

## FOOD AND DRUG ADMINISTRATION

## ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE

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Food and Drug Administration  
Rockville, Maryland 20857

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

(8:34 a.m.)

1  
2  
3 DR. BYRN: While we're getting ready, let's  
4 introduce the guests to the committee. On my right is Arzu  
5 Selen.

6 DR. SELEN: Good morning.

7 DR. BYRN: Good morning.

8 Larry Lesko: Then on my left is Shinya Ito and  
9 Patrick McNamara. The rest I think are all accounted for.  
10 Oh, yes, and Dr. Peg Neville also. I was just introducing  
11 the speakers, but there's another. So, we have five  
12 guests. Thank you very much for coming.

13 I'd like to call the meeting to order and read  
14 the conflict of interest statement.

15 DR. CHAMBERLIN: Thank you.

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

20 Since the issues to be discussed by the  
21 committee at this meeting will not have a unique impact on  
22 any particular firm or product, but rather may have  
23 widespread implications with respect to entire classes of  
24 products, in accordance with 18 U.S.C. 208(b), all required  
25 committee participants have been granted general matters

1 | waivers which permits them to participate in today's  
2 | discussions.

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

7 |           With respect to FDA's invited guests, Dr.  
8 | Patrick McNamara, Dr. Frank Martin, and Dr. Leon Shargel  
9 | have reported interests which we believe should be made  
10 | public to allow the participants to objectively evaluate  
11 | their comments.

12 |           Dr. McNamara would like to disclose that his  
13 | employer, the University of Kentucky, has received research  
14 | funding from FDA and NIH for studies concerning drugs in  
15 | breast milk.

16 |           Dr. Martin would like to disclose ownership of  
17 | stock in Johnson & Johnson, Imclone System and Alkermes.  
18 | He is also a consultant to Target Protein Technologies, and  
19 | he is employed one-third of the time with Johnson & Johnson  
20 | Alza.

21 |           Dr. Shargel would like to disclose that he is  
22 | employed by Eon Labs Manufacturing Company.

23 |           In the event that the discussions involve any  
24 | other products or firms not already on the agenda for which  
25 | an FDA participant has a financial interest, the

1 participants are aware of the need to exclude themselves  
2 from such involvement and their exclusion will be noted for  
3 the record.

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

8 DR. BYRN: Thank you very much, Nancy.

9 We can begin the clinical pharmacology group  
10 discussion with Larry Lesko who will provide an  
11 introduction and background.

12 DR. LESKO: Well, good morning. It's a  
13 pleasure today for me to be here to discuss what I think is  
14 a very important topic, perhaps one that's under-  
15 appreciated, and that is the drug transfer in breast milk  
16 to infants. It's important because, when this occurs, the  
17 infant is in a state of rapid development so it becomes a  
18 critical situation, particularly in the hospitalized mother  
19 who may be breastfeeding or in the neonatal period, in the  
20 first 30 days of life where drugs in breast milk can have  
21 an impact on development of the child.

22 Now, we've had probably more than 500 years'  
23 experience with the fact that breast milk is perfectly  
24 suited to nourish infants. You see reference to it in our  
25 culture going back to the 15th century in paintings, more

1 | recently in stamps. You can find statues, and very  
2 | recently a report from the HHS that talked about public  
3 | health goals for the next decade.

4 |           If you go to that HHS document, section 16,  
5 | which talks about maternal/pediatric health, there's a  
6 | section there that deals with breastfeeding, and the goal  
7 | in the United States is to raise the percentage of mothers  
8 | that breastfeed from the current number to 75 percent in  
9 | the early days following birth. Further, that report  
10 | targets 50 percent of mothers for breastfeeding within the  
11 | first 6 months. So, it's a substantial public health goal,  
12 | and in light of that, we feel we need to know more about  
13 | drug transfer into breast milk.

14 |           Let's talk about demographics a bit. We're not  
15 | talking about an orphan population, a small population  
16 | here. 61 million, the number of women between 15 and 44  
17 | years of age. 4 million, the number of newborn infants.  
18 | 65 percent, the fraction of infants who breastfeed in the  
19 | hospital shortly after birth. 2.6 million. This is the  
20 | number of potential recipients of unwanted drug residues  
21 | that might come from therapeutics in the mother and  
22 | transferred into breast milk. We can compare this  
23 | population -- maybe we want to call it a special population  
24 | -- to other populations we study routinely in drug  
25 | development, renal patients, hepatic patients. Those

1 numbers are not as large as this group.

2 Now, new parents want to give their babies the  
3 very best in nutrition and they have choices to make about  
4 breastfeeding or using commercial formulations. Many  
5 choose breastfeeding. In fact, the American Academy of  
6 Pediatrics has authored a couple of articles in some of the  
7 FDA journals. FDA Consumer, for example, in September 1998  
8 had an article by the American Academy of Pediatrics. They  
9 talked about a lot of things but the fact that human milk  
10 is made for human infants. It meets all their specific  
11 needs.

12 They say in that article that we have a very  
13 scarce amount of information on the transfer of drugs.  
14 Oddly enough, commercial formulas for infants is closely  
15 regulated by the FDA. In contrast, we have no FDA guidance  
16 or regulations that pertain to drugs that might appear in  
17 breast milk and be fed to the infant.

18 Now, when it comes to medications for the  
19 breastfeeding mother -- let's say she has a chronic  
20 condition, diabetic condition, epilepsy, hypertension,  
21 maybe short-term problems like infections -- a big decision  
22 has to be made about therapeutics and what we're going to  
23 give to that mother. We have to weigh, on one hand, the  
24 benefits of the medication for the mother, which are  
25 obviously substantial. On the other hand, we have to weigh

1 the risks of medication to the infant. What may be safe  
2 for the mother may not be safe for the infant.

3 And where do mothers frequently go? They  
4 frequently go to where a lot of us go for health care  
5 information when we can't find it in the package insert.  
6 We go to the Internet. This poster is from a Breastfeeding  
7 in the Information Age Week that is going to begin this  
8 year, next month, August 1st, to try to promote  
9 communication about drug transfer into breast milk.

10 I went to one of the sites to see what I would  
11 find in the area of drug transfer in the breast milk, one  
12 of the more respected sites, the one on perinatology. And  
13 this is only one of many. This one is for professionals as  
14 well as educated lay people. I started at the front  
15 alphabetically, and I went through a few drugs. I want to  
16 share with you some of the things I found.

17 Look at what it says. Acyclovir, excretion  
18 into milk is concentrated. Albuterol, excretion into milk  
19 is negligible. Aminoglycosides, most excreted into milk.  
20 And this one, excreted into milk but affects on infant are  
21 unknown. They may be of concern. And then the last one,  
22 very common, caffeine, excreted into milk, but acceptable  
23 when not used excessively. These were the drugs for which  
24 data was available. And you imagine there were other  
25 categories of drugs that had no information or were

1 | contraindicated. But this was by far the biggest chunk of  
2 | drugs in this reference place on the Internet.

3 |           Now, when you look across all of these drugs  
4 | and pay attention to all of those statements, because there  
5 | was a last column on this Internet web page, which told the  
6 | mother about the safety of these drugs if she was  
7 | breastfeeding. What was amazing, despite that information,  
8 | is that all were rated compatible with breastfeeding. So,  
9 | if you're reading that, to me it was very confusing about  
10 | whether these drugs were safe, and I'd have a bit of a  
11 | problem that they're all compatible, given the statements  
12 | that appeared on the web page. So, this went on for  
13 | hundreds and hundreds of drugs, and at the end of the day  
14 | you walk away saying I don't know a heck of a lot about it.

15 |           Well, what happens when you're faced with that  
16 | kind of uncertain information? Well, a couple of things  
17 | will happen. The mom will stop breastfeeding, and that  
18 | results in some detriment to the infant in terms of the  
19 | benefits of feeding, ranging from nutrition to protection  
20 | against disease states, and there are a lot of down sides.

21 |           The other problem is the mom decides I'm not  
22 | going to take the drug. There's a risk there because in  
23 | particular if this is a chronic condition, there may be an  
24 | aggravation of that disease state.

25 |           Now, I think it's interesting, as we talk about

1 | drugs in breast milk, that we turn our attention to another  
2 | source of milk, the bovine milk, and the fact that the  
3 | dairy industry for a long time has had a systematic system  
4 | in place to monitor the drug transfer into breast milk.  
5 | Cows get antibiotics. Cows get a lot of things for  
6 | therapeutic as well as nutritional reasons. But the FDA  
7 | Center for Veterinary Medicine has been concerned about  
8 | this for a long time and has set up a procedure to monitor  
9 | drug transfer. Antibiotics are one class, and there are  
10 | systematic screenings in place to determine the safety of  
11 | milk with regard to drug transfer. CVM has put out  
12 | protocols for the measurement of drug in cow milk, and in  
13 | many ways we could do the same thing for human breast milk.

14 |           With that introduction, let's talk about why  
15 | we're bringing this to your attention for your discussion  
16 | today. We feel that there's a public health  
17 | responsibility, given the size of this population, as a  
18 | regulatory agency to do something about the paucity of  
19 | information in the area. We would like to convey ways to  
20 | identify and reduce barriers related to medications, which  
21 | may keep women from initiating or continuing to breastfeed  
22 | their infants.

23 |           We feel that the major barrier is the absence  
24 | of reliable data, the absence of comprehensive studies on  
25 | drugs in breast milk. We've gone through our NDAs. We've

1 failed to find well-designed breast milk studies in any of  
2 our NDAs. If they're there, they're very rare. We do see  
3 some information. Frequently it's incomplete, almost to  
4 the point where we feel uncomfortable putting any  
5 information into the label. So, what the patient and the  
6 physician gets then is a label without any information.

7 We'd also like to encourage improvements in the  
8 science of drug development so that somewhere in an  
9 efficient, informative, and cost effective way this  
10 information is obtained during the course of drug  
11 development so that we can use it for conveying the  
12 information to the public.

13 We'd like to see data on the transfer of  
14 medications in the breast milk with some hypothesis about  
15 the potential risk to infants. We'd like to include this  
16 information in our product labels related to breast milk,  
17 not unlike the information we currently are including in  
18 labels with regard to pediatric patients, with regard to  
19 pregnancy. This is a very similar issue and a problem.

20 And we'd like to empower women and their  
21 physicians to be able to make these rational choices about  
22 benefits and risks, to weigh the drug therapy against the  
23 risk to the infant, to weigh the benefits of breastfeeding  
24 against the benefits to the mother. You need information  
25 to do this, and we don't think it's a big stretch to get

1 | the information.

2 |           We're going to proceed with this discussion  
3 | through three presentations. Dr. Arzu Selen will talk  
4 | about the current initiative within the center to develop a  
5 | framework for a guidance for industry on determining drug  
6 | transfer into breast milk. The methods to do this I think  
7 | are very much within our reach. In many ways, they're  
8 | clinical pharmacology issues.

9 |           We're going to hear from Dr. Ito who has  
10 | considerable experience in this field and in particular the  
11 | mechanisms of transport in mammary tissue and getting drugs  
12 | into breast milk that way.

13 |           Then finally, Dr. McNamara, who has also  
14 | conducted extensive research in this area, and he'll touch  
15 | upon some things.

16 |           What we're looking for here is a hierarchy of  
17 | methodologies that could be used in drug development to  
18 | gather the information that we need. These may be in vitro  
19 | methods. They may be in vivo methods. And there may even  
20 | be drugs that we can take off the table and say that we  
21 | don't need information for these drugs because we have a  
22 | high degree of certainty that they don't transfer into  
23 | breast milk.

24 |           If they do transfer into breast milk, we have  
25 | some questions about the magnitude of the clinical effect

1 of that drug. How do we estimate that? Is there a  
2 threshold level below which we can feel safe about that  
3 exposure in the infant?

4 So, these are the type of issues that hopefully  
5 we'll get a good discussion of today. Thanks.

6 DR. SELEN: Good morning. This morning we  
7 would like to get your thoughts and your views on drug  
8 transfer into breast milk. We want to specifically talk  
9 about the methods, the in vivo methods and also in vitro  
10 methods.

11 So to talk about these issues that we would  
12 like to discuss with you, I'd like to go over some of the  
13 background material. Now, the outline for this talk this  
14 morning is, following Larry and after my talk, there will  
15 be Dr. Ito and Dr. Pat McNamara. Before we go into their  
16 presentations, I will highlight some of the areas that we  
17 would like to discuss with you in terms of the key points  
18 and the key elements of the questions, and then we'll go to  
19 the questions and open it for discussion.

20 So, this guidance that we referred to is the  
21 Clinical and Nonclinical Studies for Drug Transfer into  
22 Breast Milk. We fondly refer to it as the Lactation  
23 Studies Guidance. There's a big guidance working group.  
24 Actually it's a very efficient group of individuals. There  
25 are 16 core members. Members are from CDER, CBER, which is

1 the biologics, CVM, and we also have a member from the  
2 Office of Women's Health. So, it's a huge, big group but,  
3 as I said, a very efficient group, and because of their  
4 energy and input, we achieved a lot in a very short period  
5 of time. And I'm looking forward to continuing to work  
6 with them, as well as our supervisors, Drs. Lesko and Sandy  
7 Kweeder. It's a privilege.

8 Now, the driving force of this guidance, what's  
9 behind this guidance, is really in this slide. I just want  
10 to take you through the figure. This bar chart has four  
11 clusters. The first three clusters represent data, and of  
12 these, the light colored bars are the percentages of babies  
13 that are breastfed at the time of birth or close to birth.  
14 The dark colored, the pink colored bar is the  
15 representation of the percentages of children that are  
16 still being breastfed 5 or 6 months after birth.

17 Now, this chart illustrates that there's an  
18 increased awareness and acceptance of breastfeeding because  
19 we could see that over the years, starting from 1980, 1997  
20 and 2000, the percentage of babies that were breastfed  
21 increased from 35 percent to 46 and to 65 percent. So,  
22 there's an accepted interest on the benefits of  
23 breastfeeding.

