And along the same line, we do need to remember that everyone stops nursing eventually.

CHAIR RAPPLEY: Dr. Rosenthal.

DR. ROSENTHAL: I had a different comment which I want to make, but I just want to have you talk to my wife after this.

(Laughter.)

DR. ROSENTHAL: I'm just wondering. I took from this morning a very clear understanding that rats don't provide a good animal model for studying any of these issues and I'm wondering whether some of the nuances in the studies in the designs that we are discussing can be informed using other animal models. So, I just throw that question out to the experts at the table.

DR. HALE: The only animal model studies that I have seen are mice and rats, the only ones I have really seen reported. And as I say, they are both way too high and the levels are far far higher than what you see in human. So most of us have just generally accepted the fact that drug studies in animal models are not very useful.

There may be an animal that is good,

but I don't know what that would be.

DR. NEWMAN: Whales.

DR. HALE: There's fat content in whales.

CHAIR RAPPLEY: Dr. Kweder?

DR. KWEDER: We actually looked into this extensively when we developed the Draft Guidance. And we spent a lot of time talking to our FDA college and the Center for Veterinary Medicine and in the Center for Food Safety. There was a group in Food Safety that was looking very carefully at how good a predictor the cow could be. They also looked at sheep and another animal. I can't remember. They were doing it for a different reason, but basically found that none of them were particularly reliable predictors of human drug or chemical transmission. Because we thought, you know, perhaps its just you need a different animal than the typical laboratory model. And they were not very encouraging.

CHAIR RAPPLEY: Dr. Lawrence.

DR. LAWRENCE: Historically the original data was collected on ruminants. And it was very unsatisfactory, gave us all sorts of misinformation. The only thing that really comes close is primates. And that's a very expensive and troublesome model.

CHAIR RAPPLEY: Other thoughts, then about question number six? Have we given you enough food for thought on number six?

DR. FEIBUS: You've given me many things to think about. Thank you.

CHAIR RAPPLEY: Question number seven. "When in the drug regulatory process should clinical lactation studies be requested and done?"

So let's think about the model that Dr. Murphy presented yesterday, the European model where they are requiring a plan for pediatric studies for all medications to move forward for authorization for marketing. And that in fact they must justify why it is not

appropriate or necessary to study in a pediatric population in order to move forward. I mean, we're not there with pedes, but that would be a place to begin thinking.

Dr. Ward, you look ready.

DR. WARD: Yes, I think the only justifiable place for these is after phase three. I think we have to know population affects and kinetics. And I think at that point, this qualifies from my perspective as a special population. And I think only for a disorder that is occurring just in lactating women, for example, would you go to it earlier. Just, as I wouldn't be inclined to take -- I wouldn't be looking for volunteers in my NICU, okay, for studies that didn't apply to that population. And I'm glad Dr. Nelson isn't here.

CHAIR RAPPLEY: Dr. Garofalo.

DR. GAROFALO: Yes, I mean, I would concur with that. You would need to know the dose, you know, have very well established

the dose so that you weren't studying the correct dose. And those sorts of things happen. And I think just from a purely company perspective, it's something that you would want to make sure that the compound was making it to the market, really, before you thought about the special safety considerations.

CHAIR RAPPLEY: And would that be because of the cost of doing these studies?

DR. GAROFALO: I think the safety profile, just making it all the way through. We had an example yesterday of a submission that was made and it was rejected based on safety. So --

DR. WARD: I think it's almost an ethical one at that point. You don't want to expose a vulnerable population to a drug that may have some problem that prevents it from going to market. And that would usually be safety, a safety issue.

CHAIR RAPPLEY: Would it need to be

approved for children? So for example, the product --

DR. WARD: No.

CHAIR RAPPLEY: -- that we discussed yesterday was not approved for children but it is approved in adults. And we specifically continued that not approved in children because of information we are gaining about that.

DR. WARD: I would like to change your verb. It wasn't labeled for children. It was approved or not approved. But off-label usage is so much a part of pediatric medicine still that I think we must practice with off-label use.

CHAIR RAPPLEY: Dr. Gorman.

DR. GORMAN: The labeling or approval for children I think would be not required in this particular population as a prerequisite for a study because there will be conditions that we would never treat infants for that we will treat the mothers

for. And I was thinking about the SSRIs. Maybe there is some use for them in some condition that we, well, it's possible. But there will be exposure and we'll never treat children with, babies with SSRIs.

CHAIR RAPPLEY: Dr. Cnaan.

DR. CNAAN: Dr. Ward said most of what I was going to say. Basically, until after the Phase III, we don't have accumulation of sufficient safety information that would justify doing this study. And I agree with Dr. Gorman that we don't need the approval in children because the reality is that there will be moms out there receiving treatments that may transfer to the milk that the children would never receive.

CHAIR RAPPLEY: Dr. Newman.

DR. NEWMAN: So just to clarify. So, I think we all agree after Phase III. But were you also saying before marketing to the public? And then how about drugs that are already on the market?

DR. WARD: Tom, my impression would be that if we could provide that information to the population that may be taking this. And if they are lactating women, I think we would improve their decision-making by having that information.

DR. NEWMAN: No, I'm just trying -- I think it would be wonderful. I'm trying to figure out are you suggesting that we need to have this information? I guess as is going to be happening in Europe, this would be one of the things that is required before it can be marketed to the public is studies in lactating women. Those studies would have to be completed. I think that would be great. But I'm just trying to get clarity on that. Is that what you are recommending?

CHAIR RAPPLEY: So some justification for that would be the number of women in the reproductive age group who are consumers of medications that go to market.

DR. NEWMAN: But I guess, as we

think about it, we describe how all of these studies have been done, we are all envisioning women who are already taking these medicines. So the obstacles to being able to do the study before it's on the market seemed considerably greater.

CHAIR RAPPLEY: Dr. Kweder.

DR. KWEDER: Yes, this is Sandy Kweder. Let me just say that, you know, one of the things to keep in mind here, and maybe this is part of the discussion, is that to open another can of worms, we have not historically addressed drugs in breast milk under the framework of pediatric trials.

If you think about things that have come before this Committee, to my recollection, there has not been much in that area. It's not been part of the discussions for any of the legislation. You know, we start the age groups at birth, but we always think about direct administration of the drug to the child with the intent of therapy for

the child.

This is a little bit of a hybrid and it is a little different. You're treating the mother with the potential consequence of exposing the child. I don't think that the Europeans view it differently. I think the European model continues to look at intentional administration of drugs to children in their model of pediatric product development. So I'm not sure the European model really helps us, particularly in this case.

CHAIR RAPPLEY: Only that it is being tied to authorization to market.

DR. KWEDER: Well it is, except that this isn't part of their model. This isn't part of what they tie.

CHAIR RAPPLEY: Yes.

DR. WARD: Well, could you go ahead and discuss a little bit farther then, Phase III versus post-approval from a regulatory perspective?

DR. KWEDER: Say a little more about what you mean, Bob.

DR. WARD: What I'm thinking about is then I liked Skip's paradigm in which he referred to the breastfeeding baby as really an extension of the mother, essentially. That, if the mother is going to get this drug and the infant is breastfeeding, then the child has the same condition.

But that, I think, applies in particular for a marketed drug being given to the mother therapeutically for a disorder. As opposed to, at Phase III this mother is receiving this drug. She does have the disorder but you are still collecting data.

Is the fact that we're still collecting data and it has not reached the magnitude to allow approval by the agency, does that set it apart?

DR. KWEDER: I think that it could set it apart, simply because you haven't established that there is a specific role for

the product in the mother. You haven't clearly established that the primary, the person receiving it primarily, has demonstrated a positive benefit to risk ratio.

And so, just off the top of my head, I would say this is probably the next step. Does that help you?

DR. WARD: It does, except, historically, if we wait until after approval, obtaining data in a meaningful way from a sponsor of a product doesn't always occur.

DR. KWEDER: That's correct, unless you make it part of the discussion at the time of approval with post-marketing commitment in this special population.

DR. WARD: I'm reminded of a slide the pediatric team used to put up ten years ago about requested studies, post-marketing studies in children that have been promised. And one out of seven was done.

DR. KWEDER: Well, we're encouraged that the new legislation will help that.

CHAIR RAPPLEY: Is there any rule that currently exists that requires us to view the infant as an extension of the mother? We could rethink how we view the breastfeeding infant and the relationship to the mother and include that under the pediatric rule. Is that possible?

DR. KWEDER: That's not a question I am authorized to answer.

(Laughter.)

CHAIR RAPPLEY: Dr. Gorman.

DR. GORMAN: I would like to make a suggestion that there may be another path to get the same answer, which is to, I hate to use the word require because it sounds so formal, but I'm going to say require that lactating women be included in Phase III trials.