24 But what else is happening? If you look at the  
25 solid colored bars, that's the percentage of babies that

1 | are still breastfed 5 or 6 months after birth. We have 14,  
2 | 20 and 16 percent. So, the mothers are not continuing to  
3 | breastfeed. Really that outlines an issue, as Dr. Lesko  
4 | was presenting, that there's a serious concern that there's  
5 | a lack of information that people feel the choice. They  
6 | either continue breastfeeding or they do not take their  
7 | medications. There's a conflict.

8 |           And this is the area that we have to improve on  
9 | because the fourth cluster, which is the Healthy People  
10 | 2010 Goals, says, as Dr. Lesko also pointed out, that at  
11 | the time of birth or close to that period, there will be 75  
12 | percent of babies that will be breastfed, and of those, we  
13 | still hope that by 5 or 6 months after birth, 50 percent  
14 | will be still breastfeeding. This is a significant  
15 | increase.

16 |           And if we're looking for such an increase, then  
17 | we're looking for a ways and means to close the gap in  
18 | information. So, we have to have the science supporting  
19 | this objective and, in addition to that, of course,  
20 | providing information in a way that the mothers who read  
21 | the prescriptions, read the package inserts, can really  
22 | utilize the information, and can continue breastfeeding and  
23 | the level of information is communicated at the level that  
24 | is clinically meaningful.

25 |           So, I think this is the most important slide of

1 | my slides, and this is really the background, the driving  
2 | force of the guidance, why we want to have this  
3 | information.

4 |           Now, objectives of the guidance are, of course,  
5 | along those lines. We're looking to get information on the  
6 | amount of drug and/or significant metabolite in breast milk  
7 | as a percentage of maternal dose, or if there's a  
8 | therapeutic infant dose, as a percentage of that dose. We  
9 | just don't want to end the information at that point. In  
10 | addition to providing the percentage of dose, we also want  
11 | to make a clinically meaningful recommendation for the  
12 | mother. So, if it is 2 percent or 3 percent or 5 or 10  
13 | percent, what does it really mean? Can she continue taking  
14 | the drug or is she going to take it at a certain time? So,  
15 | this is the type of information we would like to include in  
16 | the guidance.

17 |           Now, as I mentioned, this working group  
18 | efficiently went through a lot of information and  
19 | literature and spent quite a bit of time looking at two  
20 | types of studies essentially, two major groups of studies.  
21 | They could be clinical or nonclinical.

22 |           Under the nonclinical group, which is on the  
23 | left-hand side, you can see that there's the area for the  
24 | mathematical methods, which is what we also call the log-  
25 | phase distribution model. These are the calculations that

1 one can utilize drug characteristics to estimate the amount  
2 of drug that will be in milk. Following that is another  
3 approach which is the animal studies, or another approach  
4 is the bottom one, the in vitro methods where the mammary  
5 cell lines can be utilized to determine or estimate,  
6 depending on the various parameters, what percent of drug  
7 is going to be in milk. Of course, there are other  
8 approaches such as equilibrium dialysis. So, there's a  
9 huge series of nonclinical methods.

10 In addition to that, on the right-hand side,  
11 there are the clinical studies that can be conducted, which  
12 will include studies that will be conducted in the  
13 breastfeeding women, in the lactating mother, just the  
14 mother alone, and then the second group will be only the  
15 babies who will be given the milk that will contain the  
16 drug. Then in the very last box on the right-hand side, it  
17 will be both the lactating mothers and also the breast  
18 milk-fed infants. So, the data will be collected from  
19 those patient populations.

20 Now, we're repeating. The usefulness of  
21 measuring drug and/or significant metabolites is one of the  
22 topics that we want you to discuss with us this morning.  
23 We need your views on this. And then, of course, the  
24 methods. How reliable are those methods and what are the  
25 limitations is going to be the other item.

1                   Now, this is a fairly complex area where we  
2 talk about drug transfer and exposure in the infant. We're  
3 looking at pharmacokinetics not only in the infant, not  
4 only in the mother, but also at the mammary cell level.  
5 There are the kinetic changes that will occur. The drug  
6 may undergo metabolism. There's the transport. So, in  
7 assessing exposure in the infant, we have to have  
8 information in all of these areas and a better  
9 appreciation, and then the size, at what level this is  
10 useful or its clinical meaning.

11                   Now, the drug transfer into breast milk. I  
12 oversimplify this in a way. Dr. Neville, you presented to  
13 us on the 18th. There are clearly many subsets of these,  
14 but if we're going to look at the basic breast drugs, it's  
15 facilitated diffusion, diffusion, or active transport. So,  
16 one of the things in here is sort of an easy way to get a  
17 handle of is the diffusion. For this one, there are many  
18 parameters that are related to drug physicochemical  
19 characteristics. With utilizing dose, there are  
20 publications that show that one can estimate how much drug  
21 gets into breast milk.

22                   So, although this is a simple and maybe sort of  
23 a soft approach, it does have some value. So, we also want  
24 to discuss this and see your views, what percent of drugs  
25 really go by diffusion and can we utilize this tool to

1 estimate and the value of the tool as a first step or maybe  
2 not so valuable. We'll discuss that.

3           If we're going to go with this log-transformed  
4 phase distribution model, it includes information on pKa,  
5 log P values, octanol water partition coefficients, or  
6 protein binding, which all of this information is readily  
7 acceptable, and it's not really difficult to get a handle  
8 on. But again, maybe we'll make some assumptions on the  
9 way, and can we really accept all of those assumptions?  
10 We'll discuss those as well.

11           So, essentially one of the parameters we'll  
12 also bring up for questions and discussion is milk-to-  
13 plasma ratios. This is the amount of drug in milk to  
14 amount of drug in plasma. In lactation studies, there are  
15 a lot of publications that report this number, milk-to-  
16 plasma ratios, and there are also issues with the  
17 methodology. It's a single point or a comparison of the  
18 area under the curve values. In any case, whichever  
19 methodology -- of course, let's work with the best method,  
20 which is the ratios of the area under the curve -- we can  
21 assess the value of this parameter then. Can we utilize  
22 this and how far can we utilize it?

23           There are publications, as I mentioned before,  
24 that look at the maternal drug concentration as C average,  
25 uses the milk-to-plasma ratio, and then milk intake, which

1 I have an equation at the bottom of that slide, which is  
2 somewhere around 150 mls per kilogram per day. This is  
3 essentially for a child, depending on the body weight of  
4 the infant. The bigger the body weight, the more milk the  
5 infant is going to ingest. So, it reflects that.

6 And if we are going to work with Dr. Ito's  
7 exposure index model -- and he's here also. He will refer  
8 to it to some extent, and I think Dr. Pat McNamara will  
9 also discuss it. His equation looks at a more adjusted  
10 value for the clearance in the infant. So, in the first  
11 equation, it really doesn't have a component that relates  
12 to the infant, but the exposure index has the clearance of  
13 the infant as a denominator. That utilizes that ratio.  
14 So, the information is normalized in terms of the infant's  
15 clearance of the drug, which is one of the very important  
16 components because the drug may be cleared at a faster rate  
17 in the mother, but at a very slow rate in the infant. So,  
18 it will become a very important consideration, and I'm  
19 looking forward to these discussions.

20 So, essentially I just want to highlight key  
21 components of the questions and after Drs. Ito's and Pat  
22 McNamara's presentations, we'll go back to these questions  
23 and discuss them.

24 The first question is really based on the  
25 importance of measuring drug and/or significant metabolites

1 | in milk. Is this information important? In what cases is  
2 | it? Again, the first question continues. These are things  
3 | to be kept in mind while you are listening to the  
4 | presentations because we're going to come back to them.

5 |           So, we're looking at what type of methods to  
6 | utilize. Can we use some information as estimates?

7 |           Further on, what parameters can we use to  
8 | assess safety risk in the infant? This is very, very  
9 | important because we just don't want to end up with a  
10 | number that says it's 5 percent or 10 percent, but put that  
11 | into context, what does it mean clinically.

12 |           Following that, question 2 deals with the  
13 | diffusion in some ways because we talk about the M/P ratios  
14 | and the log-transformed phase distribution. So, we're  
15 | saying if you were going to use the log-transformed phase  
16 | distribution equation or a model, could it be an acceptable  
17 | first model? And what percent of drugs are transferred  
18 | into breast milk by diffusion? And that's fairly important  
19 | because is this a tool that can accommodate most drugs.

20 |           Further on, we want to talk about, of course,  
21 | the potential of actively transported drugs, and are there  
22 | screens that will help us to identify those?

23 |           Finally, the third question deals with M/P  
24 | ratios. M/P ratios have some limitations and advantages.  
25 | Let's work with the one that has the best method, best

1 | calculations based on the area under the curve. After  
2 | that, are there other methods? Are there other approaches?  
3 | Can we also consider approaches such as utilizing only milk  
4 | data? That's based on information comparing milk-to-plasma  
5 | ratios.

6 |           So, with that, I would like to turn it over to  
7 | Dr. Ito. After their presentations, we'll go over the  
8 | questions. Thank you.

9 |           DR. ITO: Good morning. I'll be brief.

10 |           I have four discussion points today. The first  
11 | is I would like to discuss why we need data. The second  
12 | point is what kind of data we need in terms of the drug  
13 | excretion in breast milk. The third point is I'm going to  
14 | describe briefly drug transporting proteins in the mammary  
15 | gland. Finally, I will summarize my thoughts about this  
16 | issue in terms of what kind of research should be done in a  
17 | drug development process.

18 |           First of all, why do we need data? As Larry  
19 | said before, the uncertainty about the information  
20 | compromises breastfeeding, which has tremendous benefits in  
21 | the infant. I'm going to describe this using the  
22 | antibiotics and PTU as an example.

23 |           Also, if we have data, we can identify certain  
24 | drugs or groups of drugs which we can adapt therapeutic  
25 | drug monitoring to individualize our management plan.

1 Lithium is a good example.

2 Also, if we have data, we can identify  
3 contraindicated drugs in breastfeeding.

4 First, the benefits of breastfeeding.  
5 Breastfeeding can reduce many different diseases,  
6 especially infections. The infection rate goes down.  
7 Diarrhea, pneumonia, bacteremia, otitis media. There are  
8 many epidemiological studies. Not only that, this is not  
9 good news for people like me who were not breastfed, but  
10 cognitive function can increase.

11 (Laughter.)

12 DR. ITO: There are many studies. Especially  
13 the key paper is Lucas. On average there is probably an 8-  
14 point difference in IQ, which is half the standard  
15 deviation of IQ in the general population.

16 However, if the data are not there, the  
17 breastfeeding is compromised. Number one, we did a study  
18 to look at the compliance of lactating women who were  
19 prescribed antibiotics. If the information about risk  
20 assessment of this issue to the women is kind of equivocal,  
21 they don't comply with the study. So, we found that out.

22 The second, PTU. I characterize it as labeling  
23 the issue, but it's a chronic medication to treat  
24 hyperthyroidism. But again, even if there are data, if the  
25 physicians are not aware of the data or the physicians

1 receive negative imprinting from the original labeling of  
2 the drug, breastfeeding is compromised. I will give you an  
3 example as PTU.

4 Now, the amount of PTU excreted into milk is  
5 less than .3 percent of the therapeutic dose on a weight  
6 basis. If this is less than 10 percent of the therapeutic  
7 dose, the current wisdom is that it's not a big deal. This  
8 is the case for PTU.

9 On top of that, even if the mothers received  
10 PTU and breastfed the infants, the infants' thyroid  
11 function is not compromised. So, we have pharmacodynamic  
12 data here. Based on that, most experts believe it's all  
13 right.

14 CPS, the bottom, is the Canadian version of  
15 PDR. Even this year, the 2001 version, it still says it's  
16 contraindicated.

17 Then what's going to happen? Less than half of  
18 the women taking PTU start breastfeeding. This is our  
19 data. Look at the control. In the Toronto area, the  
20 breastfeeding initiation rate is around 80 percent. So, a  
21 tremendous decline in the initiation of breastfeeding in  
22 women receiving PTU.

23 We wondered why. We asked them, and they said  
24 those who breastfed while taking PTU said the physician  
25 advised them to breastfeed. That's good news. What about

1 | those who didn't breastfeed? They said the physician also  
2 | told them not to.

3 |           We surveyed all the endocrinologists in the  
4 | Province of Ontario, and we found out about half of the  
5 | physicians don't believe PTU is all right in breastfeeding.  
6 | So, I think it's negative imprinting. If the labeling had  
7 | been clear that PTU is all right in breastfeeding, probably  
8 | it wouldn't have happened.

9 |           Everything is in your handout. I changed a  
10 | little bit some slides and they're are a little bit  
11 | different. But to save time, I'll skip this.

12 |           What kind of data do we need? What do we need  
13 | to know? We need to know the infant exposure level, how  
14 | much drug the infant will be exposed to if the mother is  
15 | breastfeeding while taking drugs. So, to estimate that, we  
16 | need to know the actual dose of the drug in milk. It's  
17 | called the infant dose. Or we can express it as percent  
18 | weight-adjusted maternal dose. It's a percentage of the  
19 | mother's therapeutic dose. As I said, if it's less than 10  
20 | percent, currently we believe it's all right.

21 |           To estimate that, we need to measure the drug  
22 | level in milk. Secondly, we probably need the information  
23 | about infant serum drug concentration because clearance of  
24 | the drug in infants is quite different from adults. We may  
25 | need some pharmacodynamic endpoints if possible.

1           Also, we can utilize the exposure index. Ours  
2 was just briefly mentioned. I'll come back to that later.

3           Also, we need to assess the effects of maternal  
4 drugs on milk yield. Some drugs can decrease milk supply,  
5 and that might compromise the breastfeeding.

6           To understand the transfer mechanisms, probably  
7 we need to have an index such as the M/P ratio. It's not  
8 crucial but it will be very helpful.

9           The exposure index is a concept to understand  
10 the determinants of the infant exposure level. As you can  
11 see, the M/P ratio times 10 is the coefficient which is  
12 milk intake, expressed as milliliter per kilogram per  
13 minute times 100, because this is a percentage index,  
14 divided by infant clearance.