If ten percent of women are lactating at any one time, the pharmaceutical

companies will be enthusiastic because there will be a ten percent larger population for them to recruit from.

(Laughter.)

CHAIR RAPPLEY: Dr. Garofalo.

DR. GAROFALO: I don't concur with that. I think it's going to be hard to have lactating women that weren't exposed when they were pregnant. And that's an issue. We always try to exclude that. We don't, you know, we often, we have toxicology work, we have concerns, almost never pregnancy category A, right? So, there are a lot of issues with exposing pregnant women and then lactating women before you know that the risk-benefit exists for this product.

CHAIR RAPPLEY: Dr. Cnaan.

DR. CNAAN: I think that many of my colleagues would argue that you just introduced more variability. And then you would need to stratify on the lactating women and those strata would be too small to be

meaningful. And you would be opening such a can of worms from a design perspective, a pure statistical design perspective, that it wouldn't fly.

CHAIR RAPPLEY: Ms. Vining.

MS. VINING: I know that the Congress recently passed the drug safety bill. And I don't have enough information on it to be able to really speak to it but I believe that there were some post-marketing requirements in there that may address some of the issues that we've got going here. So there may be something in the works that will help us move forward in this --

DR. KWEDER: Yes, actually, in the bill it does give the Agency the authority to require certain post-marketing studies and nicely carves out, particularly, for special populations. Pregnant women are considered under that. I don't recall if it says lactating. But it is written in a general manner that would allow us to do this.

The challenge before us, of course, is to determine what kinds of conditions, what is enough to make us be able to say this is a requirement and not just somebody's whim?

But I am encouraged that this will give us a little bit more of an opportunity to look at these special populations and special questions. One of the challenges will be, for us, is under what circumstances would we require it? You know, if we had to say that we're going to require, if we went out and said you know, we're going to start interpreting this to say that every drug that is used in women, likely to be used by women of reproductive age, we're going to require these studies, I guarantee you I'd be looking for another job.

CHAIR RAPPLEY: Dr. Newman.

DR. NEWMAN: Yes, it seems like a reasonable approach to this, in terms of the timing would have it be related to how often

the drug is used in lactating women. And so drugs which are very very commonly used, we would request it sooner and expect to get it sooner. And when there are some minimum number of prescriptions reached, that is when you need to know it.

If it's a drug that it will take 15 years to accumulate very many lactating taking it, then you give them a lot more time to do the studies.

DR. KWEDER: I guess the question, of course, would be, is it the number of women who are lactating and taking the drug? What about the number of women who chose not to nurse their baby in order to take the drug?

DR. NEWMAN: So we would say, I guess, woman who would like to lactate taking the drug.

(Laughter.)

CHAIR RAPPLEY: Dr. Fant.

DR. FANT: Yes, this sort of goes

back to a question that came a little earlier and sort of relates to what we are talking about now. You know, I'm really not that familiar with the animal models that people have referred to, but it seems like, I think Dr. Lawrence mentioned, which was kind of my suspicion, that I guess the primate models were sort of the closest that came. But I'm not sure which primates people looked at.

And I'm wondering if it wouldn't be worth just revisiting the question of whether or not there is a decent animal model out there. Because if this is going to be a major thrust of clinical research in the future, and we're talking about doing an awful lot of human studies, clinical research studies using humans, and from what little I know about the expense of doing clinical studies in humans, assuming we did find a decent primate model that could give us at least some decent preliminary basic information which could then allow us to

focus some of the human studies in a better way, then the expense that would be involved with that would be dwarfed by the expense that we're going to incur during studies in the humans. And so on balance, you know, it may actually be cost effective if we had a decent animal model.

And so I don't know if we are at the point where any decent model has been excluded or whether it is worth rethinking the question.

CHAIR RAPPLEY: Any response to that? Dr. Lawrence.

DR. LAWRENCE: I would just comment that Dr. John Wilson, about 20, 30 years ago, did use primates in some of his original work in his drug dissolution curves and things like that in milk. But I don't know if he's still working. Do you know, Tom?

So there is historical data. I don't know of anybody who has done it in the last decade.

DR. BIER: I'll bet the cost of primate studies is more than the cost of human studies.

DR. WARD: Absolutely. Yes, there is the San Antonio Primate Center and there is one in Oregon as well. I don't think John is still working with primates. I think he's still at LSU, though.