15           Those are the drugs which have a very high  
16 exposure index, and that fits actual observation. This is  
17 a conceptual index; however, it fits the observation. So,  
18 if we can derive those things in a newly introduced drug to  
19 the market, we may be able to standardize our assessment.

20           Now, the mammary gland has a carrier-mediated  
21 systems, active transporters or drug transporting proteins.  
22 The clinical implications are there may be some drug  
23 interactions in that area. There are not much data on  
24 that, and maybe down the road, potential intervention is  
25 possible to decrease further the drug transfer into milk.

1           Even if there are transporting proteins, net  
2 transfer may or may not deviate from a diffusion model.  
3 That's something we have to consider when we apply the  
4 diffusion model to estimate the drug transfer into milk.

5           I will just focus on the organic cation  
6 transporters. Milk is a little bit acidic than plasma.  
7 So, the cationic drugs are ionized and entrapped in milk.

8           On top of that, there are at least several drug  
9 transporting proteins for organic cations. So, the  
10 excretion of cationic drugs into milk sometimes exceed what  
11 we expect from a simple diffusion model. In this area, Dr.  
12 McNamara's group contributed quite a lot.

13           Now, if you look at the organic cation  
14 transporting proteins, they're P-glycoprotein, other  
15 organic cation transporters, OCT1, 2, 3, N1, and N2, and so  
16 on and so forth. Probably by the end of today, I think  
17 there may be others.

18           Now, we checked the expression of those  
19 transporters in the human mammary gland. I will come back  
20 to P-glycoprotein later. OCT2 is not expressed. However,  
21 OCT1, as you can see; MCF12A is a human mammary epithelial  
22 cell line. HMEC is a myoepithelial cell line. Actual  
23 mammary tissue. Same thing. OCTN1, OCTN2. OCTN2 is a  
24 carnitine transporter, which is an essential nutrient for  
25 the infants for the energy metabolism and lipid metabolism.

1 P-glycoprotein, which is a multi-drug resistant  
2 protein, is actually expressed in the mammary gland. As  
3 you can see, panel b, the surface -- it's confocal. But  
4 plasma membranes of the human mammary gland cells express  
5 P-glycoprotein, and we don't know yet what kind of  
6 contribution P-gp has in overall drug transport in the in  
7 vivo situation.

8 Using the MCF12A in vitro cell model, we can  
9 demonstrate, for example, typical organic cation uptake  
10 saturation curve. As you can see, carnitine uptake can be  
11 also characterized using this in vitro model, and  
12 saturation can be also demonstrated.

13 Using this model, we can try a lot of drugs to  
14 derive the IC50 value for the inhibition of carnitine  
15 transport. Cimetidine, TEA, choline, guanidine. We are  
16 now doing a panel of drugs to look at the relationship  
17 between IC50 values of probe compound transport in this  
18 model to actually in vivo derived M/P ratio to see whether  
19 we can apply this technique to estimate the drug transfer  
20 into milk in the in vivo situations.

21 So, in summary, I think this is what I think in  
22 my view we should do. I just took the liberty of naming it  
23 levels. Level 0, preclinical study. Physicochemical  
24 model, in vitro cell model, animal models should estimate  
25 drug excretion into human milk in the in vivo situation.

1 Based on that, that will give the ethical framework to go  
2 on to clinical studies.

3 In the first clinical study, level 1, in my  
4 mind probably we should recruit lactating but non-  
5 breastfeeding women, for example, women who are weaning  
6 breastfeeding. Then we can check a lot of pharmacokinetic  
7 parameters, and then detailed clinical studies can be done.

8 Based on that, then that will increase our  
9 confidence level to go on to the actual clinical study  
10 using the actual breastfeeding dyad.

11 So, level 0, as I said, various models to  
12 estimate the in vivo drug excretion into milk in humans.

13 Level 1, using lactating, non-breastfeeding  
14 women we can build detail up from pharmacokinetic studies.  
15 How detailed? That's a point of discussion.

16 Level 2, we can go on to the actual  
17 breastfeeding dyad to check the dose-milk concentration  
18 relationship to estimate variations in the population.  
19 Serum concentration of drug in the infant or some  
20 pharmacodynamic endpoints.

21 I think I will stop here.

22 DR. BYRN: Thank you very much, Dr. Ito.

23 I think we should wait until Dr. McNamara  
24 finishes and then we can have questions for both of you.  
25 It's also a very good way to present a lot of material in a

1 | brief amount of time. Thank you very much.

2 |           DR. McNAMARA: Thank you. Given the time, I'll  
3 | go quickly through these. You have the slides in front of  
4 | you, so you won't need all of the information that I'm  
5 | going to talk about. I want to thank Larry and Arzu for  
6 | the invitation.

7 |           I'm going to talk a little bit more about the  
8 | clinical studies in terms of the design. I sort of looked  
9 | at the questions that Arzu sent out and sort of then  
10 | tailored the talk to address a couple of those issues.

11 |           This is one variation of that same relationship  
12 | in terms of looking at serum concentrations in terms of the  
13 | dose exposure. This is just my version of that same  
14 | equation.

15 |           Again, in terms of what's the important point,  
16 | I think it's what concentrations are we going to achieve at  
17 | steady state. I think most of us would agree that it's  
18 | probably the chronic dosing situation rather than acute  
19 | dose that we're concerned more about. So, an average  
20 | steady state in the neonate is a function of the dose  
21 | derived from milk and the clearance mechanisms, and I'll  
22 | get to some of those issues in a minute.

23 |           One of the questions was a single time point  
24 | versus area under the curve approach, milk concentration  
25 | versus M to S and M to S and neonatal concentrations.

1 Certainly somebody who's not here who's done a lot of work  
2 in the area, Dr. Wilson, has talked about the time-  
3 dependent milk-to-serum ratio and has been looking at drug  
4 distribution into any tissue or other area. There is a  
5 potential for a time lag, and he has cited several examples  
6 in clinical studies. Here I'll present one study that we  
7 had in cimetidine in rabbits that we were using at the time  
8 as an animal model.

9 Here's the blood concentration and here's the  
10 milk concentration. This just gives you an example of what  
11 the milk-to-serum ratio could be if you picked one point in  
12 time to take that, and you see it graphed here where the  
13 milk-to-serum ratio could vary anywhere from less than .2  
14 to 15 depending on what point in time you picked that  
15 sample. Whereas, the area under the curve ratio is here,  
16 somewhere around 1. When we did infusion studies to steady  
17 state, indeed they came up with a value of around 1. So, I  
18 think this speaks to the issue that one should look at area  
19 ratios rather than single time points if one is going to  
20 use that milk-to-serum ratio. Again, there are examples in  
21 human literature as well.

22 Milk concentration versus M to S. I think that  
23 milk concentrations, while they're sufficient for  
24 estimating exposure, I think M to S gives us a better value  
25 in terms of getting some idea of the kinetics that are

1 present in lactating women, which may be different. Some  
2 insight into mechanism, which is something that's near and  
3 dear to my heart. Then it gives us some additional  
4 information where we might look at overall modeling of that  
5 drug distribution into milk.

6 M to S versus neonate concentrations.  
7 Obviously, neonate concentrations would be very valuable,  
8 but there are logistical and ethical issues that make some  
9 of these studies maybe difficult to carry out.

10 I was asked to talk a little bit about some of  
11 the models that are out there. I'll touch briefly on some  
12 of the physicochemical models, a little on animal models,  
13 and some on cell culture models.

14 There have been efforts to model this for a  
15 long time. As you can see, Rasmussen back in 1958 and 1959  
16 talked about the unbound distribution model, trying to look  
17 at drugs -- that should say unionized -- where they looked  
18 at the pH partition hypothesis and then the various  
19 variations of that where we start to account for other  
20 things, the fact that drugs interact with proteins in the  
21 milk, the fact that drugs can partition into milk fat.  
22 There have been various models. It was mentioned the  
23 Atkinson and Begg model, a log-transformed model, and one  
24 of the papers that I believe was in your binder was one on  
25 the neural network where these individuals looked at a

1 | variety of components trying to predict M to S, with a  
2 | number of things.

3 |           This is my favorite. It's an equation that we  
4 | used a lot. It says the milk-to-serum ratio can be  
5 | accounted for in terms of the ionization, the differences  
6 | in protein binding where this is the fraction unionized in  
7 | serum and the fraction unionized in milk. Likewise,  
8 | unbound in serum and milk, and then a whole-to-skim milk  
9 | partition ratio.

10 |           This sort of breaks it up into the ionization  
11 | difference. Because the pH of the milk is slightly lower,  
12 | then you get the possibility of cations being trapped in  
13 | the milk.

14 |           Protein binding. Usually what we see is  
15 | there's more extensive binding in serum than in milk.  
16 | Hence, the milk-to-serum ratio tends to be lower for more  
17 | highly bound drugs.

18 |           Then for very lipophilic drugs, the question of  
19 | partitioning into lipids comes into play which may boost  
20 | that milk-to-serum ratio very high, especially if we start  
21 | talking about some more lipophilic drugs, the amiodarones  
22 | and maybe even pesticides, insecticides that have very high  
23 | partition coefficients.

24 |           This was that neural network modeling, and I  
25 | simply have transformed the data. Here is the predicted,

1 and here it is on a log-log plot. One of the problems with  
2 this is that many of the drugs of interest lie down here,  
3 and it's hard to see whether they're predicting or not. In  
4 a log-log plot, you can see that a little better. It does  
5 a pretty good prediction of those values, although there  
6 are some significant outliers that you'll see here. But  
7 this might be a good place to start in terms of no data at  
8 all.

9 Cell culture model. This is some data that we  
10 did in our lab with help from Peggy Neville who developed  
11 the CIT3 model which is a murine model for studies. They  
12 form a nice monolayer and you can look at flux studies.  
13 Here we look at one drug that we think is actively  
14 transported, nitrofurantoin, and you see there's a basal to  
15 apical difference here over apical to basal lateral,  
16 suggesting a transport process. That transport process is  
17 saturable, and you can inhibit with dipyridamole. And if  
18 you look in vivo in rats and look at the influence of  
19 dipyridamole on nitrofurantoin M to S, you also can see an  
20 inhibition. So, again, there's an active transport  
21 process. It is inhibitable.

22 The CIT3 cells are quite valuable, but it is a  
23 murine cell system. Now, one thing that that cell line  
24 doesn't do is actively transport cimetidine, and cimetidine  
25 is one of those other compounds that is actively

1 | transported. So, why that is, we're not quite sure yet.

2 |           Animal models. My lab and others have used the  
3 | rat, as well as the rabbit, as animal models. This is some  
4 | work that Frank Kari did with Peggy Neville looking at  
5 | nitrofurantoin. Here you see predicted based on that  
6 | binding and partitioning of .3, and when they actually  
7 | observed the milk-to-serum ratio, they see something that's  
8 | quite a bit larger than that, suggesting an active  
9 | transport process.

10 |           I'll quickly go through this. This is, again,  
11 | milk-to-serum predicted based on this model versus  
12 | observed, either in rat, human, or rabbit. And those are  
13 | conducted either at steady state or by looking at the  
14 | ratios of areas. We started with the rabbit, liked it  
15 | because it was easy to work with. You get lots of milk, do  
16 | multiple time points, but then found an article by the  
17 | folks at NIEH where they looked at cimetidine and saw what  
18 | looked like active transport in the rat. But they did a  
19 | single time point. We thought we were better kinetics  
20 | people than they are, so we did cimetidine in the rabbit  
21 | and saw no active transport in the rabbit, and then said,  
22 | well, see, they just did it wrong. Then we said, well,  
23 | maybe it's species.

24 |           So, we decided to do the rat ourselves, and did  
25 | infusions to steady state, and lo and behold, the rat does

1 actively transport cimetidine. You see the predicted value  
2 off the line of identity.

3 So, the rabbit doesn't look like it's a good  
4 model. Now, in my discussions with Peggy, it may be  
5 because they don't form tight junctions, and maybe Peggy  
6 can comment a little bit on that.

7 But the rabbit, in terms of predicting an  
8 active transport component for cimetidine and  
9 nitrofurantoin, did a pretty good job of predicting that.  
10 We've done also acyclovir and there is some literature  
11 evidence that also suggests acyclovir is accumulated at  
12 concentrations greater than predicted by diffusion.

13 So, the rat is a pretty good model in terms of  
14 mechanistically predicting something. Now, if you wanted  
15 the rat as an animal model to tell you what the human M to  
16 S is going to be, that won't work because the rabbit and  
17 the rat have concentrations of lipids and proteins that are  
18 much higher than human milk. Also, the pH, at least in our  
19 hands, tends to be slightly lower. So, if you're looking  
20 for an animal model that you can get an M-to-S ratio that's  
21 exactly the same as it is in humans, you won't find that,  
22 but we found the rat to be useful mechanistically.

23 Active transport issues. I'll show you a  
24 little bit about clinical evidence. I'll sort of skip the  
25 carriers since Dr. Ito presented some of that.

1           This is data that we generated in cimetidine in  
2 humans, looking at different size doses, and I'll just  
3 focus your attention down here. This is M to S observed,  
4 looking at the ratios of those, versus predicted of 1. So,  
5 we see something about six-fold greater. Again, animal  
6 studies in the rat that showed saturability, inhibition.

7           This is something we just published that looked  
8 at nitrofurantoin in human milk. We see here a ratio  
9 consistent with what we saw in the animal studies both in  
10 Frank Kari's work and some that we did, a considerable  
11 accumulation of nitrofurantoin as well.

12           We are also looking at transporter gene  
13 expression and looking at that as a potential way of  
14 identifying what candidate genes there might be. We've  
15 found a number of genes, not just in the cation family,  
16 some that are negative. Dr. Ito and I can talk about this  
17 one since he sees it and we don't. But we're progressing  
18 down this, and I think the next is to do protein gene  
19 expression studies to look to see if those drugs are  
20 transported by these carrier systems.

21           Then I think we need some sort of a database  
22 that would identify which drugs are substrates for these  
23 carrier systems. Then we might have an idea of what to  
24 expect in vivo.

25           Neonatal exposure issues. I'm going to go

1 through this quickly. It was covered quite a bit before  
2 this. Again, to save time for questions, I'm going to talk  
3 about this.

4 Obviously, developmental patterns vary with  
5 regards to clearance. The most varied is the cytochrome  
6 P450 system, and some phase II reactions are inefficient at  
7 birth.

8 Here is some in vitro data that was gathered  
9 looking at human microsomes and looking at functional  
10 activity as a percent of adults based on a milligram  
11 protein. Here you see CYP-1A2, 2C. This was protein  
12 levels. 2D6, 2E1, and 3A4. You see these protein levels  
13 and functional levels start out very low and progress  
14 upwards. So, clearly in the past we've talked about  
15 putting up one value of clearance. I think what you should  
16 realize is that clearance varies as a function of  
17 developmental age here.

18 I'll skip this one. This one was simply to  
19 show you that timing dosing versus when you nurse is sort  
20 of a non-issue in terms of trying to avoid the peak  
21 concentrations of exposure. I think one needs to think in  
22 terms of an overall steady state exposure and not trying to  
23 time nursing to miss the peak of drug levels. That's just  
24 not going to happen.

25 Again, this table is a little busy, but the

1 | real point here was that if you're looking at percent of  
2 | dose exposure, you look at this number. Interestingly  
3 | enough, something we don't think about but actually the  
4 | maternal clearance, to a certain extent, defines what that  
5 | percent of dose will be; that is, the lower the maternal  
6 | clearance, the higher the dose exposure is actually for the  
7 | newborn.

8 |           But if you're interested in concentration  
9 | ratios, that is, the neonate-to-maternal concentration  
10 | ratios, it is indeed a function of that neonatal clearance.  
11 | So, higher exposures of the neonate are a result of either  
12 | higher M-to-S ratios, lower clearance, either maternal or  
13 | neonate, and questions about what the first pass effect may  
14 | be or bioavailability may also be something one wants to  
15 | think about in terms of exposure.

16 |           So, in conclusion, most drugs -- and I would  
17 | say all drugs -- are going to be present in milk. It's  
18 | only a question of whether we can measure them with their  
19 | analytical sensitivity. So, it's not a question of whether  
20 | they're present or not. They all will be.

21 |           Many of them can be predicted based on their  
22 | physicochemical properties, governed by diffusion. You'd  
23 | expect the unbound, cationic, lipophilic drugs to be higher  
24 | M-to-S ratios.

25 |           There are some transporter issues. We're just

1 | now finding out which transporters are present, which may  
2 | lead to an accumulation or an M-to-S greater than what we  
3 | can predict.

4 |           I think the real issues here are neonatal  
5 | exposure. The thing that seems to be missing the most is  
6 | the neonatal clearance and then whether that concentration  
7 | that we ultimately do achieve actually results in the  
8 | pharmacologic or toxicologic response in the neonate.

9 |           I think that's it.

10 |          DR. BYRN: Thank you very much.

11 |          DR. SELEN: So, now we'll go back to the  
12 | questions.

13 |          DR. BYRN: We have them on our handout if you  
14 | want to go ahead that way. It's up to you. It would be  
15 | very nice to have them up there.

16 |          DR. SELEN: Since everyone has the questions,  
17 | perhaps we can go to the questions. They were in the  
18 | handout.

19 |           Let's look at the first question, question  
20 | number 1. I would like to get your thoughts on this one.  
21 | Now, the first question is asking if it is important to  
22 | estimate or measure drug and/or significant metabolites in  
23 | breast milk. I'll open that question to you.

24 |          DR. BYRN: Thoughts of the committee?

25 |          DR. LEE: I think the answer is yes. Right?

1 DR. BYRN: Yes. We're saying it's a no-  
2 brainer.

3 (Laughter.)

4 DR. SELEN: So, it looks like we're going to  
5 move through the questions very quickly. The first one was  
6 the answer was a sound yes.

7 Part A says, for what type of drugs do we need  
8 this information on the extent of drug transfer into breast  
9 milk? Are there certain drugs that we don't want this  
10 information on?

11 Yes, Dr. Venitz.

12 DR. VENITZ: I think there are two ways of  
13 looking at it. One is what do we know, what can we predict  
14 in terms of their potential extent of delivery. And that  
15 seems to be able to be predicted based on some of the stuff  
16 that we heard today.

17 The second approach is how likely are they to  
18 be administered to women who are lactating, and what are  
19 the potential consequences.

20 So, we can kind of triage how important the  
21 information is and, further down the list, what kind of  
22 data would you require in order to make the decision.

23 If the drug is unlikely to be administered to  
24 lactating women, if the consequences are benign, then in  
25 vitro data or predicted based on physicochemical

1 characteristics might be sufficient. If, on the other  
2 hand, like PTU, the consequences could be disastrous, you  
3 might require what you call I guess a level 1 or level 2.

4 DR. SELEN: Thank you.

5 DR. BYRN: One other idea might be to have some  
6 kind of flow chart that would take you through these  
7 decisions, a decision tree, flow chart.

8 DR. SELEN: I see the members of the committee  
9 are raising their hands on that one. We went through  
10 several decision trees. It's very close to the hearts of  
11 many.

12 Yes.

13 DR. LESKO: Can I interrupt here? I think in  
14 this idea of the hierarchy and the framework for ethical  
15 studies, I would think we wouldn't want to advocate studies  
16 that we feel are unnecessary to get this information. So,  
17 looking at this question another way, can you think of ways  
18 in which you can take drugs off the table and be confident  
19 that certain pieces of information would suggest that these  
20 drugs are not going to be a problem, therefore I won't go  
21 any further?

22 I don't know if what Dr. Venitz laid out is all  
23 of the criteria one might think about. Certainly the  
24 clinical consequences are one thing. Potential for use may  
25 be another. For example, could I conclude that if the

1 | milk-to-serum ratio is less than a certain value, I might  
2 | take that off the table for consideration in doing a  
3 | clinical study. If I conclude that the drug is not  
4 | absorbable in neonates, for example, large molecules,  
5 | aminoglycosides, I could take that off the table.

6 |           Can you see the value of an approach like that,  
7 | or is that perhaps taking some risks that would not be  
8 | acceptable?

9 |           DR. JUSKO: Larry, what you indicated is  
10 | largely a great deal of common sense. But I'm not sure you  
11 | would exclude drugs only on the basis of a low milk-to-  
12 | plasma ratio because of differences in potency and  
13 | differences in clearance, exposure in the infants. It's  
14 | too simplistic to do it that quickly.

15 |           DR. DOULL: I guess I have that same kind of  
16 | concern. Larry, in the introduction you said if you can  
17 | prove the drug doesn't get into the milk, fine, take all  
18 | those drugs off. And Dr. Venitz said, well, if it has a  
19 | great therapeutic ratio, you might take a bunch of drugs  
20 | off for that reason.

21 |           I think the guidance needs to recognize that it  
22 | needs to be a case-by-case decision rather than blanket.  
23 | Dr. McNamara, you mentioned pesticides, and I'm thinking of  
24 | the Food Quality Protection Act which is blanket-issued for  
25 | pesticides and was a factor of 10. You have to say

1 something about the susceptibility of the infant to the  
2 agent. Therapeutic index may not blanket-predict for both  
3 the mother and the infant. So, I think the argument for a  
4 case-by-case analysis rather than a blanket kind of  
5 approach should be part of the guidelines to ensure that we  
6 don't really make the same mistake that we made with  
7 pesticides.

8 DR. BARR: I'd like to thank the speakers for  
9 what I thought was an incredible review of an awful lot of  
10 information, a lot of concepts in a very clear and concise  
11 and comprehensive manner. Thank you.

12 I wanted to get back to this issue. It seems  
13 to me that the biggest unknown we have in most cases is  
14 what this real exposure rate is to the infant because we  
15 just don't know how they metabolize those drugs in most  
16 cases and all of those factors. So, that's number one. We  
17 almost have to go back and say how do we collect that  
18 information. That, of course, is the biggest mystery.

19 So, it means that we really have to be very  
20 cautious I think in how we view any kind of transfer into  
21 the milk, particularly for drugs that may have  
22 consequences, significant pharmacologic consequences.

23 One of the other factors that I wanted to ask  
24 about that I didn't see up there is if you have drugs that  
25 are relatively lipid soluble, of which the membrane may not

1 | be the rate-limiting step, then you get into kind of a  
2 | Renkin dialysis method in which the actual milk flow may be  
3 | the rate-limiting step. So, this single point ratio may  
4 | not be valid and may be, in fact, milk flow dependent. If  
5 | you had low flow versus high flow, it may change. Have you  
6 | got any data on that?

7 |           DR. SELEN: Well, that's a very good point, but  
8 | I think most of the literature I have seen works with the  
9 | concept of like six feedings per day at 150 mls per  
10 | kilogram per day. Now, if you're saying if the baby is  
11 | more frequently fed. But, of course, they'll be ingesting  
12 | more milk and they could be getting more drug. But I don't  
13 | have an answer for you. I don't think so.

14 |           DR. BARR: Not just the volume, but just  
15 | actually the blood flow. In other words, you've got plasma  
16 | flow on one side of the membrane and then you've got milk  
17 | flow, which depends upon the milk production rate. And  
18 | that may alter, I think, the number for drugs that are  
19 | fairly lipid soluble in which the membrane is no longer --

20 |           DR. SELEN: Dr. Neville is an expert on this,  
21 | but I'm not quite sure I can see the milk flow to be as  
22 | fast or as rapid as the plasma flow.

23 |           DR. NEVILLE: So, it's different than, for  
24 | example, if you're looking at the kidney. Milk accumulates  
25 | in the breast until the baby actually feeds, and then it's

1 | pushed out all at once. So, basically it's a question of  
2 | how fast does the drug -- and Patrick does this much better  
3 | than I. I'm a physiologist. How fast does the milk  
4 | transfer across the mammary cell? Where does it  
5 | distribute? Is it in the milk fat, which makes it a very  
6 | different system from any other because 4 percent of the  
7 | human milk is fat. If the drug is lipophilic, that makes a  
8 | difference.

9 |           In terms of the amount of milk produced per  
10 | day, on average at 1 month it's about 600 mls per day, and  
11 | at 6 months it's about 800 mls per day. So, we're not  
12 | dealing with huge differences there.

13 |           One of the points I wanted to make at some  
14 | point -- and since I've got the microphone, I'll make it --  
15 | is that a group of infants that we must consider very  
16 | carefully are the premature infants. These are very small  
17 | infants. It's becoming very clear that these infants need  
18 | human milk. The anti-infective properties, the brain  
19 | development properties of the polyunsaturated fatty acids  
20 | -- that 8 percent change in intelligence actually came from  
21 | premature infants, not from term infants. There are some  
22 | real issues with premature infants. Then, of course, you  
23 | have the problems of metabolism compounded enormously. So,  
24 | in designing therapeutic guidelines, I think this  
25 | particular group really needs to be taken into account.

1 DR. SELEN: I think the premature infants is a  
2 great point because also, like Dr. Lesko was presenting  
3 with the 4 million babies being born, of that 4 million,  
4 11.5 percent is premature infants. This is just in the  
5 white population. If you look in the black, it goes up to  
6 16 percent apparently. So, it's a serious number. We're  
7 looking at 400,000 or more per year.

8 Yes?

9 DR. MEYER: It seems like one approach, rather  
10 than thinking of drugs you can take off the table, which is  
11 always difficult because you can come up with examples why  
12 nothing should be removed from the table, is to work first  
13 on those drugs where it would be very important to know  
14 whether they're transported or not.

15 DR. SELEN: Thank you.

16 DR. SHARGEL: I presume these studies are going  
17 to be for drugs going for an NDA submission for new drugs.  
18 Since women are already taking drugs that are already on  
19 the marketplace, how much information is going to be tried  
20 to be gained from those drugs that are already marketed,  
21 being consumed, realizing that there is a lack of knowledge  
22 on many of these drugs? Is there any attempt to provide an  
23 incentive to obtain this information?

24 DR. SELEN: Incentive is a different question,  
25 but at least I can answer one part that doesn't deal with

1 | the incentive.

2 |           You were noticing that in the chart that a big  
3 | percentage of mothers discontinue breastfeeding. So, if  
4 | they're taking a chronic medication, they have to be on it.  
5 | It's already approved. I think they still deserve to have  
6 | the information to use the medication properly. So, we  
7 | would rather that they have the information and they  
8 | continue taking their drugs. I think it's critical that  
9 | this information is available not only for new drugs, but  
10 | also for drugs that are out there.

11 |           In terms of incentive, that becomes a different  
12 | issue that Dr. Lesko might want to address.

13 |           DR. LESKO: I was just going to suggest,  
14 | because of timing -- and Steve is watching the timing of  
15 | the discussion, I think we should turn the discussion over  
16 | to Steve to sort of make sure we stay on track, at least to  
17 | moderate the discussion.

18 |           DR. BYRN: We can do it together, if you want,  
19 | Arzu. I think it's good if you stay up there because you  
20 | have a little bit more knowledge than I do about the field,  
21 | but I'll proceed with the discussion or try to summarize  
22 | what people are saying. So, we'll do it together, sort of  
23 | like a talk show.

24 |           (Laughter.)

25 |           DR. BYRN: I think we've got a pretty good

1 answer or some ideas for item A here. The ideas are that  
2 we look at drugs that are dangerous, and that would be one  
3 approach. The other approach would be to look at a case-  
4 by-case basis but try to take drugs off the table on a  
5 case-by-case basis. Is there anything more on item 1A?

6 DR. BARR: Going back to Marv's statement I  
7 think really makes a lot of sense. It seems to me that the  
8 priority ought to be to really look to those drugs which  
9 are already on the market which are widely used, likely to  
10 be used by women and may have consequences. Make up that  
11 list first. I think that would be the place to start.

12 DR. BYRN: So, look at the risk and -- go  
13 ahead, Marvin.

14 DR. MEYER: Drugs that women are on that they  
15 can't get off of. Anticonvulsants, for example.

16 DR. BYRN: Let's go ahead to the next one. Go  
17 ahead, Arzu. You just couch it. We'll discuss it, and  
18 then I'll summarize.