But I think Denny is right. It's cheaper to do them in humans.

CHAIR RAPPLEY: Dr. Rosenthal.

DR. WARD: You have fewer demonstrators.

DR. ROSENTHAL: Let me start talking before the discussion continues. But I am going to open up or revisit a can of worms that has already been opened.

But you know, I am sitting here wondering about the scope of the Pediatric Advisory Committee. And I'm not trying to make work for the Pediatric Advisory Committee, but I'm wondering, I'm just

wondering whether for drugs that are commonly used, and I don't know which these would be, but for drugs that are commonly used in lactating women, whether the Pediatric Advisory Committee shouldn't have a more scheduled regular review role for the potential impacts in kids who are nursing for those agents.

So, it's just a question.

CHAIR RAPPLEY: Dr. Mathis.

DR. MATHIS: We would certainly take that into consideration. And having worked frequently and for a long time with this committee, I can't think of a better committee to think about these things. So we would definitely consider that.

CHAIR RAPPLEY: And I would guess along the lines of reconsidering the infant as something other than an extension of the mother.

DR. ROSENTHAL: And I just want to apologize to my colleagues.

CHAIR RAPPLEY: That's another three day meeting. Any other thoughts about that? Yes, Dr. Hale.

DR. HALE: I think one thing we need to think about for sure when we do or promulgate these studies is that someone has to look at the drug we're talking about. If you're talking about an anticancer drug, a nasty deoxyrubicin or something like that, no, you don't want to do lactation studies in those mothers.

If you're talking about a new penicillin or something that is relatively innocuous, sure. But there has to be somebody that, because you guys are going to have to make a decision, oh, yes, you do have to do a lactating or a study in lactation group. There needs to be some mechanism for doing that.

DR. WARD: I think we're back to an issue that was raised earlier about frequency of use. We actually, as plebeian as it may

be, we actually need survey information about what drugs and how often are used during the first year after delivery.

CHAIR RAPPLEY: Dr. Kocis.

DR. KOCIS: Which brings back the question, I think we spent the whole afternoon figuring out how to do them. I think we have come a long way. And certainly, I have learned a whole lot and most of you have much more experience in this.

It comes back to a couple of things, you know, requirements versus asking, and wish lists for that, and how that is going to be done. Because I can imagine, given the costs and complexities that we've talked about in doing these studies, that there is going to be great reluctance on the part of the manufacturer to undertake these studies, unless it is an exclusively postpartum drug. Unless they are forced to, they will simply put in there under lactation there is no

data, or we don't recognize, use one of the old drugs, or use something.

And then I'm afraid that then is going to preclude drugs that may be very helpful and useful and efficacious for young women of childbearing age and thereafter from getting that.

And so, you know, I don't know how you are going to decide that. Well, I'll just stop there.

CHAIR RAPPLEY: Dr. Scialli.

DR. SCIALLI: The concern is that it doesn't preclude the use of new drugs. It more often precludes breastfeeding. And we don't have any way of knowing how many women would have breastfed on the drug.

You know, a woman is on the drug. It's a new drug, she's using it for whatever reason during pregnancy and she doesn't want to stop the drug and that may be the appropriate decision, given her health condition, but she decides not to take the

risk, so to speak, of nursing. And that happens a lot.

CHAIR RAPPLEY: This may be a totally silly idea, so I'm putting it out there to get your impressions. But we have the National Children's Study Centers that were just funded. And these were centers across the country that were selected to provide prospective studies 20 years in duration. They have to do with mothers and infants and all sorts of prematurity, perinatal issues. I don't know that breastfeeding or lactation is a component or a focus of any of these, but these are site-selected to provide assessment of very diverse populations. The infrastructure exists. And in a reasonable world, we might look to seeking federal funding to support a breastfeeding component where we could follow mothers and children, long-term, as they naturally evolve in their decisions about breastfeeding and medications that they use.

DR. WARD: I sat on the working group for the pharmacology section of the National Children's Study. And we struggled at some length simply to figure out how to measure and carefully determine exposure during pregnancy. And our site is one of the vanguard sites. And our ultimate conclusion that we would simply have to take historical information. What did the mother report and how much?

But I think your proposal is one that is very timely. They are expanding the National Children's Study from the vanguard sites now. And they are collecting a number of other things such as environmental exposures that has never been done with this detail.

CHAIR RAPPLEY: And they are building biorepositories.

DR. WARD: Yes.