19 DR. SELEN: So, if we need this information,  
20 when would it be appropriate to estimate or when shall we  
21 be collecting data? Of course, the type of studies are the  
22 in vitro, nonclinical studies, or clinical.

23 Dr. Jusko.

24 DR. JUSKO: It would seem that the FDA would be  
25 able to encourage pharmaceutical companies to carry out

1 animal studies to determine milk/plasma kinetics of drugs.  
2 Dr. McNamara suggested that the animal data is sort of  
3 confusing in that lipid and pH differences exist between  
4 animals and humans. But I would encourage the development  
5 of animal scaling principles in conjunction with the  
6 kinetic principles that you have been using in order to  
7 develop a way to convert the animal data into predictable  
8 human parameters. That way one could mine the great deal  
9 of information that one could get from animals and use that  
10 for assessment of potential human exposure.

11 DR. BYRN: I also like Dr. Ito's idea of using  
12 women that are weaning children because there you could get  
13 probably quite a bit of good data. You'd have to work  
14 fairly quickly, but you could get good data and there would  
15 be no exposure risk. I don't know how feasible that is,  
16 Dr. Ito. Is that feasible to do that in general?

17 DR. ITO: I think so. Of course, there are  
18 some limitations such as they are weaning, so it's not  
19 quite really a physiological state. However, it's going to  
20 be a good starting point, probably as good as good animal  
21 data.

22 DR. BYRN: Dr. Neville?

23 DR. NEVILLE: There's another population that I  
24 think, with proper organization, might be very good for  
25 studies, and these are the mothers of premature infants who

1 | are pumping milk for their infants. Some of them make a  
2 | good deal of milk so that they can store up for a couple of  
3 | days and have some extra milk for a double. So, I would  
4 | encourage people to get in touch with their neonatal  
5 | nurseries. That actually might be a population where you  
6 | can also look at the premature situation.

7 | DR. BYRN: Are there any other ideas on this  
8 | one?

9 | DR. BARR: Just one comment. It seems to me  
10 | that if you were to set up one or several centers in which  
11 | you obtain women who are weaning who would be willing to  
12 | serve as a milk donor, not necessarily weaning, because you  
13 | can continue the production of milk for a long period of  
14 | time if one chooses to do so. And if you were to get a  
15 | cohort of women who were willing to do that in a center in  
16 | which several drugs could be done in succession, take those  
17 | which are most important and put them out, it seems to me  
18 | that some of these could be done fairly quickly.

19 | DR. BYRN: Should we go to the next question?

20 | DR. SELEN: So, what parameters can be used to  
21 | assess the safety risk in the infants? Let's say the drugs  
22 | that get into milk or they're predicted to get into milk.  
23 | What are the parameters that we can utilize? For example,  
24 | like a certain percentage is acceptable or not.

25 | DR. JUSKO: I think you need a hierarchy of

1 | information as you've been discussing. It's perhaps  
2 | easiest to get the percent of the maternal dose that gets  
3 | into breast milk, but that's not as important as having  
4 | milk/plasma ratios that you can factor in with maternal  
5 | exposures and different dosage levels. But then that's not  
6 | as important as having the infant exposure index and having  
7 | additional information about potential toxicity in the  
8 | infant. You may not be able to get all of this level of  
9 | information at one time, but all should be part of a  
10 | composite body of the data.

11 | DR. DOULL: I agree. That's the case-by-case  
12 | argument.

13 | I do object to using both words "safety" and  
14 | "risk." Safety is a yes/no question; risk has no bottom.  
15 | What you're talking about is toxicity.

16 | DR. SELEN: Yes. Risk in terms of it's a  
17 | safety risk.

18 | DR. DOULL: But in order to define that for an  
19 | individual drug, you need to know whether the toxicity  
20 | comes from the kinetics or whether it comes from the  
21 | dynamics. Those are safety questions which can be  
22 | answered. It's just the two words together that disturbed  
23 | me.

24 | DR. LESKO: One of the things that Dr. Ito  
25 | presented was the exposure index as a way of combining the

1 factors that would influence exposure in the infant, and a  
2 suggestion was made of a 10 percent cutoff. Presumably  
3 below that, one would feel relatively safe; above that, one  
4 would be perhaps concerned.

5 The other part of the exposure concept, I  
6 noticed, in the slide was a bit of variability in it. For  
7 example, lithium had 2 to 30 percent variability.

8 It sort of gets me to the question of  
9 variability. If clinical studies were deemed to be  
10 important in this area, obviously there are factors that  
11 will limit the size of those studies. I wonder if people  
12 that have conducted these studies can comment on what they  
13 feel would be the logistical aspects of it and the number  
14 of subjects or volunteers that would have to come into a  
15 study to try to get some data that would be credible.

16 I guess the other part of that is the exposure  
17 index. Is 10 percent something that people feel good  
18 about?

19 DR. BYRN: Dr. Ito, can you talk about the  
20 variability in these studies?

21 DR. ITO: I think if we know a certain drug has  
22 quite a variability in terms of the exposure level to the  
23 infant, that tells me at least that we need to monitor,  
24 individualize the approach. So, I think to me that's good  
25 enough. At least we can tell that there are huge

1 | variabilities in the drug excretion to milk. I think  
2 | that's good information to have.

3 | DR. BYRN: So, you're saying we could do maybe  
4 | a rather small study. If it's tight data, we're fine. I  
5 | guess you would recommend the 10 percent level. If there's  
6 | a lot of variability, then we know there's a problem and  
7 | there's going to have to be monitoring.

8 | DR. ITO: Right. That would be my approach.  
9 | 100 percent exposure index is actually the same as a  
10 | therapeutic dose to the infant, and 10 percent is one-  
11 | tenth. So, I'm quite comfortable with 10 percent as far as  
12 | dose-dependent effects are concerned.

13 | DR. BYRN: Is the committee comfortable with 10  
14 | percent? That's a key thing I think if we could say we're  
15 | comfortable or not.

16 | DR. BARR: I don't feel comfortable with 10  
17 | percent mainly because I don't really know what it means.

18 | I think the problem is that we have a given  
19 | dose and we're assuming that we know something about the  
20 | relative toxicity of that dose to a neonate, to an infant.  
21 | In most cases, we probably don't know that simply because  
22 | we don't even know it for pediatrics, let alone neonates.

23 | If we do this project, which I think we  
24 | certainly should -- I think it's very necessary to do -- it  
25 | means that more drugs will be used by women who will be

1 nursing presumably, that we will be telling them that it's  
2 going to be reasonably safe. So, there almost needs to be  
3 a second phase in which that actually is monitored sometime  
4 in a clinical way once that begins to be done, particularly  
5 for critical drugs.

6 DR. BYRN: Now, are you willing to use the 10  
7 percent level for that second phase? In other words, if it  
8 was below 10 percent, you could say it's presumed safe and  
9 then do a second monitoring, or do you think a second  
10 clinical trial should be done?

11 DR. BARR: Well, I'm not sure I have the  
12 information to make that judgment. I think 10 is a  
13 reasonable arbitrary number, but I think it ought to be  
14 considered on an individual basis. If we have, for  
15 example, a drug which is very essential to a woman but may  
16 have some toxicity to the woman -- one of those critical  
17 drugs that we're talking about -- then I think that would  
18 have to be evaluated with all the knowledge that's known at  
19 that point in time.

20 DR. MEYER: Steve, I support Bill. I can't  
21 pick a number based on a 20-minute presentation, and I  
22 don't think I could pick a number if I heard a 30-day  
23 presentation because everything is going to be different.

24 We haven't talked much about intra- or inter-  
25 subject variability. If the woman is on a drug that has a

1 30-fold inter-subject variability, what's the infant's  
2 variability? Is that comparable? Does that go up? Does  
3 the infant tolerate more drug as the woman tolerates more  
4 drug, or are the receptor sites growing like the  
5 metabolizing enzymes are changing during those early days?  
6 There's no complication? What about drugs where a woman  
7 starts on a drug after the first 10 days of life? That  
8 infant is going to respond, according to the one slide,  
9 differently than if she starts on the drug or is taking the  
10 drug on day 1.

11 I might feel comfortable in picking a number if  
12 the drug is used, say, in a newborn center and you could  
13 say, well, the infants there take this drug routinely and  
14 tolerate such and such a dose. I'd have a feeling that  
15 might be safe, but there are an awful lot of unknowns out  
16 there that really deserve careful consideration before I'd  
17 put it in a label, okay to take.

18 DR. BYRN: We probably now need to go much  
19 faster. So, let's go ahead.

20 DR. SELEN: So, essentially this is dealing  
21 with the diffusion model. So, if you go to 2A, using the  
22 model such as the log-transformed diffusion equation, which  
23 incorporates PKs and log P's, and that information, protein  
24 binding, now would we consider that as a useful first step?

25 DR. BYRN: Everybody is saying yes.

1 DR. SELEN: Okay.

2 So, then the following question is what percent  
3 of drugs can we estimate -- this is going to be an  
4 approximation -- are going to be transferred into milk by  
5 diffusion?

6 DR. JUSKO: That seems to be a major research  
7 question. Drugs that are actively transported. The number  
8 of those needs to be evaluated much more extensively.

9 DR. LEE: Yes, I agree. I think the question I  
10 had is the pattern pretty similar to kidney?

11 DR. SELEN: Can you repeat the question, Vince?

12 DR. LEE: Yes. I was just wondering whether or  
13 not the process of secretion of drug into milk is like  
14 secretion into urine.

15 DR. McNAMARA: I don't think we have enough  
16 data on that. I think there are some examples like  
17 cimetidine and probably nitrofurantoin that would suggest  
18 that it looks like that, but you can find other examples of  
19 drugs that are excreted into the kidney by active transport  
20 processes that don't seem to have that same pattern in  
21 milk. So, it's not something that you can equate one to  
22 one in terms of the numbers of drugs. I'd say that the  
23 percentage is small. There's probably a handful, but it's  
24 based on how many drugs have been studied, which is also  
25 not a large number.

1           I think the 10 percent number -- I'm going to  
2 get back to that earlier point. I think the question  
3 really has to do with the clearance mechanisms in the  
4 neonate, and if one can anticipate, based on what we now  
5 have to know in terms of a new drug, is this drug cleared  
6 by one mechanism, is it predominantly renal, and do we know  
7 something about that in the neonate, or is it predominantly  
8 3A4 or 2D6, or how is it predominantly cleared? The more  
9 pathways there are for clearance, the better chance that  
10 that drug will be cleared to an extent, on a body weight  
11 basis, more like the adult, than if you were depending on  
12 one particular clearance pathway and that one happens to be  
13 undeveloped.

14           DR. BYRN: So, the answer to B is we need more  
15 research. It's a research question.

16           And C?

17           DR. SELEN: So, if we were going to look at  
18 active transport, what type of approaches could be possible  
19 screens, reliable screens?

20           DR. JUSKO: I think what's very nice is that  
21 the physicochemical principles provide the first screen  
22 because of the great degree of predictability based on pH  
23 and pKa and such. Then when the predictions for the models  
24 are not confirmed by either animal data or human data, one  
25 then sees the probability that there's some additional

1 transport mechanism. But fundamentally these things need  
2 to go hand in hand, more research into investigation of  
3 transport mechanisms, which will then identify additional  
4 drugs that may be transported by those mechanisms. In  
5 turn, evaluation of the toxic drugs that women may take.

6 DR. BYRN: So, we're hearing that C is  
7 obviously a research topic.

8 Yes, Larry.

9 DR. LESKO: Question 2 more or less pertains to  
10 methodologies that we characterize as in vitro based on  
11 concepts of physicochemical characteristics and so on. For  
12 several drugs -- I think Dr. McNamara showed nitrofurantoin  
13 and some others -- we have pretty good data.

14 I guess my question is, would we derive more  
15 information from these studies if we, in fact, included  
16 "internal" standards in the procedures, in other words, put  
17 in drugs we know about in terms of M/P ratios and drugs we  
18 know about in terms of drug transfer into milk, and then  
19 use those as reference points to assess the relative risk  
20 of the new drug that we might be talking about? It's a way  
21 of interpreting the data instead of trying to interpret it  
22 in terms of an absolute risk. What do people think about  
23 that notion, and could people see that as a framework for  
24 moving forward on these types of studies?

25 DR. BARR: I think that's an excellent idea.

1 | It really brings up the issue. Most of the industry now  
2 | spends a fair amount of time determining permeability by a  
3 | variety of in vitro methods, and they characterize them  
4 | exactly that way. You standardize your system, make sure  
5 | that it's working well relative to known ingredients or  
6 | products.

7 |           It would seem to that this is an area that in  
8 | the NDA process ought to be looked at. It's something that  
9 | would be obtained routinely. This would be the place where  
10 | you'd like to collect that information. For those drugs  
11 | that are likely given to women who may be nursing, it would  
12 | seem to me that this would be a reasonable thing to ask in  
13 | the IND process.

14 |           DR. BYRN: Let's go ahead.

15 |           DR. SELEN: The third question is with the M/P  
16 | ratio, and we want to discuss the advantages and  
17 | limitations. Of course, as Dr. Pat McNamara illustrated,  
18 | there's a difference between if it's a single point or an  
19 | area under the curve comparison. If we just work with the  
20 | area under the curve comparison, the best approach, then  
21 | what are the advantages and limitations?

22 |           DR. BYRN: Area under the curve. Are there  
23 | thoughts on that? Bill?

24 |           DR. JUSKO: It's always better to get more data  
25 | whenever possible. So, again, there's a hierarchy. Maybe

1 | in some women one can only screen to get an M/P ratio, but  
2 | whenever possible a full profile should be obtained.

3 | DR. BYRN: I think that's a general consensus  
4 | of the committee.

5 | DR. MEYER: But the caveat is whenever  
6 | possible.

7 | DR. BYRN: Right.

8 | DR. MEYER: These women have other things to do  
9 | than get stuck 12 times in a 24-hour period. And they  
10 | certainly don't want an AUC done on their infant.

11 | DR. SELEN: So, the M/P ratio would be in the  
12 | mother. That's the intent. However, do you see any  
13 | limitations with it, in addition to being stuck for 12  
14 | hours.

15 | DR. VENITZ: Well, you're assuming that you're  
16 | measuring all the active moieties. Maybe you don't measure  
17 | the metabolite and it's the metabolite that does something  
18 | untoward to the infant. Right now we are talking about  
19 | areas under the curve of the active moiety.

20 | DR. SELEN: The intent is it's the drug and/or  
21 | significant metabolites because we're interested in that.

22 | DR. VENITZ: Known metabolite, right? You're  
23 | asking about limitations. That's an intrinsic limitation.

24 | DR. SELEN: Yes, good point because it might be  
25 | a different metabolite. So, the value of this may not be

1 really pertinent for the baby.

2 DR. VENITZ: Right.

3 Another kinetic limitation would be, do you  
4 have dose proportion kinetics in terms of the maternal  
5 pharmacokinetics? So, a single dose might not predict  
6 what's going to happen at a higher level.

7 DR. BYRN: Larry?

8 DR. LESKO: I was going to go a little bit  
9 beyond these three questions, but it's relevant. Assuming  
10 that a sponsor develops this information during the course  
11 of drug development and provides some information to fill  
12 the gaps that we've been talking about, what do members of  
13 the committee think about how to transfer this information  
14 to knowledge within the label? There are a couple of  
15 possibilities.

16 One is obviously to just put descriptive  
17 information, say, in the clinical pharmacology section of a  
18 label. People may or may not read that or be able to  
19 interpret it.

20 There's another way and that is to interpret  
21 the data as we might, say, drug interaction data that comes  
22 out of drug development.

23 Do people have thoughts on what they see as the  
24 most effective way to transfer information to knowledge so  
25 that it gets out to the clinician and to the patient so

1 | that they can make some sense of it in making decisions?  
2 | What would be the format for that communication of  
3 | knowledge?

4 | DR. BYRN: Ideas?

5 | DR. SHARGEL: Larry, I think I'd approach that  
6 | as a marketing kind of thing, looking at labeling in  
7 | general. I think you have a group looking at revising  
8 | labeling, just recently a guidance, and how labeling is  
9 | reviewed by practitioners, pharmacists, and others. So, I  
10 | would take that to a different level than this committee.

11 | DR. MEYER: And you can't beat the Internet for  
12 | disseminating to patients.

13 | DR. BYRN: Are we done? Bill, one more  
14 | comment.

15 | DR. JUSKO: Yes. The NIH, the Women's Health  
16 | Initiative, and probably the FDA have a program ongoing  
17 | where there are going to be RFPs issued to solicit more  
18 | extensive pharmacokinetic/pharmacodynamic drug efficacy  
19 | studies in pregnant women. It would seem like this whole  
20 | initiative should also be connected to that one since it's  
21 | the logical final stage to study this question.

22 | DR. SELEN: In fact, it is. There's one  
23 | individual from that group from the Office of Women's  
24 | Health. In the interest of time, I didn't want to go into  
25 | the background and the details of this, but there is a big

1 initiative, as Dr. Lesko has mentioned I think at one point  
2 in time, about the pregnancy labeling and all of these are  
3 the subcomponents. \

4 DR. BYRN: I think we should conclude this  
5 session.

6 DR. SELEN: There's one more.

7 DR. BYRN: Okay, there's one more question.

8 DR. SELEN: There's the last one, and this is  
9 the last one. What other approaches would be acceptable?  
10 Sometimes we hear points made such as instead of obtaining  
11 milk-to-plasma ratios, just obtaining milk-drug  
12 concentrations. Will that be adequate or do we want to  
13 normalize it with exposure in the mother by obtaining  
14 plasma data? And what other approaches do we think might  
15 be useful?

16 DR. JUSKO: I think we've seen that you get  
17 much more mechanistic information by having the milk/plasma  
18 ratios. But once again, sometimes only one may be  
19 obtainable, but it would be better to get more  
20 comprehensive information whenever possible.

21 DR. MEYER: What's the reproducibility? If I  
22 took the six feedings and measured a drug concentration in  
23 that total 150 mls, how much variability would I have  
24 throughout the day and night? Would a concentration tell  
25 me anything, or does it vary by a factor of 2 or 3 or 4?

1 DR. SELEN: The point you're making is a very  
2 good one because there are so many changes in the milk  
3 composition that affect the amount of drug in milk. So,  
4 like we mentioned in the draft guidance, it's important to  
5 collect all of the milk. There's a difference in the fat  
6 content in the foremilk versus hindmilk, as Dr. Neville can  
7 also elaborate on. So, depending on how you collect it,  
8 there's going to be variability, and depending on when you  
9 collect it, there's going to be variability. So, I think  
10 it's very important in these studies to collect all of the  
11 milk at all collection times and then having a sample from  
12 that, because the foremilk versus hindmilk -- this is  
13 published information. The big difference is in  
14 concentration of a lipophilic drug.

15 Does it address that adequately? Or Dr.  
16 Neville might wish to add more.

17 DR. NEVILLE: The sampling of milk. You don't  
18 just go take a milk sample. There are some very standard  
19 ways to do this, but it has to be done right. I don't  
20 think this is the place to talk about that.

21 The other thing that ought to be considered is  
22 are there drugs that have effect on milk yield? It's very  
23 clear that estrogens have an effect on milk yield.  
24 Estrogen-containing contraceptives at high doses definitely  
25 have an effect on milk yield. At low doses, I'm not so

1 certain of the data. But there very well may be other  
2 drugs, particularly drugs that interfere with the hormonal  
3 mechanisms that regulate lactation that may affect milk  
4 yield as well. While that isn't a purview of this  
5 particular group, it's something that in the long run we  
6 really need to work on if we're going to have women getting  
7 starting breastfeeding even properly.

8 DR. BYRN: Other comments?

9 (No response.)

10 DR. BYRN: I think we are done. Thanks very  
11 much for the presentations, and I thought we had a very  
12 good discussion.

13 Let's break until 10:30. We have two  
14 presentations in the public hearing. Then we will try to  
15 start the liposome discussion at 11:00 if we're able to.

16 (Recess.)

17 DR. BYRN: We'll begin the open public hearing.  
18 We have two presentations in the liposome area. The first  
19 speaker is Dr. Chris Swenson who's going to make a  
20 presentation on liposome drug products, the importance of  
21 supramolecular structure.

22 Just as a comment for the committee, these two  
23 speakers are going to present important issues about  
24 liposomes that they think the committee should be aware of.  
25 That's the purpose of these presentations.

1 DR. SWENSON: Well, thank you. You just made  
2 my introduction for me. My name is Chris Swenson. I  
3 represent Elan who are involved in discovery, as well as  
4 drug delivery, including liposomes. I just wanted to make  
5 a brief presentation today and also make you aware that  
6 Elan is willing, indeed eager, to assist the committee in  
7 any way they can on these subjects.

8 I wanted to talk about the importance of  
9 supramolecular structure of lipid-based and liposomal drug  
10 products. The supramolecular structure can affect the  
11 biological properties. Therefore, I think understanding  
12 the physical as well as the chemical characteristics of  
13 these types of drug products is essential during process  
14 development, scale-up, and manufacturing, and in  
15 establishing appropriate release specifications.

16 Abelcet I'm going to use as an example. This  
17 is a lipid formulation of an amphotericin B, which is an  
18 antifungal drug. During its development, we looked at a  
19 number of physicochemical characteristics. We evaluated  
20 morphology by microscopic techniques. We evaluated the  
21 homogeneity of these lipid-based suspensions by density  
22 gradient techniques. We characterized the complexation,  
23 the nature of the complexation, between the lipid and the  
24 drug by spectroscopic techniques, as well as a biological  
25 assay, which was hemolysis in vitro or red blood cells.

1 The supramolecular organization was evaluated using  
2 differential scanning calorimetry, NMR, and both small- and  
3 wide-angle x-ray diffraction.

4 By using these techniques, we were able to  
5 devise a model for what the real organization of the  
6 molecules in this drug product were. We found that the  
7 amphotericin B alternated with the phospholipid -- and here  
8 the phospholipid is blue; the amphotericin is yellow -- in  
9 a cylindrical structure with the hydrophilic face of the  
10 amphotericin facing towards the inside. These cylinders  
11 were actually interdigitated membranes with a length of --  
12 actually that should be 25 Angstroms, not .25, which is  
13 about the half the width of a normal bilayer. That's  
14 because this is an interdigitated membrane. Then these  
15 complexes then associated to form a larger membrane of  
16 associated complexes.

17 Understanding this supramolecular structure  
18 gave us the ability to control our manufacturing process,  
19 but also to establish appropriate quality control tests.  
20 On the left-hand side, these are the normal sorts of tests  
21 that you would use for a parenteral pharmaceutical. On the  
22 right-hand side, are those tests that are specific for  
23 lipid-based or liposomal products, as well as those that  
24 have a supramolecular structure, and therefore you have to  
25 consider things like particle size and the nature of the

1 | complexation and the drug-to-lipid ratio.

2 |           We were not the only ones to recognize that  
3 |           formulating amphotericin B with lipids resulted in a drug  
4 |           that was less nephrotoxic and had an enhanced therapeutic  
5 |           index. There are three products marketed in the U.S. that  
6 |           are based on amphotericin B-lipid interactions. The  
7 |           Fungizone is formulated with a detergent, deoxycholate, but  
8 |           Abelcet is a large, ribbon-like complex. AmBisome is a  
9 |           small unilamellar vesicle, and Amphotec is a small, disc-  
10 |          like complex. So, they're all very different.

11 |           And this is borne out by their pharmacokinetic  
12 |          properties. Abelcet has a much greater clearance than  
13 |          Fungizone, whereas Ambisome's clearance is much less than  
14 |          that of Fungizone, and Amphotec is in between.

15 |           So, the supramolecular structure, in addition  
16 |          to the lipid composition, affects the biological properties  
17 |          of these drug products, and I think should be considered  
18 |          when you're considering the pharmaceutical equivalence and  
19 |          the bioequivalence of these products.

20 |           Thank you.

21 |           DR. BYRN: Are there any questions for Dr.  
22 |          Swenson?

23 |           Actually I have one very brief question.  
24 |          Obviously, these are solution liposomes, so they're  
25 |          dynamic. Things are moving. Is that correct? How fast

1 | does an amphotericin molecule, if we could sit on it, move  
2 | from one liposome to another or move --

3 | DR. SWENSON: When these are in aqueous  
4 | solution, as they are in the bottle, they don't move.

5 | DR. BYRN: They don't equilibrate.

6 | DR. SWENSON: No.

7 | DR. BYRN: Interesting.

8 | DR. JUSKO: I have one question. I assumed  
9 | that what you're presenting for pharmacokinetics represents  
10 | the total quantity of drug, both free and in the  
11 | formulation, which is generally the problem with these  
12 | products. You can't make the separation?

13 | DR. SWENSON: That is absolutely correct.

14 | DR. BYRN: Our next speaker is Dr. Gerard  
15 | Jensen from Gilead Sciences, and he's going to make a  
16 | presentation on liposome therapeutics.

17 | DR. JENSEN: What I wanted to do today is just  
18 | contrast the role of process and material quality control  
19 | versus formulation. Most of the literature on liposomes is  
20 | dominated by formulation dependence of properties. I  
21 | wanted to highlight the process of manufacturing of them  
22 | is, in many cases, of equal importance.

23 | Similar to the previous speaker, we're speaking  
24 | of the third dimension here. We're looking at the  
25 | chemistry of multiple components, physical assembly of many

1 thousands of molecules. There are elements of that  
2 assembly that are critical: size and the distribution of  
3 size, the level to which the drug is entrapped or  
4 encapsulated in the species, and related to that is the  
5 structure. So, if I have a drug molecule, is it in the  
6 interior solubilized, is it in the interior precipitated,  
7 is it in the membrane, that sort of thing.

8 This is a table of stress and consequences, and  
9 actually they're not meant to be paired up, but on the left  
10 side are the things that we do to liposomes, filtration,  
11 refrigeration, freeze-drying. Brownian collisions result  
12 from their natural motion in the bottle. IV  
13 administration, that sort of thing. And then on the right  
14 are consequences that, depending on how a liposome is  
15 assembled, can be the result of those stresses.

16 The usual way that this liposome technology is  
17 represented involves if I need to make a new product, I  
18 want to have reproducibility of that product from lot to  
19 lot. I want to maintain the therapeutic index enhancement,  
20 whatever that is, whether it's on the efficacy or on the  
21 toxicity side, and I need to have a stable formulation. I  
22 need to have a commercially viable shelf life. Again, most  
23 of the formal literature describing these situations  
24 involves composition, lamellarity. Is this an SUV, a small  
25 unilamellar vesicle, or is this a large liposome or that

1 | sort of thing?

2 |           What we'd like to emphasize, though, just as  
3 | important is how it's all put together, material quality  
4 | and characterization, and I'll give a few examples.

5 |           Again, going to the literature, this is a paper  
6 | that's only three years old basically reviewing liposome  
7 | science. They're showing a couple of pharmacokinetic  
8 | plasma half-life curves. In the white triangles, we've got  
9 | a so-called conventional PC:cholesterol liposome. The red  
10 | circles are a trace in this article where they're  
11 | illustrating the effect of putting this polymer coating on  
12 | the outside. The implication is that without that polymer  
13 | coating, conventional liposomes wouldn't survive.

14 |           But going back through the history of our own  
15 | company, many years ago we had an imaging agent called  
16 | Vescan and the yellow squares are a rendering of what the  
17 | blood stability of those particular liposomes were. Those  
18 | were also simple, conventional PC:cholesterol liposomes of  
19 | very similar composition to those cited in the article.