CHAIR RAPPLEY: So they are storing both serum and they could store breast milk.

DR. WARD: Well I think they actually may be storing breast milk, but I don't think they are sure what they are going to do with it. And I am almost positive it is not anywhere close to a comprehensive collection like we have been discussing that we think would be pharmacologically meaningful. It has not been hypothesis driven. And I think here we have an opportunity to add a semi-hypothesis driven aspect to it.

CHAIR RAPPLEY: Would it be the kind of survey you just described?

DR. WARD: I think the survey aspect would be important, but when we discussed herbals, they come in such a wide spectrum. One particular molecule may have a methyl group added, taken away, a double bond inserted. So, but for medications, I think we could really do that kind of quantitation, because we could ask specific questions. By ELSIM aspect, you can analyze a large number

in a very small quantity.

But I think adding that as an aspect to measure drugs given to women as part of their health care, seems both meaningful and an opportune time.

CHAIR RAPPLEY: And we might could also use it as an opportunity to understand how women make decisions about both breastfeeding, duration, medication use and other things.

Dr. Garofalo.

DR. GAROFALO: I just wanted to add that anything that you could do that would help with the infrastructure of getting these trials done will help the industry respond.

So, if these are Phase IV commitments, I think many times, certainly, we did this for the anticonvulsant that I worked on, knowing that it would be used in lactating women. So it does happen. But the more complicated the trials get, the more difficult it is. And these are generally the

Phase I folks, you know, and not the clinical trials folks.

And so, if you were a clinical pharmacologist that had never had any interaction with us and you were told go out and do this kind of trial. And then it looks very complicated because you open up the guidelines. So that was where I was going with the, do we need the mother-infant pair, et cetera? The simpler, but you know, it has to be meaningful, scientifically meaningful and rigorous, but the simpler we can make it for industry, then the more likely you are to get these trials done.

So, I think there is a recognition, but it's going to take sort of multiple points of impact to get these things done.

CHAIR RAPPLEY: Dr. Mathis.

DR. MATHIS: Just to add on to that, I am curious, and perhaps Dr. Hale can provide some information on this, what kind of an infrastructure exists now? We've

certainly seen with pediatric studies that initially, there wasn't a huge infrastructure, but as the infrastructure became more sophisticated and more built up, more complex studies were indeed easier to get. I'm wondering how many other people, other than you, are doing this?

DR. HALE: Maybe three or four that actually do drug studies in milk. Ken Ilett in Australia has done more than anyone and he has just retired. Gideon Koren and Shino Ito from Canada at the MotherRisk, do some. There are a few anticonvulsant studies that come out of Atlanta.

Other than that, I don't know of a lot that are done.

DR. WARD: The other aspect, as Dr. Giacoia is sitting here, there is the perinatal, obstetric and perinatal research unit. There are four of those. And here you've got obstetricians that are really focused on pharmacology. And I think that

what can happen is that individual sites can serve as the nidus around which studies are conducted at multiple sites with their peers and colleagues that can recruit at other hospitals and in other populations. It just takes money.

DR. HALE: It takes a lot of skill to analyze drugs in milk. It is a whole new ballpark. It's not like plasma at all.

DR. WARD: But I would maintain that the analytics, I wouldn't say they are a sitting duck, but a good chemist can do it. Berlin and I used to share a lab. And I think if you develop techniques, and I think the techniques are actually relatively straightforward and have been published, they can be adopted. And I agree, I would not maintain it as absolutely easy because it is very different from serum and plasma, but it is doable.

CHAIR RAPPLEY: Are there other comments around question seven?

(No audible response.)

CHAIR RAPPLEY: Is the Agency satisfied with comments so far?

DR. FEIBUS: I think we are very satisfied and I would like to thank you all for all of the thought and creativity that you have put into this discussion. I think we got the answers to our questions. And the enthusiasm with which you have explored possible other avenues and possible participation that you, as a group, might have, is very encouraging. And thank you very very much for your time and for sharing your expertise with us.

CHAIR RAPPLEY: Does anyone wish to make further comments or have a final opportunity to make a comment?

(No audible response.)

CHAIR RAPPLEY: Well thank you, also, on behalf of the Pediatric Advisory Committee, all of you who have come out, especially today and for those of you who

stayed through three days of meetings. I think it was very rewarding. Again, it is gratifying to be part of this important process. Thank you.

(Whereupon, at 2:33 p.m., the meeting was adjourned.)