20 |           More recently, we've seen a clinical  
21 | development product, MiKasome, which has a 100-plus hour  
22 | terminal half-life, and the other two traces I've shown is  
23 | Doxil, which is the long-circulating peg-coated liposomal  
24 | doxorubicin, and the yellow boxes are a research  
25 | formulation of the same drug with no peg on the outside. I

1 don't mean to imply by this that those two are equivalent,  
2 but I do mean to show that within the range of so-called  
3 conventional liposomes, with the same composition, you can  
4 get very different biological stabilities based on how  
5 they're made.

6 Another area of interest involves  
7 characterization of liposomes. I did mention earlier  
8 particle size determination. What I've shown here is a  
9 very common looking size distribution that you might get  
10 from any of the commercially available dynamic light  
11 scattering instruments that are used to control liposomes,  
12 median particle size. Those instruments give you many  
13 reported parameters, but the only one that has a  
14 validatable precision is the mean and median particle size,  
15 and it has a precision of about 3.5 percent.

16 However, we know that liposomes are a  
17 distribution of sizes and that there is a heterogeneity of  
18 size. The real question is how are we sensitive in these  
19 techniques to change in that distribution and most  
20 importantly detection of small subpopulations, for example,  
21 of larger particles.

22 If you reprocess the data on a linear scale,  
23 you get a more realistic picture of what we're looking at.  
24 So, the squares are a linear scale rendering of size  
25 distribution based on volume weighting. What you can see

1 quite clearly to larger size is a tail. The importance of  
2 that tail can, just for example, be in two different areas.  
3 In one case, it's been shown long ago that liposomes of  
4 greater than 100 nanometers will, for example, be  
5 accumulated by Kupffer cells in the liver, and those  
6 smaller than 100 nanometers won't. So, having a difference  
7 in this tail, in terms of the number of particles that are  
8 in there, can give you a different biological response just  
9 from that.

10 Then the other plot here, which are the open  
11 circles, is a shell to interior volume ratio. So, this is  
12 the ratio of the lipid shell to the interior aqueous base.  
13 Across the size distribution, you can see that for small  
14 liposomes, they're dominated really by the lipid portion,  
15 and for larger liposomes, they're dominated by the aqueous  
16 portion. So, that can affect how the drug is held in a  
17 liposome. And there are many other consequences of size  
18 distribution. I just wanted to point out a couple of them.

19 So, what techniques do we have to study that?  
20 This is the median diameter, which I mentioned was the  
21 validatable, precise value, as a function of spiking with  
22 large liposomes. So, for a 50 nanometer liposome, if I'm  
23 spiking 230 nanometer liposomes into it, I don't see much  
24 happening in median diameter. Even some of the less  
25 precise, but more sensitive passing diameters, so 90

1 | percent and 95 percent passing diameters, you can have up  
2 | to 5 percent larger particles in there and not really  
3 | notice that in your measurement.

4 |           So, at Gilead years ago, we took advantage of  
5 | turbidity and we developed a proprietary method for  
6 | screening liposomes. We call it normalized quantitative  
7 | turbidity. It takes advantage of the  $r$  to the sixth  
8 | dependence of light scattering on size in the range 50 to  
9 | 300 nanometers. What I want to point out here is the first  
10 | phrase here, which is man versus machine. Experienced  
11 | liposome folks will look at a bottle and they'll be able to  
12 | tell you whether there's a tail in the distribution or not.  
13 | What we wanted to do was be able to quantitate and validate  
14 | that kind of measurement. So, that's what we've done with  
15 | this assay.

16 |           This is an example of two preparations of  
17 | liposomal product, DaunoXome, both of them over 15 months'  
18 | shelf life exhibit stable median particle size diameters.  
19 | One of them is a commercial lot and one of them is a  
20 | development lot that was identical in formulation but had  
21 | different processing parameters. This is what this  
22 | normalized quantitative turbidity is doing. So, in the  
23 | case of the commercial lot, it's stable as a rock for 14-  
24 | month period that we're looking at here, but in the case of  
25 | the other lot, which had different processing parameters,

1 | we start to see the growth of larger particles in the tail.

2 |           There are other characterizational tools that  
3 | may be available. In each case for each product, you need  
4 | to evaluate whether there is or is not value in them. You  
5 | certainly don't want to use them all for every product, but  
6 | these are some examples.

7 |           This is an intermediate. So, from the  
8 | processing point of view of liposomes, you usually have to  
9 | prepare a lipid intermediate, which is the combination of  
10 | lipids and sometimes drug. This is a differential scanning  
11 | calorimetry. It's basically a thermal melting of those  
12 | liposomes, identical formulation, but very different  
13 | structure resulting from that. And then that in turn leads  
14 | to different properties of the resulting liposomes.

15 |           This is a cell-based assay we developed around  
16 | the liposomal amphotericin B product AmBisome. This is a  
17 | very simple thing, essentially a titration of amphotericin  
18 | B in rat blood and looking for potassium release after  
19 | incubation. We're comparing this to Fungizone, which is  
20 | the detergent formulation. So, we see quite a shift in  
21 | concentration needed to induce potassium leakage, and this  
22 | is a measure of how tightly held the drug is. We developed  
23 | this into a quality control assay, which has a 9 percent  
24 | RSD and a good correlation to lethal dose testing, which is  
25 | what we used to do.

1                   But I want to illustrate the point of process  
2 versus formulation. I want to show this slide.  
3 Essentially on the x axis we have a K50, which is a 50  
4 percent potassium leakage parameter derived from that  
5 assay, and on the y axis, we have an LD50, which is the  
6 corresponding lethal dose. These are three available  
7 commercial products of amphotericin B, and this is the  
8 commercial AmBisome product.

9                   These lots here were made again with different  
10 processes by identical formulation. This shift here is  
11 basically the result of those different processing  
12 conditions. Chemically those formulations are identical.  
13 And I want to emphasize that those differences would not be  
14 evident in a PK analysis because since the free drug is so  
15 toxic way down here on this end of the scale, these  
16 differences are the result of far less than a percent of  
17 the total amphotericin B behaving differently in those  
18 formulations. If you have a drug that's beginning to push  
19 up the toxicity curve like this, tiny amounts of drug that  
20 is not entrapped in the same way are going to give you some  
21 significant consequences biologically.

22                   So, just to finish I want to say that we're not  
23 trying to say that making liposomes is magic, and we also  
24 want to emphasize that it's not all in the formulation.  
25 But it does involve high quality, well-controlled

1 components -- I didn't go into that, but that's a key issue  
2 -- precision assembly and rigorous quality testing and  
3 control.

4 This is just an example. This is 10 years of  
5 AmBisome production going back to about 1990. Over the  
6 last 100 or 150 batches, for median size we have an RSD  
7 median size that's the same as the assay precision. It is  
8 an achievable reality, but it does require a significant  
9 investment of time.

10 DR. BYRN: Any questions for Dr. Jensen? One  
11 question.

12 DR. ANDERSON: Under characterization, you had  
13 ESR. This is the first time I've seen anyone put that up  
14 there. What were you looking at?

15 DR. JENSEN: ESR can sometimes be used. It's a  
16 technique where you use spin labels and you can put them in  
17 the membrane. Sometimes if you have a drug that's supposed  
18 to be encapsulated in the interior of the liposome, you can  
19 determine whether or not some drug is in the membrane as  
20 well by looking at the response to a spin probe.

21 DR. ANDERSON: So, you tag this.

22 DR. JENSEN: You can tag a lipid or that kind  
23 of thing, yes. We've never used that in a quality control  
24 setting, though.

25 DR. BYRN: Thank you very much.

1 I think we should go ahead now with our formal  
2 program on complex drug substances, liposome drug products.

3 I'd like the special participants to come up  
4 and sit at the table, and these would be Klaus Gawrisch,  
5 Burton Litman. Okay, they may be stuck in traffic or  
6 something. They're not here yet. We are a little bit of  
7 ahead of time.

8 Mei-Ling, should we go ahead and start?

9 DR. CHEN: Sure.

10 DR. BYRN: Okay, we'll go ahead and start, and  
11 our participants hopefully will join us in process. We are  
12 a little bit ahead, which is unheard of, so we can accept  
13 their late arrival.

14 DR. CHEN: They may show up after 11:00 I  
15 think.

16 Good morning, everyone. This session will be  
17 devoted to the discussion of liposome drug products.

18 Liposome drug products, as you may know by now,  
19 represent a unique class of dosage forms that has been  
20 developed in the past two decades.

21 So, what are liposomes? Liposomes are  
22 microparticulate lipoidal vesicles that are used as a  
23 carrier for improved delivery of a broad spectrum of  
24 therapeutic agents, and these may include chemotherapeutic  
25 agents, imaging agents, antigens, immunomodulators,

1 | chelating compounds, hemoglobin, and others.

2 |           Liposomes can be given by various routes of  
3 | administration. It could be delivered by intravenous,  
4 | subcutaneous, intramuscular, topical, or pulmonary route of  
5 | administration. But most drugs that we have seen so far  
6 | are for intravenous administration.

7 |           In the Center for Drug Evaluation and Research,  
8 | we have a coordinating committee that deals with scientific  
9 | and technical issues related to complex drug substances,  
10 | complex dosage forms, or complex reagents used to  
11 | manufacture drugs. This coordinating committee is  
12 | currently co-chaired by Dr. Yuan-Yuan Chiu, who is sitting  
13 | here to my left, and myself.

14 |           As you may know, under this coordinating  
15 | committee, we have a liposome working group that is  
16 | involved in the policy and guidance development for  
17 | liposome drug products. This working group has recently  
18 | prepared a draft guidance for industry on the submission of  
19 | new drug applications for liposome drug products, which is  
20 | currently going through internal review in the agency.

21 |           This is the cover of the draft guidance. As  
22 | reflected by the title, the guidance talks about chemistry,  
23 | manufacturing, and controls, human pharmacokinetics and  
24 | bioavailability, as well as labeling information. The  
25 | document, however, doesn't provide corresponding

1 | information for abbreviated new drug applications, that is,  
2 | generic drugs.

3 |           The key issues that are not addressed in the  
4 | draft guidance are related to the equivalence comparison in  
5 | the area of chemistry, manufacturing, and controls, CMC,  
6 | and bioavailability/bioequivalence. These are the core  
7 | issues for this advisory committee discussion today. Dr.  
8 | Shaw and Dr. Kumi from the working group will present these  
9 | issues later on, so I will not get into the details now.

10 |           The agency has, in fact, broached these issues  
11 | on liposome drug products to a public workshop in April of  
12 | this year. The workshop was cosponsored by the American  
13 | Association for Pharmaceutical Scientists, AAPS, FDA, and  
14 | USP. The workshop focused on ensuring quality and  
15 | performance of sustained and controlled release parenterals  
16 | that included liposome drug products.

17 |           The participants discussed critical  
18 | formulations and process variables in order to develop  
19 | necessary specification/characterization that assure  
20 | product quality and performance. They also discussed  
21 | bioavailability, bioequivalence, and pharmaceutical  
22 | equivalence. However, no conclusion was reached at the  
23 | workshop regarding the appropriate approaches for  
24 | demonstrating the sameness between two liposome drug  
25 | products.

1                   So, to continue the AAPS workshop discussion,  
2 we are bringing the topic to this committee for your  
3 consideration. What we would like to do today is to share  
4 with you the advances in pharmaceutical technology, the  
5 unique features of liposome dosage forms, and some of the  
6 regulatory concerns for these drug products.

7                   This is the agenda for today for this session.  
8 After my talk, Dr. Francis Martin will give you a brief  
9 overview of the liposome drug products with an interesting  
10 example comparing two liposome products with the same drug  
11 substance, doxorubicin. Dr. Martin is from Alza  
12 Corporation, and he's the key person who's involved in the  
13 development of Doxil, doxorubicin liposome injection. He  
14 has over 25 years of experience in liposome-based systems.  
15 I personally thank him for his participation today.

16                   Following Dr. Martin's talk, our FDA staff, Dr.  
17 Shaw and Dr. Kumi, will present the CMC and the  
18 bioavailability/bioequivalence issues respectively.

19                   Today actually we are also expecting two  
20 experts from the National Institutes of Health, Dr. Litman  
21 and Dr. Gawrisch. I had hoped that they would be here by  
22 now. They will join us for the discussion.

23                   The topics for discussion, after all the  
24 presentations, are shown on this slide. The main purpose  
25 of today's discussion is to share with you the general

1 information and regulatory issues. Recognizing the  
2 complexity of the questions and issues involved, we will  
3 not be seeking specific advice from this committee today at  
4 this time, and we would like to come back to the advisory  
5 committee sometime at a later date for further  
6 deliberations after we've conducted more research and  
7 investigation.

8 Finally, I would like to take this opportunity  
9 to thank all the committee members, our speakers, guests  
10 for your time and effort in helping the agency to address  
11 these regulatory questions so that we can move forward in  
12 the area of liposome drug products. Thank you.

13 DR. BYRN: Thanks very much, Dr. Chen.

14 DR. MARTIN: Thank you, Mei-Ling, for inviting  
15 me to speak today on this issue that's near and dear to my  
16 heart, liposome drug products. What I would like to do is  
17 give an overview and, as Mei-Ling had mentioned, an  
18 interesting example, interesting comparison. I have to  
19 make the disclaimer that the proposed classifications and  
20 observations I make today are those of my own and don't  
21 necessarily reflect the opinions of others.

22 Traditional drug delivery systems, DDSs, have  
23 been designed really to control the input rate of drugs  
24 into the central compartment. If you look at this list of  
25 drug delivery devices on the left, oral devices, patches,

1 pumps, implantable depot formulations, inhalation  
2 formulations, these are really designed to control the  
3 input rate into the central compartment, which then  
4 controls the input rate into tissues and presumably  
5 controls or influences the pharmacodynamic effect.

6 Drug delivery devices are able to affect this  
7 input rate constant and therefore affect the entry of the  
8 active ingredient into the central compartment and  
9 presumably into the tissue compartment. So, this is sort  
10 of the basis of the simpler drug delivery systems.

11 Now, liposomes represent a drug delivery system  
12 that actually enters the central compartment, because I'm  
13 going to restrict my comments to intravenously administered  
14 liposomes. So, they introduce an additional compartment.  
15 Any pharmacokinetic model, one has to consider now the  
16 volume within the liposome. The liposome itself enters the  
17 central compartment with the drug on board and distributes  
18 to tissues and can distribute differentially to tissues  
19 depending on the formulation, and I'll describe that in a  
20 moment.

21 The kinetics then describing these  
22 distributions must include liposome-specific rate constants  
23 as well as drug-specific rate constants. Just to confuse  
24 you all -- it certainly confuses me -- this is a diagram of  
25 a liposome entering the central compartment. Now, this

1 drug could leak from this device or the device could be  
2 taken up by a tissue, such as the mononuclear phagocyte  
3 system, or it could be taken up by another tissue, and then  
4 the drug released from the device within the tissue. So,  
5 it gets very complicated in terms of interpreting  
6 pharmacokinetic information, and this is just one example.

7           What I'm going to try to do is describe sort of  
8 retrospectively my take on the evolution of liposome  
9 design, and some of this is retrospective but it falls into  
10 interesting categories. So, based on selection of drug and  
11 the clinical indications, technology families have evolved  
12 in liposomes. The existing products I would maintain  
13 represent members or species of these families. The reason  
14 I'm trying to categorize this is I think it will be helpful  
15 in terms of drafting some guidelines on how to see whether  
16 or not these members or species within the same family are  
17 equivalent in different ways.

18           These are the four liposome intravenous  
19 products that are approved. AmBisome you've already heard  
20 about. DaunoXome you've heard about. This is daunorubicin  
21 in a liposome. Doxil, which is doxorubicin in a liposome.  
22 And Myocet, although it is not approved in the U.S., it is  
23 approved in Europe and there's a lot of information around  
24 on it. It also includes doxorubicin.

25           So, what I would like to do, since these are

1 comparables, in that the drug is identical, is I would like  
2 to Doxil and Myocet in terms of the formulation and some of  
3 the pharmacokinetic parameters and then propose that  
4 liposomes be classified based on pharmacologic behavior.

5 One possible classification would just be a  
6 vehicle where the majority of a drug in the liposome is  
7 released immediately upon introduction of the particle into  
8 the central compartment. So, this is less of a carrier.  
9 It's a carrier into the blood stream only, and then the  
10 drug and the liposome part company. And there are possible  
11 safety advantages relative to other vehicles, such as  
12 cremophor, less hemolysis, for example. But there are also  
13 infusion reactions associated with liposomes. So, the  
14 tradeoff here in terms of safety is uncertain, but there  
15 are certainly examples in development of what I would call  
16 vehicle formulations of liposomes.

17 Then another possible classification would be  
18 liposomes that are designed to be taken up by the MPS  
19 system or the RES system. They're synonymous. These are  
20 the macrophages which reside primarily in liver, spleen,  
21 and bone marrow. MPS liposomes that are designed for  
22 uptake into the MPS do have advantages, the most important  
23 of which is a safety advantage because they avoid peak  
24 levels, and they form a depot within the MPS cells. The  
25 drug then reenters the central compartment, but does so at

1 a rate which avoids peak levels, yet maintaining, more or  
2 less, the AUC of the free drug administered at the same  
3 dose. And clinical benefits, in terms of safety, have been  
4 documented for these types of liposomes in the form of both  
5 Myocet and AmBisome.

6 Then the other classification I would propose  
7 is liposomes that are designed to avoid the MPS by surface  
8 modifications. You want to, in this case, keep the drug on  
9 board the liposome because what you'd like it to do is  
10 distribute to the tissues and not necessarily to the MPS  
11 tissues but to other tissues. So, this is a design feature  
12 that has led, I think, to an interesting spectrum in terms  
13 of the rate at which these particles are taken up by the  
14 mononuclear phagocyte system. So, these are the ones that  
15 would be designed to be uptaken by the RES and these to be  
16 avoided.

17 And there are some intermediate ones here that  
18 have been described already. DaunoXome, for example, has a  
19 half-life of a couple of hours. There's another one under  
20 development with vincristine that has a half-life in that  
21 same order. These others have half-lives on the order of  
22 minutes. And as I'll show you in a moment, Doxil has a  
23 half-life on the order of several days.

24 So, this would be my family tree in terms of  
25 the evolution of intravenously administered therapeutic

1 liposomes: the MPS uptaken ones, those that avoid the MPS,  
2 and the vehicle.

3 The way this has all worked out over the years  
4 is that design strategies have been introduced. For  
5 example, let me take the ones that are designed for MPS  
6 uptaken. They are just made large without any surface  
7 modification, and they are taken up rapidly by the RES or  
8 MPS.

9 In terms of avoiding the MPS uptake, two paths  
10 have been taken over the years: the pure lipid path, that  
11 is, make liposomes out of just lipids, but design them in  
12 such a way that they avoid RES uptake as long a possible.  
13 There are two versions of these, different lipids that are  
14 very solid lipids and small particles, and one is in  
15 development, a vincristine product, another one, the NX211  
16 is in development, and DaunoXome I believe is a product of  
17 this pathway. Surface modified, polymer modified. There's  
18 one example which is Doxil that I'll talk about more.

19 And one vehicle formulation is under  
20 development with Taxol.

21 Now, these families, if one thinks of liposomes  
22 in this way, will help in terms of issues of equivalence  
23 and bioequivalence and pharmaceutical equivalence because  
24 comparing a product of one of these to another, as I'm  
25 going to show you in a moment, may not be very useful. But

1 comparing members of the same family or the same lineage  
2 may be helpful. So, let me get to the comparison.

3 This list is sort of a redundant list of what  
4 was discussed at the AAPS/FDA/USP workshop. Just what were  
5 the critical influences on pharmacology of liposomes?  
6 Well, the drug, the size of the lipid it's made from, and  
7 surface properties.

8 In terms of the drug, the class of drug, the  
9 drug's intrinsic properties, clearance, its toxicity side  
10 effects, these are all pretty obvious things. Where's the  
11 target site? And how the drug is encapsulated depends a  
12 lot on the chemistry of the drug. So, the drug itself has  
13 important effects.

14 The liposome size has important effects. As  
15 was just mentioned by the earlier speaker, distributions in  
16 sizes are usually the case with liposomes. There are these  
17 outliers sometimes on the edges that have to be considered  
18 for safety and other reasons. And very large liposomes can  
19 actually cause micro-occlusions in the lung and the brain.  
20 So, these things have to be carefully examined.

21 Also, with respect to targeting to tissues,  
22 there are windows in terms of extravasation. If one wants  
23 a particle of these sizes to extravasate into tissues such  
24 as tumors, there is a window of opportunity there. If  
25 they're too large, they will not enter. The size of these

1 windows in tumors now has been probed and there's some  
2 information about the dimensions of the defects in these  
3 capillary beds that will permit particles to extravasate.

4 The structural lipid is important. Including  
5 cholesterol in the liposome is important. The fatty acids  
6 that the phospholipids carry are important in terms of  
7 their phase behavior and so on. So, these are all things  
8 that will influence the pharmacology of the liposome.

9 Surface properties, whether it's a naked lipid  
10 or whether or not it is polymer coated. Does it have a  
11 surface charge or not? If it does have a surface charge,  
12 what is the charge density? All of these things do have  
13 effects on the interaction of these particles not only with  
14 each other but with formed elements in blood, with proteins  
15 in blood, because there's a lot of electrostatic  
16 interactions that go on.

17 What I would like to do now is compare the two  
18 doxorubicin products for which there is the most clinical  
19 information, Myocet and Doxil. What I will do is go  
20 through quickly the design features, morphology,  
21 pharmaceutical properties, the format the products are in  
22 actually as products, pharmacokinetics, and then a few  
23 observations about the comparison.

24 Myocet's size and its loading battery was  
25 selected to maximize the payload, and it has a fluid lipid

1 matrix, a very simple phospholipid cholesterol matrix.  
2 This product is designed to rapidly be taken up by  
3 macrophages. This is to avoid peak levels and attenuate  
4 the toxicity associated with doxorubicin, namely  
5 cardiotoxicity. This creates this depot from which the  
6 drug reenters the blood stream, mimicking a slow infusion,  
7 which was the objective because slow infusions were known  
8 to reduce the cardiotoxicity of doxorubicin. Yet, it does  
9 maintain the plasma and tissue AUC, comparable to similar  
10 doses of the free or the conventional doxorubicin.

11 Myocet is about 180 nanometers in diameter.  
12 You can read the lipid components here. One thing I would  
13 point out is the very high lipid-to-drug ratio, so there's  
14 a lot of drug per particle in this particular system. The  
15 drug is loaded by a nifty pH gradient in the pharmacy, and  
16 when the drug enters the liposomes, it forms these very  
17 interesting organized fiber bundles shown here in an  
18 electron micrograph. So, these are the Myocet liposomes  
19 and you can see the drug has formed a precipitate here in  
20 the form of fibers, very organized fibers within the  
21 liposome itself. The formation of these fibers in some  
22 cases deform the liposome from its normal spherical shape  
23 into what I call the coffee bean shape.

24 The product format for Myocet is a three-vial  
25 system. So, it comes to the pharmacy as a three-vial

1 system. The contents of the vials are listed here. This  
2 is from the product labeling in Europe. One is just  
3 doxorubicin. The other is the empty liposomes and the  
4 other is a buffer. Instructions are included for  
5 reconstituting this system. Those are listed here. You  
6 reconstitute the doxorubicin as you would normally  
7 reconstitute doxorubicin. You turn on your heat block  
8 because a heat block is required, and then adjust the pH of  
9 the liposomes in the liposome vial by just shooting in the  
10 buffer from the third vial, so this creates a pH gradient  
11 low inside the liposomes and high outside the liposomes.  
12 Then the last step is shown here, shake vigorously. The  
13 drug enters the liposomes and the loading is done in the  
14 pharmacy. So, this is quite a bit different than some  
15 other systems.

16           And this is the reason why because once the  
17 drug is loaded, it will start to come out of the liposomes  
18 over a few-hour period. So, this is just showing the  
19 release of the drug from the Myocet liposome at two  
20 different pH's at 37 degrees. You can see that, in just a  
21 few hours, going from 100 percent down to 20, 30, 40  
22 percent of the drug comes out of the liposomes. This is  
23 why the drug cannot be supplied as loaded. It must be  
24 loaded in the pharmacy and used before there is much  
25 release from the liposome.

1                   This is the pharmacokinetics, recently  
2 presented at ASCO, of Myocet. Shown here is the liposome  
3 encapsulated doxorubicin, the total doxorubicin, and the  
4 metabolite, doxorubicinol. And I think this is an  
5 interesting plot, so I'm going to spend just a few minutes  
6 on it because I think it tells a very interesting story.

7                   First of all, the investigators worked out a  
8 way of separating encapsulated from free doxorubicin in  
9 plasma. This is not a difficult thing to do with a little  
10 column separation technique. What you can see is during  
11 the initial period here, as the drug is being cleared, it's  
12 still in the liposome. So, the drug is not bioavailable at  
13 this point. It is being cleared in the form of liposomes.  
14 When you look at the tissue distribution, at least in  
15 animals, where it is going is to the RES cells. You can  
16 see after about 24 hours, the free drug, the liposome  
17 encapsulated drug, and the total drug part company  
18 indicating that the drug now is separated from the carrier.  
19 Very likely this is drug that is reentering the central  
20 compartment from the macrophages. Moreover, the appearance  
21 of a metabolite pretty early in this whole story would  
22 suggest that there is some release of drug immediately from  
23 the liposomes which enters tissues and then is metabolized  
24 and reenters the central compartment.

25                   So, it's a complex sort of a composite of

1 reactions that's going on. Clearance of liposomes. There  
2 is some leakage of drug from the liposomes, uptake by the  
3 MPS cells, destruction of the liposome, reentry of the drug  
4 into the central compartment. So, you can see it is, from  
5 a pharmacokineticist's point of view, a very complex system  
6 to interpret.

7           These are the pharmacokinetic parameters of  
8 Myocet, and I would just point out the differential between  
9 the half-life of the encapsulated doxorubicin, which is  
10 just a few minutes, versus the half-life of the total  
11 doxorubicin. So, this disconnect suggests that the drug  
12 and the carrier are parting company.

13           Again, Doxil's size and payload and loading was  
14 also selected to maximize loading. The size was selected  
15 also to be smaller than the Myocet liposome because of the  
16 potential for it to circulate longer and to extravasate.  
17 It is pegylated; that is, the surface is coated with  
18 polyethylene glycol. And it was intended to passively  
19 accumulate in tumors by extravasating from blood vessels in  
20 tumors into the interstitial spaces of tumors. And the  
21 lipid matrix was designed for plasma stability, yet to  
22 break down in the tissues. So, this was a delicate  
23 balancing act.

24           These again are the attributes of the product.  
25 It's about 100 nanometers in size. The lipid components

1 are listed there. You'll notice it has a lower, about  
2 half, drug-to-lipid ratio than the Myocet product. And  
3 this is loaded using an ammonium ion gradient instead of a  
4 hydrogen ion gradient. But the drug precipitates in the  
5 liposome similarly to the Myocet liposome, as I'll show you  
6 in a moment.

7 This is from the product labeling. Doxil is  
8 supplied already to go in a vial, ready to be diluted.

9 This is a cross section view of the product.  
10 It's about, as I say, 100 nanometers in diameter. The drug  
11 is inside the liposome precipitated in the form of a  
12 sulfate salt of doxorubicin. The polymer is loaded onto  
13 the outer surface. It actually is on the inner surface as  
14 well. It's not illustrated here, but there's a dense layer  
15 of polyethylene glycol on the surface and there's a single  
16 membrane between the external medium and the drug.

17 This is an electron micrograph of the Doxil  
18 liposomes, and you'll see similar features to what you see  
19 with the Myocet. The drug precipitates in the form of a  
20 striated gel inside the liposome. There is some  
21 deformation from the spherical shape. This we believe is a  
22 critical feature to keep the drug in the liposome.

23 So, we now have a precipitated drug, and this  
24 is not unexpected. What we do is we load it in a way where  
25 we have a sulfate salt inside the liposome, and as the